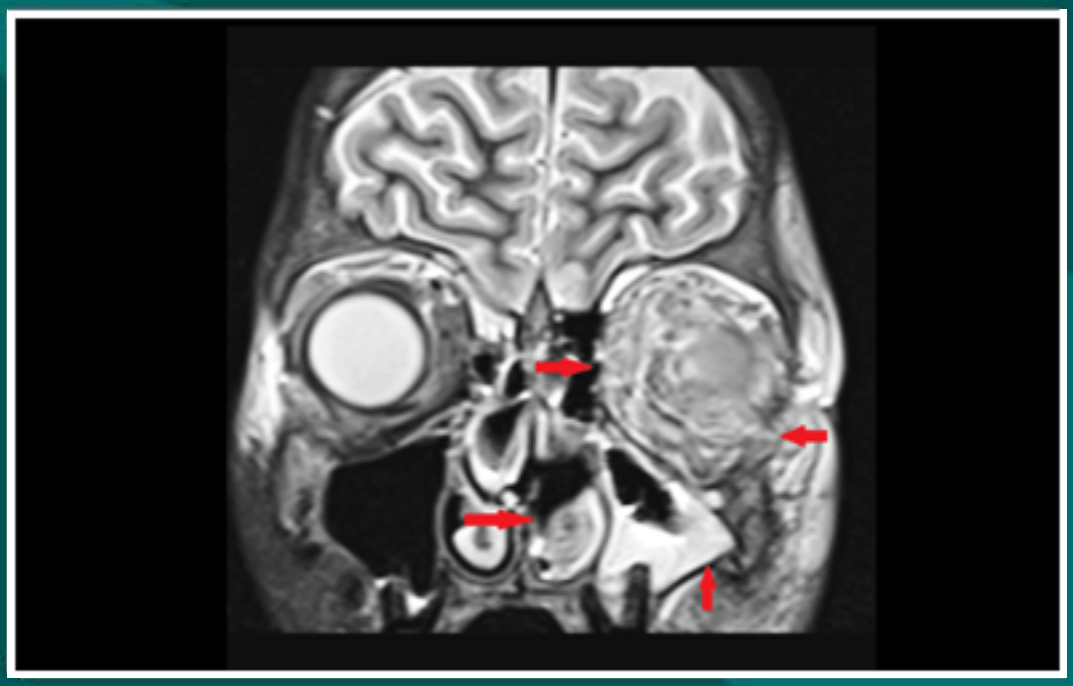
November 2015; Volume 6; Number 11

IJCRI

www.ijcasereportsandimages.com

International Journal of

CASE REPORTS AND IMAGES



Online submission at:
www.ijcasereportandimages.com/submit

ISSN: 0976-3198

International Journal of Case Reports and Images

Contact Details:

Editorial Office

Email: meditor@ijcasereportsandimages.com
Fax: +1-773-409-5040
Website: www.ijcasereportsandimages.com

Guidelines for Authors

Full instructions are available online at:
www.ijcasereportsandimages.com/submit/instructions-for-authors

Manuscript submission:
www.ijcasereportsandimages.com/submit

International Journal of Case Reports and Images

EDITORIAL BOARD

International Journal of Case Reports and Images (IJCRI)

Contact Details:

Editorial Office

Email: meditor@ijcasereportsandimages.com
Fax: +1-773-409-5040
Website: www.ijcasereportsandimages.com

Guidelines for Authors

Full instructions are available online at:
www.ijcasereportsandimages.com/submit/instructions-for-authors

Manuscript submission:
www.ijcasereportsandimages.com/submit

International Journal of
Case Reports and Images

Cover Figure:

All Articles:

Open Access

Contents

Vol. 6, No. 11 (November 2015)

SUBMISSION INSTRUCTIONS
All manuscripts, including illustrations, should be submitted at: www.ijcasereportsandimages.com/submit or email to: submit@ijcasereportsandimages.com
Author Guidelines: www.ijcasereportsandimages.com/submit/instructions-for-authors.php
For any questions contact the Editorial Office via e-mail at: info@ijcasereportsandimages.com or Fax: 1-773-409-5040

REVIEW ARTICLE

PEER REVIEWED | OPEN ACCESS

Chemistry, pharmacology and medicinal property of *Rhodiola rosea* from the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases

Rafie Hamidpour, Soheila Hamidpour, Mohsen Hamidpour, Mina Shahlari, Mahnaz Sohraby, Nooshin Shahlari, Roxanna Hamidpour

ABSTRACT

Rhodiola rosea **is a remarkable herb that has been a part of traditional medicine system in order to stimulate the nervous system, to protect the body against oxidative stress, free radical damage, inflammation, and virus infection.** ***Rhodiola rosea*** **is included among a class of plant derivatives called adaptogen, an agent that help the body adapt to various stressors. Adaptogens have been claimed to treat a wide variety of medical conditions, from fatigue to cancer. The studies on** ***Rhodiola rosea*** **have shown that the plant has anti-stress, anti-anxiety, anti-fatigue, and anti-depressant properties with no significant side effects.** ***Rhodiola rosea*** **has been considered in drug development because of its pharmacological activities throughout the world, especially in parts of Europe, Asia, and Russia.** ***Rhodiola rosea*** **has shown more efficiency and safety than pharmaceutical drugs for anxiety and depression, which typically can have side effects, such as digestive upset, mood and sleep disorders. This research paper, suggests that** ***Rhodiola rosea*****, in addition to cure common disorders such as depression, binge eating, anorexia, generalized anxiety disorders, and physical and mental fatigue, might contribute to prevent, reduce and treat serious diseases such as Alzheimer's disease, Parkinson's disease, cardiovascular disease, diabetes, and cancer. The aim of our future research is to extract** ***Rhodiola rosea*** **in to the filtration equipment then by purification and extended quality control produce tablets for the animal trials.**

Keywords: Alzheimer's disease, Anti-fatigue, Antidepressant, Cancer and memory enhancement

Rafie Hamidpour[1], Soheila Hamidpour[2], Mohsen Hamidpour[3], Mina Shahlari[4], Mahnaz Sohraby[5], Nooshin Shahlari[6], Roxanna Hamidpour[6]

Affiliations: [1]President, Pars Bioscience, Leawood, Kansas, United States; [2]School of Medicine Department of Pathology University of Kansas City Missouri, Kansas City Missouri United State; [3]Department of Hematology and Blood banking- Faculty of Paramedical Sciences- Shahid Beheshti University of Medical Sciences-Tehran-Iran; [4]BA in Biology, Pars Bioscience, Leawood, Kansas, United States; [5]BA, Pars Bioscience, Leawood, Kansas, United States; [6]Summer intern, Pars Bioscience, Leadwood, Kansas, United States.

Corresponding Author: Dr. Rafie Hamidpour, Pars Bioscience LLC 14109 Cambridge Lane, Leawood, Kansas 66224, United States; Ph: (913) 432-0107; Fax: (913) 432-5708; Email: rafie@parsbioscience.com

Received: 07 March 2015
Accepted: 01 July 2015
Published: 01 November 2015

How to cite this article

Hamidpour R, Hamidpour S, Hamidpour M, Shahlari M, Sohraby M, Shahlari N, Hamidpour R. Chemistry, pharmacology and medicinal property of *Rhodiola rosea* from the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases. Int J Case Rep Images 2015;6(11):661–671.

doi:10.5348/ijcri-201458-RA-10013

INTRODUCTION

Rhodiola rosea, also known as golden root or Lignum rhodium is a perennial herbaceous plant in the Crassulaceae family which has been used as a natural medicine from ancient times. This perennial plant reaches a height of 30–70 cm with a thick rhizome and yellow, fragrant flowers. It is a remarkable herb that is valued in traditional medicine in Eastern and Northern Europe, Asia, China, and Russia for its unique pharmacological activity [1]. The plant has been categorized as an "adaptogen" by Russian researchers due to its ability to elevate body resistance to physical, chemical or biological stressors [2], treat fatigue, promote longevity, and support cognition and mood wellbeing [3]. *Rhodiola rosea* (SHR-5 extract) has been indicated as an adaptogen in the situation of fatigue, poor mental performance and depression [3]. *Rhodiola rosea* phytochemical extracts, are the source of important biological activities which is used widely in the treatment of a wide range of diseases like those of the nervous and cardiovascular systems [2], Alzheimer's [4] and Parkinson's disease [5], cancer [2], and inflammatory diseases [6]. The studies of pharmacological activities of *R. rosea* have revealed its hepatoprotective [3] and Monoamine oxidase A (MAO-A) inhibitory effects [7], in addition to the antiviral [8] and antibacterial activities of this plant [9].

Phenylethanoid (salidroside, ρ-tyrosol), phenylpropanoid glycoside (rosarin, rosavin, rosin) and monoterpene (rosiridin) are responsible for the bioactivity of *R. rosea* [10] Salidroside, rosarin, rosavin, rosin, and ρ-tyrosol are the most critical plant constituents used for therapeutic activities [2]. Salidroside and ρ-tyrosol have been found in all *Rhodiola* species but the other active glycosides: rosavin, rosin, and rosarin have not been detected in other genus of *Rhodiola* species. The compound rosavins (rosavin, rosin, and rosarin) are the compound that contains the highest percent of *R. rosea* which was not identified in other species. The compound salidroside is the most biologically active compound which shares many of its effects with rosavin [2]. The absence of adverse drug interactions and side effects associated with *R. rosea* in the clinical trials, make it possible to be used as a safe medication [3]. *Rhodiola rosea* also can be applied as an adjuvant to enhance therapeutic effects of other medicines in a number of disorders such as chronic pneumonia, chronic tuberculosis, vascular dystonia, cancer (reduction of metastasis), and in reducing the debilitating effects of radiotherapy and chemotherapy [11] (Figure 1).

Common names

Rhodiola rosea has numerous common names. Some of the best known names include arctic root, golden root, king's crown, lignum rhodium, orpin rose, rose root, *Sedum rhodiola*, and SHR-5 extract. The term "arctic root" is used as a general name. However, arctic root is actually a trademark name for the specific commercial extract.

Chemical composition

The phytochemical analysis of the *Rhodiola* species has shown that the major beneficial components include salidroside and tyrosol, which are rich in the rhizomes [12]. The dried rhizomes contained 0.05% essential oil. Terpenes and volatile compound have been isolated from *Rhodiola rosea*. As given in Table 1, Myrtenol (36.9%), trans-pinocarveol (16.1%), geraniol (12.7%), cumin alcohol (12.1%), linalool (2.7%), perilla alcohol (1.7%) and dihydrocumin alcohols (12.1%) are the most abundant volatiles detected in the oil [13]. Geraniol and myrtenol are responsible for the rose like odor of the plant. A total number of 140 chemical compounds were identified in *R. rosea* roots. The principal components are phenylpropanoids (rosavin, rosin, and rosarin), Phenylethanoids (salidroside, ρ-tyrosol) and a monoterpene (rosiridin) which are responsible for the pharmacological effects of *R. rosea* [13, 3]. Rosiridin has attracted particular interest because of its effect in depression and senile dementia. Rhodioloside (salidroside) active principles of the SHR-5 extract were found to have neuroprotective, cardioprotective and hepatoprotective activities and can be effective in the prevention of a number of disorders related to neuroendocrine and immune system [3]. Three rosavin compounds (rosavin, rosin, and rosarin) which are unique to *R. rosea* (the most used species of *Rhodiola* genus) might be responsible for antidepressant, anticancer, neurotropic, and hepatoprotective effects of this herb [3].

Antioxidative effect

The imbalance between reactive oxygen species (ROS) generation and antioxidant defense mechanism causes oxidative damage to the proteins, membrane lipids and nucleic acids in the cells. The increased generation of ROS damages the mitochondria, the power house of the body, which account for reducing the ability of maintaining

Table 1: Chemical Composition of oil of Rhodiolarosea

Compound	Percentage
Linalool	2.7
Octanol	13.6
6,6-dimethyl-bicyclo[3,1,1] hept-2-ene-2-carboxaldehyde	1.0
Trans-pinocarveol	16.1
Myrtenol	36.9
Geraniol	12.7
Myrtanol	1.0
Perilla alcohol	1.7
Dihydrocumin alcohol	2.1
Cumin alcohol	12.1

Reference: "Chemical composition of the essential oil from rhizomes of Rhodiola rosea L. grown in Finland." Journal of Essential Oil Research 17.6 (2005): 628–629.

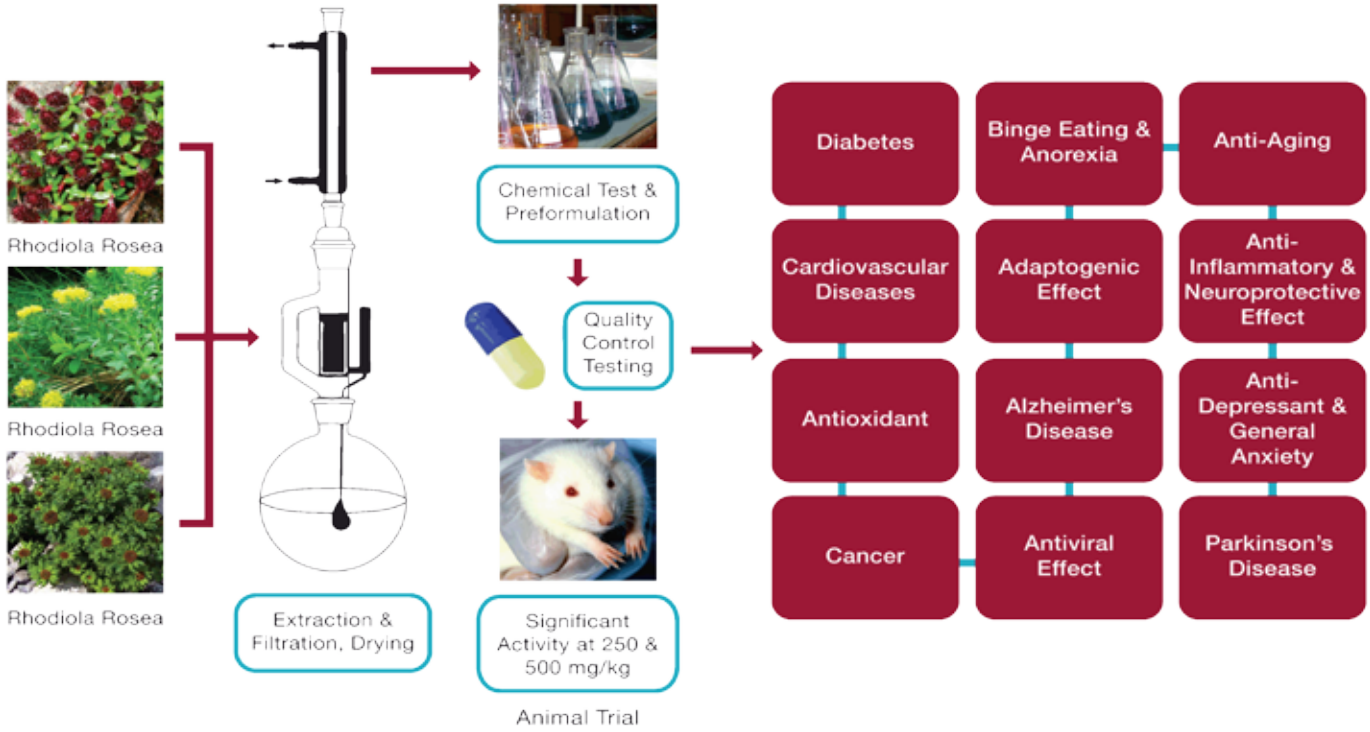


Figure 1: The aim of our future research is to extract Rhodiola rosea in to the filtration equipment then by purification and extended quality control produce tablets for the animal trials.

energy at the cellular level and results in muscular atrophy and muscle fatigue, leading to the decreased performance of an individual [14].

Antioxidants are natural substances that prevent or delay some type of cell damages and protect the body against the oxidative stress and free radicals. Various *Rhodiola* species have shown significant antioxidant activities. Among the 28 different compounds identified in *R. rosea*, P-tyrosol, salidroside, and five salidroside-like glycoside (Rhodiolin, rosiridin, rosarin, rosavin, and rosin), possess strong antioxidant activities [15].

Polyphenols in *R. rosea* neutralize oxidative reactions, which are induced by free radicals since they are excellent donors of protons and electrons. In addition, polyphenols, due to their metal chelating properties, are able to decrease oxidative stresses, induced by transition metals [16].

Salidroside (SDS), a major component extracted from *Rhodiola rosea*, is a glucoside of tyrosol which possess a broad spectrum of pharmacological properties including strong antioxidant activity. Salidroside induces its antioxidant effects to the cells by preventing collection of intracellular ROS, restoring the impaired mitochondria function and mitigating oxidative-stress-induced apoptosis [17].

Production and detoxification of reactive oxygen species (ROS) are of major importance in regulation of erythropoiesis (formation of red blood cells). Salidroside plays an essential role in maintaining normal erythropoiesis through the up-regulation of antioxidant defense mechanism. Salidroside can act as blood tonic supplement and adaptogen. Patients with anemic hypoxia can take advantage of SDS as an adjuvant for erythropoietin (EPO) or other erythropoiesis-stimulating agents. This compound also defends erythroblasts against oxidative stress through up-regulating the expression of antioxidant molecules, glutathione peroxidase, and thioredoxin, and it also nullifies ischemia-induced cardiomyocyte death through suppressing ROS overgeneration [17, 18].

Effect on cancer cells

Cancer is a class of diseases characterized by out-of-control cell growth. Complete eradication of cancer without damage to the rest of the body is the goal of the treatment. Some plant extracts that indicate potential as an anticancer agent have shown to be useful for the treatment or prevention of the cancer with minimal toxicity, and they act synergistically with cytostatic to reduce their toxicity. Study showed that the use of *R. rosea* extract in combination with the antitumor agent cyclophosphamide increased the anti-tumor and antimetastatic efficacy of the drug [2, 19].

The results of investigation in vivo show that *R. rosea* extract has cytotoxic effect on tumor cell line through its major component, polyphenols [20]. The cytotoxicity effect of polyphenols on tumor cells are induced by reaction oxygen species (ROS) mediated mechanisms. Polyphenols including tannins and gallic acids, induce apoptosis in tumor cells by increasing intracellular

peroxides [20]. The results show that salidroside, a component isolated from plants *Rhodiola* genus, causes growth inhibition in several human cancer cell line in concentration between 1 μg/ml and 32 μg/ml dose dependently by induction of G1-phase and/or G2-phase arrest [21]. A number of studies have investigated the inhibitory effect of salidroside on the growth of stomach adenocarcinoma cells, leukemia cells, and parotid carcinoma cells in vitro [22]. In a few studies performed in China, was found that Salidroside could inhibit tumor-induced angiogenesis in mice [22].

Breast cancer is the most common cancer diagnosed in woman in the United States. It develops by the mammary cell proliferation induced by estrogen. Resistance of estrogen receptor negative (ER^-) tumors to anti-hormone therapy is the main concern in breast cancer treatment. Investigations of the effects of salidroside on the breast cancer showed its inhibitory properties on human breast cancer MDA-MB-231 cells. The result indicated that salidroside in concentration between 5 μm and 80 μm dose dependently induced cell-cycle arrest and apoptosis cell death in ER-negative and ER-positive tumors in human breast cancer [23].

Thyroid cancer is the most frequent endocrine neoplasia and accounts for about 2% of cancer-related deaths. Management options for thyroid cancer include total or near total thyroidectomy, radioiodine therapy and pharmacotherapy. These patients may have neuropsychological concerns such as depressive moods or developed cardiovascular problems such as hypertension, electrocardiogram abnormalities, and diastolic dysfunction. In numerous studies, *R. rosea* has demonstrated CNS stimulating, neuro-protective, cardio-protective and antidepressant effects [2]. Since most of these symptoms are in fact the clinical aspect of hypothyroidism, *Rhodiola rosea* is recognized to aid in patient preparation during the hormone withdrawal period. Oxidative stress increases when thyroid hormones are missing during hypothyroidism [24]. In vitro experiments using human erythrocyte reveal that supplementation with *R. rosea* extract can protect cells from oxidative injuries in dose-dependent manner [25]. These findings have also been replicated in human. *Rhodiola rosea* have potentially additional benefits as an adaptogen that tends to be a regulator, having normalizing effects on the organism. Hypothyroidism can be considered as a stressor and then *R. rosea* as an adaptogen that could help the organism's responding [24].

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive brain disorder characterized by the memory and cognitive impairments. Neuropathologically, AD is defined by the accumulation of amyloid plaques and neurofibrillary tangles in certain region of the brain which are important in memory and can cause the loss of synaptic connection between cells. One of the most important parts of unraveling the AD mystery is discovering what causes the disease. It has been suggested that oxidative stress and dysfunction of neurogenesis play important roles in pathogenesis of AD [26]. Amyloid beta (Aβ) peptide, the hallmark of Alzheimer's disease induces an oxidative damage to neurons and finally causes neurons death. Reduced levels of anti-oxidative activity have been observed in the specific regions of the central nervous system of AD patients.

Now researchers are paying great efforts to find potent natural antioxidant with neuroprotective potentials. Salidroside, an active compound occurring naturally in *Rhodiola rosea* L. is protective against (Aβ)-induced oxidative stress by the induction of antioxidant enzymes, thioredoxin (Trx), heme oxygenase-1 (HO-1), and peroxiredoxin-1 (Prxl); the down regulation of pro-apoptotic protein Bax and the up regulation of anti-apoptotic BcL-X1. Pathophysiology of neurodegenerative diseases such as AD has shown that Aβ is associated with ROS generation which leads to mitochondrial dysfunction, lipid peroxidation and apoptosis. Exposure to ROS also inhibits neurogenesis, which is the onset of cognitive impairments and memory deficits. Salidroside could decrease the intracellular ROS level and restore the abnormal mitochondrial membrane potential (MMP). The neuroprotective effect of Salidroside may offer long-term protection in the pathogenesis of AD [26, 27].

Adaptogenic and anti-fatigue effects

Adaptogens are unique group of herbal ingredients which help strengthen the body's response to stress, enhance its ability to cope with anxiety, and fight fatigue. They have the unique ability to adapt their function according to the body's specific needs and do not disturb bodily functions at normal levels. *Rhodiola rosea* is known as a plant's adaptogens because it possesses anti-fatigue and anti-stress activities that can increase mental and physical working performance against a background of fatigue or stress [28]. The phenylpropanoid glycoside called salidroside; flavonoids, phenolic, polyphenolic, and flavonolignans are thought to be the main components of stress- protective and adaptogens of *Rhodiola rosea*. Other constituents isolated from *R. rosea* include rhodioniside, rhodioloside A-E, rhodiolin, rosin, rosavin, rosarin, rosiridin, rosiridol, rhodalgin, acetylrhodalgin, and lotaustralin might also be responsible for stimulant *of R. rosea* or adaptogenic effects. Such compounds can play an active role in increasing energy, stamina, strength and mental capacity required in fight to fight situation to help the body to adapt and resist physical, chemical, and environmental stresses [28, 29].

Clinical efficacy of adaptogens in behavioral and mental disorder has been reviewed. It is now accepted that adaptogens have shown anti-fatigue, anti-depressant, anxiolytic, nootropic, and CNS stimulating effects. Adaptogens do not possess any side effects of conventional drugs such as addiction, tolerance and

abuse potentials, or impair mental function, nor do they cause psychotic symptoms with long-term use [30].

Neuro-degenerative disorders characterized by the progressive loss of structure or function of neurons in the brain region involved in learning and memory. *Rhodiola rosea* as an adaptogen could induce a positive effect in neuro-degenerative disorders due to their inhibitory effects on the formation of p-SAPK (phosphorylated stress-activated protein kinase). Related data may be considered to add further support to the hypothesis that adaptogens have beneficial effect on mental performance and cognitive function [28]. The key point of action of adaptogens on stress appears to be related to the regulation of homeostasis via hypothalamic-pituitary-adrenal axis and regulation of molecular chaperones, stress-activated c-Jun, N-terminal protein kinase, fork head box O transcription factor DAF-16, cortisol, nitric oxide (NO) and beta-endorphin [30]. The optimal corticosteroid level is required for efficient cognitive function. Significant changes (up or down) in circulating levels of corticosteroids have been accepted as the reason for cognitive impairment. Regulatory effects of *R. rosea* on the basal level of salivary cortisol results in an improvement in cognitive function [3].

Rhodiola rosea combines well with other adaptogens and tonics in appropriate dosages. The herbal drug ADAPT-232 is based on the synergistic effect of the three most efficient adaptogen plants, *Rhodiola rosea*, *Schisandra chinensis* and *Eleutherococcus senticosus* in a fix combination. Administration of single and repeated doses of ADAPT-232 has been shown to increase physical energy as well as mental performance and cognitive function [30]. ADAPT-232 significantly increases secretion and release of stress hormones, neuropeptide Y (NPY) and Heat Shock Protein 72 (Hsp 72) which increase tolerance and adaptation to stress. These pathways contribute to the anti fatigue effect of ADPAT, increase the attention and improve the cognitive function [31].

Furthermore, a number of studies have investigated the effects of ADAP-232 on pneumonia patients. Clearly, adjuvant therapy on pneumonia patients with ADAPT-232 has a positive effect on the recovery of the patients, by decreasing the duration of the acute phase of the illness, increasing mental performance of the patients during the rehabilitation period and by improving their quality of life [30].

Anti-depressant and general anxiety

Depression is a severe despondency and sadness accompanied by a feeling of desperation and inadequacy. The mechanism of depression is complex. The therapeutic effects of anti-depressants such as Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOLs) and Selective serotonin reuptake inhibitors (SSRIs) come with a number of side effects like psychomotor impairment and dependence liability [32]. The use of alternative medicine especially natural products for the treatment of mental disorders has been increased in the US and worldwide. The most common reason for people to use complementary therapies is that they want to avoid the common side-effects of prescription anti-depressant drugs. A few natural psychotropics have been more extensively examined in well-designed, placebo-controlled, double-blind studies. *Rhodiola rosea* is one of these second-tier natural products for mood disorders [33]. The standardized extract SHR-5 (3% rosavin and 0.8% salidroside) from *R. rosea* has a significant antidepressant activity in mild to moderate depression. The symptoms evaluated were emotional instability, decreased motivation, cognitive complains and susceptibility to stress [34]. Significant improvement in the overall symptom of depression and mood deficiencies was observed in a 6-week monitoring study in Sweden, which *R. rosea* was given daily with a dosage of two tablets a day, each containing 170 mg of the extract [34]. The role of serotonin, a monoamine neurotransmitter, is usually known and associated with depression, however, serotonin also has some cognitive functions, including the enhancement of memory and learning. Regulation of serotonin at synapses is a major mechanism of action possibly contributing to pharmacological antidepressants. Central and peripheral serotonin levels decreases in patients with depression. Monoamine oxidase type A has an important role in degradation of biogenic amines such as epinephrine, norepinephrine, and serotonin. Monoamine oxidase inhibitors (MAOls) prevent the breakdown of monoamine neurotransmitters including serotonin and therefore increase the concentrations of neurotransmitter in the brain. MAOls therapy with synthetics drugs are known to interact negatively with other medications and even with food. Monoamine oxidase inhibitors can cause death if they are taken in overdose extent. There is an evident that *R. rosea* acts as monoamine oxidase inhibitors and influence the level and activity of biogenic monoamines such as serotonin, norepinephrine, and dopamine in the nerve terminal. *Rhodiola rosea* inhibits the activity of the enzymes responsible for monoamine degradation (monoamine oxidase and catechol-0 methyl transferase) [3, 7]. General anxiety disorder (GAD) is a common disorder that involves chronic worrying, nervousness and tension. There are different types of medication for GAD, including antidepressants, Benzodiazepines, and serotonin reuptake inhibitors. Patients who do respond to conventional treatment often experience adverse side effects that may interfere with their constancy. *Rhodiola rosea* is a safe and tolerable alternative medicine. Administration of *R. rosea* in a dosages of 2–3 capsules each containing 100–170 mg daily, approximate the perfect dose to gain beneficial effects [35].

Anti-inflammatory and neuro-protective effect

In general, inflammation is a localized reaction of the body tissues to infections, irritation, injuries, or disorders

of the immune system which produce redness, warmth, swelling, and pain. As we age, the level of inflammatory immune cytokines increases and we get vulnerable to a number of inflammation-linked diseases, such as cancer, arthritis, muscle weakness, fatigue, sleep disorder, Alzheimer's and Parkinson's disease. An enormous amount of researches have demonstrated the link between chronic low-level brain inflammation and elevated brain glutamate levels, which are a neurotransmitter normally involved in learning and memory. In some cases, glutamate can be an excitotoxin that involves in nerve-cell death in various neurodegenerative disorder including Alzheimer's and Lou Gehrig's disease. Glutamate not only influence amyloid β production (the cause of Alzheimer's disease), but also amyloid β can change the levels of glutamate in the brain which increase the vulnerability of cortical neurons to glutamate cytotoxicity. It has been shown in several studies that *R. rosea* could improve inflammation and neurotoxicity in cortical neuronal cells. *Rhodiola rosea* modulates the neuronal over action and endogenous anti-inflammatory [6].

Microglia, a type of glial cell, act as the first and main form of active immune defense in the central nervous system (CNS), and thus this cell play a key role in the inflammatory reaction. Inflammatory process, in the central nervous system leads to neuronal cell death, and inflammatory response is mediated by the activated microglia, which remove the damaged cell by phagocytosis. The chronic activation of microglia may in turn cause neuronal damage through the secretion of cytotoxic molecules such as proinflammatory cytokines (interleukin-1ß (IL-1), IL-6 and TNF-a), proteases, and reactive oxygen species (ROS), and nitric oxide (NO). Therefore, suppression of microglia-mediated inflammation can appear to be the most promising option in neurodegenerative disease therapy. Since overproduction of NO plays an important role in neuroinflammatory disease, the effect of the *R. rosea* on nitric oxide production was investigated in lipopolysaccharide (LPS)-induced microglia cells. *Rhodiola rosea* has shown to strongly inhibit NO production and the expression of *Inducible nitric oxide synthase* (iNOS), the key enzyme for NO in LPS-stimulated microglia cells [6].

Antiviral activity

The influenza is an acute infections disease caused by an RNA virus of the family orthomyxovirus. Influenza virus infects the epithelial cells of respiratory tract that causes acute pulmonary diseases. Influenza outbreak usually occurs in winter, killing numerous people in pandemic years. The epidemic outbreaks of influenza are associated with influenza virus type A and B. Type C virus is associated with minor symptoms. Two neuraminidase inhibitors have been approved by FDA (zanamivir, and oseltamivir) to treat influenza virus infection. Both of these inhibitors are active against influenza virus A and B, however, they have several toxic effects in the digestive and autonomic nervous system. The flavonols Kaempferol, Herbacetin, Rhodiolin, Rhodionon and Rhodiosin were isolated from *Rhodiola rosea*. The compounds showed neuraminidase inhibitory and anti-influenza virus activities. The in vitro anti-influenza virus activities of flavonoids were evaluated using two influenza viral strains, H1N1 and H9N2, testing their ability to reduce virus-induced cytopathic effect (CPE) in MDCK, Madin-Darby Canine Kidney Cells (virus tissue culture). Anti-influenza activity depends on the position and the number of hydroxyl groups on the flavonoids backbone. Kaempferol showed the highest activity against two influenza viruses, H1N1 and H9N2 with the half maximal effective concentration (EC50) values of 30.2 and 18.5 μM [36].

Coxsackievirus B3 (CVB3) is important human pathogen that belongs to picornavirus family. CVB3 is the most common cause of viral myocarditis, a serious disease that can further leads to dilated cardiomyopathy and cardiac failure and also often induce pancreatitis and aseptic meningitis. Although a few vaccine have been reported to be effective in a murine CVB3-induced myocarditis model, but there are no effective therapeutic agents against CVB3 for the clinic up to now [37]. Salidroside (p-hydroxyphenethyl-β-D-glucoside) which is extracted from *R. rosea* demonstrated antiviral activity while not affecting the normal physiological function of the host cells [8]. Salidroside exhibited obvious antiviral activity in vitro and protected myocardial cells against CVB3 infection. The antiviral activities of salidroside against CVB3 may be related to modulating serum superoxide dismutase (SOD), serum nitric oxide (NO), serum catalase (CAT), and serum malondialdehyde (MDA) activities to protect heart muscle against the harmful effect of free radicals. Also salidroside has the ability to increase the hemoglobin capacity to carry oxygen, which provides protection for the myocardial cells from hypoxemia [8]. Since salidroside also has shown antiviral activities against CVB3 in vitro, the findings have significant implications for a potential therapeutic agent for treatment of viral myocarditis and influenza virus infections which is worthy of further future researches [8].

Antidiabetic

The antidiabetic effects of dietary administration of *Rhodiola*-water extract on streptozotocin (STZ)-induce diabetes rat model were investigated. The STZ is a toxin with the ability to damage pancreatic beta cells, resulting in hypoinsulinemia and hyperglycemia [38]. The study used STZ mice as a model because it is considered an appropriate model to assess mechanisms of diabetes and evaluate potential therapies [39]. Three days administration of *Rhodiola*-water extract in STZ-diabetic rats resulted in an increase of glucose transporter subtype 4(GLUT 4) in skeletal muscle and a reduction of phosphoenolpyruvate carboxykinase in liver [38]. It has

been reported that *Rhodiola*-water extract have a long-term blood glucose level control effect and improves hyperglycemia by an increase of beta-endorphin secretion from adrenal gland to activate opioid μ-receptors to achieve the higher of GLUT 4 gene expression in STZ rats model [38].

Evidence in both experimental and clinical studies shows that increased oxidative stress is the common pathogenic factor causing diabetic mellitus and its complication. Diabetes is a chronic metabolic disorder characterized by hyperglycemia and the inability of tissues to utilize glucose. Hyperglycemia and fluctuation in blood glucose generate oxidative stress through overproduction of reactive oxygen species. Dietary *R. rosea* supplementation results in a significant reduction on blood glucose and lipid peroxide, increased levels of glutathione, glutathione peroxide, catalase, and superoxide dismutase (SOD) in the liver. *Rhodiola rosea* extracts may be effective for correcting hyperglycemia and preventing diabetic complications [40]. Managing diabetes without any side effect is still a challenge. Therefore, it is worth more investigation in the antidiabetic activity of natural products such as *R. rosea* on human in the future.

Lifespan increasing effects

Recent studies on Drosophila melanogaster and *Caenorhabditis elegans* have shown that bioactive components of *R. rosea*, particularly salidroside and/or rosavins, may have an effect on lifespan and improve health spans. The plant adaptogens can induce their effects by different routes. Adaptogens can extend the lifespan by increasing an organism's resistance against the damaging effects of different stress conditions. The plants adaptogens such as *R. rosea* interfere with the localization of DAF-16, a fork head/winged-helix transcription factor. The *Caenorhabditis elegans* DAF-16 transcription factor is critical for diverse biological processes specifically longevity and stress resistance. *Rhodiola rosea* induce translocation of the DNF-16 transcription factor from the cytoplasm into the nucleus. DAF-16 in the nucleus reprograms the transcriptional activities favoring the transcription of a large number of genes involved in stress resistance and longevity [41].

Moreover, dietary conditions are another hypothesis for anti aging effect of *Rhodiola rosea*. The effect of *R. rosea* supplement on the lifespan of fruit fly depends on diet composition particularly on the protein-to-carbohydrate ratio. Dietary compositions with the protein-to-carbohydrate ratio less than 1 extends the lifespan by 15–21%, but diets with high protein-to-carbohydrate ratio or high caloricity do not support the beneficial action of *R. rosea* on longevity [42].

Hormesis is favorable biological responses to a low dose stress-induced stimulation resulting in biologically beneficial effects on growth, reproduction and longevity. Hormesis activates defense systems of the body and the defense process repair the damage caused by the toxin and also protect body against any additional stress. It can be hypothesized that the plants adaptogen like *R. rosea* act as a mild stressor leading to activate an adaptive response which protects the cells from stressful environments and increase the life span. In this way, it can be mentioned that adaptogen acts as hormetic agents. The findings of a study support the view that low doses of *R. rosea* extract (10–25 μg/ml) works in a deliberate and systematic way in order to increase the stress resistance and lifespan of *C. elegans* between 10 and 20%, whereas the higher doses tested (250μg/ml) of *Rhodiola* showed a life span shortening of 15–25% [41].

Cardio-protective effects

Hyperhomocysteinemia (high homocysteine level in the blood) is a major risk factor of cardiovascular disease. An abnormal accumulation of homocysteine, an amino acid that is produced by human body due to consuming meat, is related to various cardiovascular diseases such as coronary heart disease, stroke and peripheral vascular disease (fatty deposits in peripheral arteries). Homocysteine exert its adverse effect on endothelial function by increasing superoxide production and decreasing the activity of nitric oxide synthase. Homocysteine could be a starting point for the development of atherosclerosis by disturbing vascular permeability, damaging the inner lining of the arteries and promoting blood clots. Salidroside extracted from *Rhodiola* protect rats aortas against homocysteine-induce impairment of endothelium by inhibiting NOX2-dependent ROS overproduction. These results suggest that salidroside significantly inhibit ROS overproduction associated with vascular dysfunction, a common pathological process in hypertension and diabetes [17].

Effect on Binge eating and Anorexia

Binge eating (BE) and Anorexia nervosa are official eating disorders. Binge eating appears to be characterized by extreme overeating without subsequent purging episodes, usually secretive, and filled with shame [43]. Topiramate or sibutramine are medications that have been suggested to reduce BE. However, their uses are associated with a variety of adverse side effects which causes serious problems, such as cardiovascular disorder and stroke. As a result they have been withdrawn from the market in many European countries. Since stress is a key factor in BE, a reduction of stress response might show an effective mechanism for the treatment of BE. Therefore, due to its anti-stress properties, the effect of Salidroside, an active principle of the dry extract of *R. rosea*, was evaluated for treatment of BE. Studies have shown that Salidroside abolishes BE by suppressing the activation of hypothalamic-pituitary-adrenal (HPA) axis, leading to a reduction of serum corticosterone flowing chronic treatment [1].

Eating disorders are associated with stress responses depending on the intensity of stress itself. Moderate stressor stimulate eating while acute stressor which causes high levels of CRF (corticotrophin-releasing factors), induce anorexia. In particular, considerable evidence suggests a role for endogenous brain CRF system in appetite regulation and the cause of eating disorder. At doses of 15 and 20 mg/kg, *Rhodiola* extract significantly inhibits the anorexia effects of stress within a 60 min after a single oral administration of *R. rosea* extract [44]. Therefore, the difference effects evoked by *R. rosea* on eating behavior could be attributed to its ability to modulate the activation of several components of stress-response system rather than a direct effect on orexigenic or anorexigenic mechanisms [1].

Effect on Parkinson's Disease

Parkinson's disease (PD) is a chronic and progressive disorder of the nervous system that affects movements of the body and the symptoms continue and worsen over the time. Parkinson's primarily affects neurons in the area of the brain called substantia nigra. Cells within the substantia produce and release dopamine, a neurotransmitter that controls the movement and balance. In patients suffering from Parkinson's, the amount of dopamine produced in the brain decreases. The shaking or tremor may begin to interfere with the daily activities of the PD patients. As these symptoms become more pronounced, patients may have difficulty walking, talking or performing other simple tasks. Although there is no cure, there are treatment options such as medication and surgery to control the symptoms [5].

The new plant preparation phytomix-40 (PM-40) is developed for the treatment of Parkinson's disease. Phytomix (PM-40) is a mixture of natural extracts of 40 medical plants, including extracts of *R. rosea*, *Eleutherococcus*, ginseng, and other adaptogens with neuroprotective properties. Animal experiments demonstrated that PM-40 had a low toxicity. The neuroprotective plant adaptogen can be used in complex therapy for the Parkinson's disease for improving its efficacy. Oral administration of 10% solution of PM-40 to mice with MPTP-induced Parkinson's syndrome reduces the severity of rigidity and increase motor activity [45]. The preparation normalized immunobiological parameters in PD patients and relieved the clinical symptom of the disease. The mechanism of action of PM-40 contributes to the recovery of the dopamine synthesis by healing of damaged neurons. PM-40 can be used with the combination of other standard antiparkinson drugs in order to improve their clinical effects and minimize side effects of Parkinson's medication [5].

Overview of toxicological and safety data

Through the doses administered in clinical trials, there is no report of serious side effects that could be attributed to the extract of *Rhodiola rosea*. The normal usage of *R. rosea* is safe, however it is important to consider that *R. rosea* a strong adaptogenic and tonic herb might have an addictive effect with other substance exhibiting stimulant properties (such as caffeine) [46].

Continuous daily use of *R. rosea* for days and months is followed by an interval with no supplementation (three weeks "on" and one week "off"). This clinical recommendation helps avoid possible side effects at higher dosages such as insomnia, irritability, dizziness, dry month, and allergy (unspecified) [35].

The most commonly used standardized extract has a minimum of 3% rosavin and 1% salidroside. The typical daily dose for chronic administration extracts range from 100–170 mg per day when standardized for 2.6% rosavin. Evidence on the safety and appropriateness of *R. rosea* supplementation during pregnancy and lactation has not been established [2].

CONCLUSIONS

Rhodiola rosea, which is also known as the golden root, is one of the most studied *Rhodiola* species. As an adaptogen, many health benefits are related to *Rhodiola* drug extracts due to their balancing and regulatory effects. Significant antioxidant activities have been documented for various *Rhodiola* species extracts. In Russian and Chinese folk medicine, the plant is used for stimulating the nervous system and decreasing mental and physical fatigue. It has been shown in pharmacological investigations that, *R. rosea* possess antioxidant, anti-aging, anti-cancer and anti-cardiovascular disease properties. As a dietary supplement, numerous preparations of extracts are used worldwide including teas, homeopathic preparations and tinctures as well as standardized extract. *Rhodiola rosea* has enormous traditional and pharmacological use in supporting mood and cognitive function.

Rhodiola rosea is a versatile, safe and easily accessible plant which offers resistance to the physical, chemical and biological stressors without interacting with other food or drugs. The remarkable therapeutic effects of this plant in prevention and treatment of variety of human diseases, makes this plant very valuable for further investigation in the area of pharmaceutical industries.

****

Author Contributions

Rafie Hamidpour – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Soheila Hamidpour – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Mohsen Hamidpour – Analysis and interpretation of data, Revising it critically for important intellectual

content, Final approval of the version to be published
Mina Shahlari – Acquisition of data, Drafting the article, Final approval of the version to be published
Mahnaz Sohraby – Acquisition of data, Drafting the article, Final approval of the version to be published
Nooshin Shahlari – Acquisition of data, Drafting the article, Final approval of the version to be published
Roxanna Hamidpour – Acquisition of data, Drafting the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

Copyright

REFERENCES

1. Cifani C, Micioni Di B MV, Vitale G, Ruggieri V, Ciccocioppo R, Massi M. Effect of salidroside, active principle of Rhodiola rosea extract, on binge eating. Physiol Behav 2010 Dec 2;101(5):555–62.
2. Kelly GS. Rhodiola rosea: a possible plant adaptogen. Altern Med Rev 2001 Jun;6(3):293–302.
3. Panossian A, Wikman G, Sarris J. Rosenroot (Rhodiola rosea): traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine 2010 Jun;17(7):481–93.
4. Qu ZQ, Zhou Y, Zeng YS, Li Y, Chung P. Pretreatment with Rhodiola rosea extract reduces cognitive impairment induced by intracerebroventricular streptozotocin in rats: implication of anti-oxidative and neuroprotective effects. Biomed Environ Sci 2009 Aug;22(4):318–26.
5. Bocharov EV, Ivanova-Smolenskaya IA, Poleshchuk VV, Kucheryanu VG, Il'enko VA, Bocharova OA. Therapeutic efficacy of the neuroprotective plant adaptogen in neurodegenerative disease (Parkinson's disease as an example). Bull Exp Biol Med 2010 Nov;149(6):682–4.
6. Lee Y, Jung JC, Jang S. Anti-Inflammatory and Neuroprotective Effects of Constituents Isolated from Rhodiola rosea. Evid Based Complement Alternat Med 2013;2013:514049.
7. van Diermen D, Marston A, Bravo J, Reist M, Carrupt PA, Hostettmann K. Monoamine oxidase inhibition by Rhodiola rosea L. roots. J Ethnopharmacol 2009 Mar 18;122(2):397–401.
8. Wang H, Ding Y, Zhou J, Sun X, Wang S. The in vitro and in vivo antiviral effects of salidroside from Rhodiola rosea L. against coxsackievirus B3. Phytomedicine 2009 Mar;16(2-3):146–55.
9. Ming DS, Hillhouse BJ, Guns ES, et al. Bioactive compounds from Rhodiola rosea (Crassulaceae). Phytother Res 2005 Sep;19(9):740–3.
10. Ma CY, Tang J, Wang HX, Gu XH, Tao GJ. Simultaneous Determination of Six Active Compounds in Rhodiola L. by RP-LC. Chromatographia 2008;67(5):383–8.
11. Ma YC, Wang XQ, Hou F, et al. Simultaneous quantification of polyherbal formulations containing Rhodiola rosea L. and Eleutherococcus senticosus Maxim. using rapid resolution liquid chromatography (RRLC). J Pharm Biomed Anal 2011 Jul 15;55(5):908–15.
12. Tsering T, Bai Z, Nan P, et al. Chemical composition of the essential oils of three Rhodiola species from Tibet. Chem Nat Comp 2007;43(6):716–18.
13. Héthelyi ÉB, Korány K, Galambosi B, Domokos J, Pálinkás J. Chemical Composition of the Essential Oil from Rhizomes of Rhodiola rosea L. Grown in Finland. J Essen Oil Res 2005;17(6):628–9.
14. Gupta V, Lahiri SS, Sultana S, Kumar R. Mechanism of action of Rhodiola imbricata Edgew during exposure to cold, hypoxia and restraint (C-H-R) stress induced hypothermia and post stress recovery in rats. Food Chem Toxicol 2009 Jun;47(6):1239–45.
15. Schriner SE, Abrahamyan A, Avanessian A, et al. Decreased mitochondrial superoxide levels and enhanced protection against paraquat in Drosophila melanogaster supplemented with Rhodiola rosea. Free Radic Res 2009 Sep;43(9):836–43.
16. Chen TS, Liou SY, Chang YL. Antioxidant evaluation of three adaptogen extracts. Am J Chin Med 2008;36(6):1209–17.
17. Leung SB, Zhang H, Lau CW, Huang Y, Lin Z. Salidroside improves homocysteine-induced endothelial dysfunction by reducing oxidative stress. Evid Based Complement Alternat Med 2013;2013:679635.
18. Qian EW, Ge DT, Kong SK. Salidroside promotes erythropoiesis and protects erythroblasts against oxidative stress by up-regulating glutathione peroxidase and thioredoxin. J Ethnopharmacol 2011 Jan 27;133(2):308–14.
19. Majewska A, Hoser G, Furmanowa M, et al. Antiproliferative and antimitotic effect, S phase accumulation and induction of apoptosis and necrosis after treatment of extract from Rhodiola rosea rhizomes on HL-60 cells. J Ethnopharmacol 2006 Jan 3;103(1):43–52.
20. Mishra KP, Padwad YS, Dutta A, et al. Aqueous extract of Rhodiola imbricata rhizome inhibits proliferation of an erythroleukemic cell line K-562 by inducing apoptosis and cell cycle arrest at G2/M phase. Immunobiology 2008;213(2):125–31.
21. Hu X, Lin S, Yu D, Qiu S, Zhang X, Mei R. A preliminary study: the anti-proliferation effect of salidroside on different human cancer cell lines. Cell Biol Toxicol 2010 Dec;26(6):499–507.
22. Skopinska-Rózewska E, Malinowski M, Wasiutynski A, et al. The influence of Rhodiola quadrifida 50% hydro-alcoholic extract and salidroside on tumor-induced angiogenesis in mice. Pol J Vet Sci 2008;11(2):97–104.

23. Hu X, Zhang X, Qiu S, Yu D, Lin S. Salidroside induces cell-cycle arrest and apoptosis in human breast cancer cells. Biochem Biophys Res Commun 2010 Jul 16;398(1):62–7.
24. Zubeldia JM, Nabi HA, Jiménez del Río M, Genovese J. Exploring new applications for Rhodiola rosea: can we improve the quality of life of patients with short-term hypothyroidism induced by hormone withdrawal? J Med Food 2010 Dec;13(6):1287–92.
25. De Sanctis R, De Bellis R, Scesa C, Mancini U, Cucchiarini L, Dachà M. In vitro protective effect of Rhodiola rosea extract against hypochlorous acid-induced oxidative damage in human erythrocytes. Biofactors 2004;20(3):147–59.
26. Qu ZQ, Zhou Y, Zeng YS, et al. Protective effects of a Rhodiola crenulata extract and salidroside on hippocampal neurogenesis against streptozotocin-induced neural injury in the rat. PLoS One 2012;7(1):e29641.
27. Zhang L, Yu H, Zhao X, et al. Neuroprotective effects of salidroside against beta-amyloid-induced oxidative stress in SH-SY5Y human neuroblastoma cells. Neurochem Int 2010 Nov;57(5):547–55.
28. Panossian A, Hambardzumyan M, Hovhanissyan A, Wikman G. The adaptogens rhodiola and schizandra modify the response to immobilization stress in rabbits by suppressing the increase of phosphorylated stress-activated protein kinase, nitric oxide and cortisol. Drug Target Insights 2007;2:39–54.
29. Buckley MS. Concentration and mental performance amplifying formulation. U.S. Patent Application 2012;13/420,409.
30. Aslanyan G, Amroyan E, Gabrielyan E, Nylander M, Wikman G, Panossian A. Double-blind, placebo-controlled, randomised study of single dose effects of ADAPT-232 on cognitive functions. Phytomedicine 2010 Jun;17(7):494–9.
31. Panossian A, Wikman G, Kaur P, Asea A. Adaptogens stimulate neuropeptide y and hsp72 expression and release in neuroglia cells. Front Neurosci 2012 Feb 1;6:6.
32. Chan SW. Panax ginseng, Rhodiola rosea and Schisandra chinensis. Int J Food Sci Nutr 2012 Mar;63 Suppl 1:75–81.
33. Iovieno N, Dalton ED, Fava M, Mischoulon D. Second-tier natural antidepressants: review and critique. J Affect Disord 2011 May;130(3):343–57.
34. Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. Nord J Psychiatry 2007;61(5):343–8.
35. Rhodiola rosea for general anxiety disorder. Kiefer D. Intregative Medi Alert 2008. [Available at: http://www.ahcmedia.com/articles/12628-rhodiola-rosea-for-general-anxiety-disorder]
36. Jeong HJ, Ryu YB, Park SJ, et al. Neuraminidase inhibitory activities of flavonols isolated from Rhodiola rosea roots and their in vitro anti-influenza viral activities. Bioorg Med Chem 2009 Oct 1;17(19):6816–23.
37. Hunziker IP, Harkins S, Feuer R, Cornell CT, Whitton JL. Generation and analysis of an RNA vaccine that protects against coxsackievirus B3 challenge. Virology 2004 Dec 5;330(1):196–208.
38. Niu CS, Chen LJ, Niu HS. Antihyperglycemic action of rhodiola-aqeous extract in type1-like diabetic rats. BMC Complement Altern Med 2014 Jan 13;14:20.
39. Biswas M, Kar B, Bhattacharya S, Kumar RB, Ghosh AK, Haldar PK. Antihyperglycemic activity and antioxidant role of Terminalia arjuna leaf in streptozotocin-induced diabetic rats. Pharm Biol 2011 Apr;49(4):335–40.
40. Kim SH, Hyun SH, Choung SY. Antioxidative effects of Cinnamomi cassiae and Rhodiola rosea extracts in liver of diabetic mice. Biofactors 2006;26(3):209–19.
41. Wiegant FA, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA. Plant adaptogens increase lifespan and stress resistance in C. elegans. Biogerontology 2009 Feb;10(1):27–42.
42. Gospodaryov DV, Yurkevych IS, Jafari M, Lushchak VI, Lushchak OV. Lifespan extension and delay of age-related functional decline caused by Rhodiola rosea depends on dietary macronutrient balance. Longev Healthspan 2013 Apr 2;2(1):5.
43. Cifani C, D.B MVM, Vitale G, Massi M. Effect of Rhodiola rosea extracts on binge eating in female rats. Appetite 2010;54(3):639–39.
44. Mattioli L, Perfumi M. Rhodiola rosea L. extract reduces stress- and CRF-induced anorexia in rats. J Psychopharmacol 2007 Sep;21(7):742–50.
45. Bocharov EV, Kucheryanu VG, Kryzhanovskii GN, Bocharova OA, Kudrin VS, Belorustseva SA. Effect of complex phytoadaptogen on MPTP-induced Parkinson's syndrome in mice. Bull Exp Biol Med 2006 May;141(5):560–3.
46. Ishaque S, Shamseer L, Bukutu C, Vohra S. Rhodiola rosea for physical and mental fatigue: a systematic review. BMC Complement Altern Med 2012 May 29;12:70.

CASE REPORT PEER REVIEWED | OPEN ACCESS

A rare case of situs ambiguous in an adult

Niki Lama, Petros Maniatis, Dionisios Haralambos Antonatos, Dimitrios Fagkrezos, Charikleia Triantopoulou, Ioannis Papailiou

ABSTRACT

Introduction: As the use of imaging increases, congenital organs malposition is detected more frequently. In order to clarify the specific anatomical complexity and features, three major categories, based on the position of the heart and the viscera relative to the midline, have been described situs solitus, situs inversus and situs ambiguous. Case Report: This is a case of a 59-year-old female presented to our hospital emergency room with dyspnea. Patient on clinical and radiological evaluation was diagnosed to have situs ambiguous with polysplenia and minor congenital heart malformations. Venous abnormalities, with double superior vena cava (SVC) and left inferior vena cava (IVC) were also present. Patient is currently asymptomatic and is on regular follow-up in our hospital, cardiology department. Conclusion: Developmental abnormalities unexpectedly found on imaging studies represent a radiological challenge. Careful analysis and understanding is mandatory, as anatomical miss arrangements can cause confusion in differential diagnosis and severe clinical implication during invasive procedures.

Keywords: Congenital anomalies, Situs ambiguous, Polysplenism

How to cite this article

Lama N, Maniatis P, Antonatos DH, Fagkrezos D, Triantopoulou C, Papailiou I. A rare case of situs ambiguous in an adult. Int J Case Rep Images 2015;6(11):672–677.

doi:10.5348/ijcri-2015106-CR-10567

Niki Lama[1], Petros Maniatis[2], Dionisios Haralambos Antonatos[3], Dimitrios Fagkrezos[2], Charikleia Triantopoulou[4], Ioannis Papailiou[5]

Affiliations: [1]Resident, Radiology Department, Konstantopouleio General Hospital, Athens, Greece; [2]Consultant, CT Department Konstantopouleio General Hospital, Athens, Greece; [3]Consultant, Cardiology Department, Konstantopouleio General Hospital, Athens, Greece; [4]Head of the Department, Radiology Department, Konstantopouleio General Hospital, Athens, Greece; [5]Head of the Department, CT Department, Konstantopouleio General Hospital, Athens, Greece.

Corresponding Author: Niki Lama, Martinegou 44-48, Nea Filothei, Athens, Attiki, Greece 11524; Ph: 00306980079133; Email: niklampatr@gmail.com

Received: 19 October 2014
Accepted: 25 December 2014
Published: 01 November 2015

INTRODUCTION

The term situs indicates the position of the heart and viscera relative to midline [1]. Situs solitus points out the normal position of the heart and abdominal viscera, with the cardiac apex, spleen, stomach, and aorta located on the left and the liver and inferior vena cava located on the right.

While the term situs inversus reveal a mirror-image location of the viscera relative to situs solitus. This can be divided in two major sub-categories: Situs inversus with dextrocardia (mirror image location of the heart and viscera relative to situs solitus, with the cardiac apex, spleen, stomach, and aorta located on the right) and situs inversus with levocardia (mirror image location of the viscera relative to situs solitus but with a left-sided cardiac apex). Situs inversus with dextrocardia is more common, while situs inversus with levocardia is an extremely rare variant [2].

When the thoracic and abdominal organs are not clearly lateralized, situs ambiguous or heterotaxy syndrome should be considered. The spleen is almost

always affected, and there is a ratio between the used terms for these congenital malformations and the corresponding type of splenic abnormality [3]. Two major subcategories of situs ambiguous have been described, situs ambiguous with polysplenia (also known as polysplenia syndrome or double left-sidedness or left isomerism) and situs ambiguous with asplenia (also known as asplenia syndrome or double right-sidedness or right isomerism or Ivermark syndrome) [1]. Heterotaxy results when the left-right symmetry, in the developing embryo, fails to be normaly established [3]. Typical manifestations include misarrangements and malposition of the thoraco-abdominal organs and vessels, accompanied by complex congenital heart diseases [3]. Although, this anomaly does not have a fixed set of characteristics, present in every case, a sufficient number of associated findings, which occur in the majority of patients, allow the establishment of the diagnosis [2].

CASE REPORT

A 59-year-old Caucasian female, with no history of disease, was admitted to our emergency department with acute unexplained dyspnea and palpitation. On admission, physical examination revealed a dyspneic patient without any other findings. The family history was negative for remarkable diseases or congenital abnormalities. Electrocardiogram showed a regular rhythm, with sinus tachycardia. Blood pressure of the patient was normal. The room air oxygen saturation was 89%, and arterial blood gas analysis revealed hypoxemia with an elevated alveolo-arterial oxygen gradient. All blood tests, except D-dimer, were normal. Chest X-ray revealed superior mediastinum widening and double shadow of thoracic aorta (Figure 1), but no other remarkable sign. A transthoracic echocardiogram showed normal left ventricle function with a patent foramen ovale, and minor degree of tricuspid and mitral valve regurgitation.

In order to exclude the diagnosis of pulmonary embolism and to investigate and evaluate the others suspected, combined abnormalities, a CT scan of chest and abdomen was performed. A persistent left SVC was revealed, connected with the right superior vena cava (SVC) by a bridging vein, which was crossing anterior to the aortic arch (Figure 2). The left SVC was running lateral to the aortic arch (Figure 3) and through the coronary sinus to the right atrium (Figure 4). Right lung was bilobed. A dilated hemiazygos vein was located posterior to the descending aorta and was draining to the left SVC. Left inferior vena cava (IVC) with hemiazygos continuation was also revealed. There was total absence of azygos vein. Hepatic veins were drained to right atrium. Portal vein was placed anterior to the midline gallbladder. The origin of left hepatic artery was the superior mesenteric artery. The liver was also midline and symmetric. Pancreas was truncated. The lobulated spleen, the multiple small satellite accessory spleens and the stomach were located at the left. Left-sided colon and right-sided small bowels indicated intestinal malrotation (Figure 5). The diagnosis was consistent with Situs Ambiguous with polysplenia syndrome, without additional findings.

DISCUSSION

Although situs ambiguous has been described in literature several times, we have found only few description of this entity presented in adults, and none completely consistent with our findings. This fact could be explained by the high mortality rates of the syndrome, which is consistent with the severity of the associated congenital heart disease [4]. However, patients with

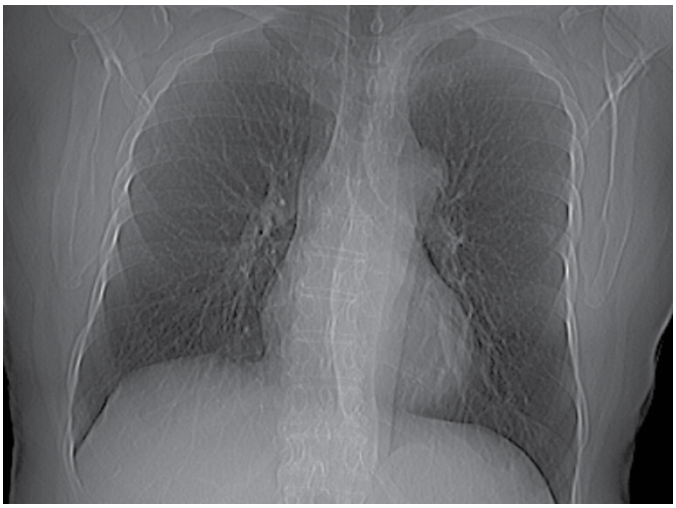


Figure 1: Postero-anterior chest X-ray. There is a widening of the superior mediastinum and a double shadow at the site of descending thoracic aorta.

Figure 2: A 3D reconstruction computed tomography angiography image of the main veins. Right superior vena cava (yellow arrow) and Left superior vena cava (red arrow) with a bridging vein between them (white arrow head).

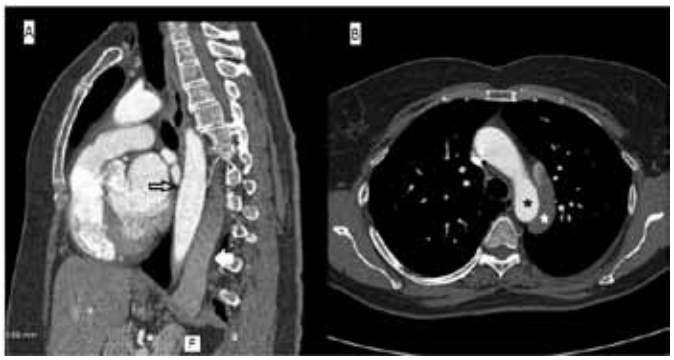


Figure 3: Contrast-enhanced computed tomography images of the patient (sagittal and axial view). (A) Hemiazygos vein (white arrow) is running in parallel and posterior of the descending thoracic aorta (black arrow), (B) Left superior vena cava (white star) passes lateral to the Aortic Arch (black star).

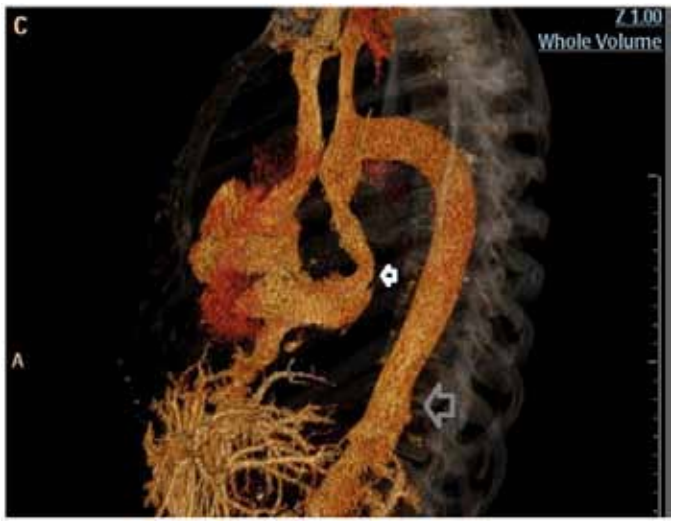


Figure 4: A 3D reconstruction computed tomography angiography image of the main veins. Left superior vena cava is running through the coronary sinus (white arrow) to the right atrium. Left inferior vena cava, through a dilated hemiazygos vein (grey arrow) is draining to the left superior vena cava.

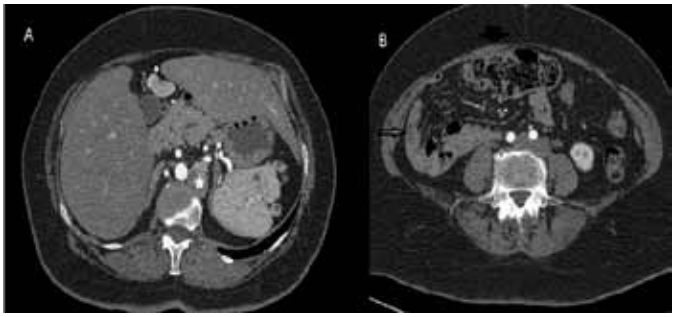


Figure 5: Contrast-enhanced computed tomography axial images of the patient. (A) There is a midline liver, a left sided stomach and lobulated spleen with multiple accessory spleens (black stars), a midline gallbladder (thin white arrow) and an anteriorly positioned portal vein (small thick white arrow). The pancreas is truncated. Inferior vena cava is located on the left side of the abdominal aorta (white star), (B) The small bowel is right-sided (black empty arrow) and a colon left-sided (black thick arrow).

minor cardiac malformations may survive to adulthood [2].

Applegate et al. proposed an individualized approach on classification of heterotaxy syndrome based on the multiple possible combinations between anatomical variants [1]. They suggested that each case should be labeled heterotaxy syndrome followed by a description of the specific patient's anatomy [1]. Jacobs et al. also emphasize the importance of the exact description of cardiac anatomy and associated cardiac malformations, as well as the relationship and location of thoraco-abdominal organs [3].

There is a wide spectrum of abdominal abnormalities consist with situs ambiguous with polysplenia. Although associated with the presence of multiple discrete spleens in the majority of patients, also patients with a single, lobulated spleen or even normal spleen have been reported [2]. There are reports of young patients with altered splenic function [1]. The correlation between spleen and stomach location, can be interpreted by the fact that splenic tissue develops in the dorsal mesogastrium [2]. Often exists a bridging midline liver, but also right-sided and left-sided (rarely) liver has been reported [2]. The gallbladder is usually in the midline [2]. The pancreas can be truncated. Only the pancreatic head located to the right of midline or midline, accompanied or not, with a small portion of the pancreatic body is often present [2]. The stomach can be right-sided or left-sided [2]. Bowel's rotation abnormalities are usually observed [1].

Thoracic findings consist in bilobed lungs with hyparterial bronchi, levocardia more often than dextrocardia and congenital heart diseases, that may vary from minor or even absent, to severe, life-threatening ones [1], [2].

Among venous malformation, the congenital interruption of the IVC is the most common finding with azygos or hemiazygos continuation [1]. In these cases a short intrahepatic segment of inferior vena cava is present [1].

In addition, in our case a few more venous variations were observed. A left IVC, the embryological substratum of it resides in the persistence of the left supracardinal vein instead of the right one [5]. Total absence of azygos vein. A very rare anomaly, that arises when the right segment of the vein fails to develop [6]. A double SVC. It can be explained by persistence of right cardinal vein, as well as, by failure of left cardinal vein to regress [6]. The left-sided SVC typically is draining into the coronary sinus via the vein of Marshall [6].

Multiple modes of inheritance are proposed for heterotaxy syndrome, including autosomal dominant, autosomal recessive, and X-linked recessive mode of inheritance [1]. But a careful genetic study supports a multifactorial inheritance [7].

Abdominal organs and gastrointestinal tract misarrangements can create a confusing clinical picture, especially in the setting of abdominal diseases such as appendicitis, cholecystitis or volvulus, while the patient's

pain and symptoms do not correlate with the expected locations of the affected organs [2].

Vascular anatomical variations can cause confusion during imaging reporting or even complications in the course of an invasive procedure. Venous abnormalities can be misinterpreted, on chest or abdominal X-ray films, as a mediastinal or retroperitoneal neoplasm, or lymphadenopathy [5]. Central venous cannulation may result in unusual catheter locations [6]. The persistent left SVC can disrupt manipulation of a cardiac venous catheter in or through the coronary sinus, which can result in hypotension, angina or cardiac arrest [8]. Additionally, the presence of this vessel has also been related to a higher risk of arrhythmias; most commonly atrial fibrillation [6]. The outcome of cannulation for cardiopulmonary bypass could lead to ineffective retrograde cardioplegia [6]. Unexpectedly, located vascular branches can cause life-threatening intraoperative hemorrhage due to vessels damage, during surgeries [6].

CONCLUSION

As the developmental abnormalities do not always cause clinical symptoms and as the use of imaging increases, situs abnormalities is likely to be detected with higher frequency in the future. So with great attention, should be considered their significance and their potential consequences, as the identification of high risk patients for congenital heart malformations, intestinal volvulus, atypical presentations of abdominal diseases or immune deficiency will improve their care. Careful analysis and understanding is mandatory, as these anatomical missarrangements can also cause confusion in differential diagnosis and severe clinical implication during invasive procedures.

****

Author Contributions

Niki Lama – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Petros Maniatis – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Dionisios Haralambos Antonatos – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

Dimitrios Fagkrezos – Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Charikleia Triantopoulou – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Ioannis Papailiou – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

REFERENCES

1. Applegate KE, Goske MJ, Pierce G, Murphy D. Situs revisited: imaging of the heterotaxy syndrome. Radiographics 1999 Jul-Aug;19(4):837–52.
2. Fulcher AS, Turner MA. Abdominal manifestations of situs anomalies in adults. Radiographics 2002 Nov-Dec;22(6):1439–56.
3. Jacobs JP, Anderson RH, Weinberg PM, et al. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. Cardiol Young 2007 Sep;17 Suppl 2:1–28.
4. Kim JG, Youn HJ, Kim GH, et al. Incidentally detected situs ambiguous in adults. J Cardiovasc Ultrasound 2011 Dec;19(4):211–5.
5. Trubac R, Hribernik M, Pac L. Congenital interruption of the inferior vena cava with hemiazygos continuation. Scripta Medica (BRNO) 2002 Dec;75(6):291–302.
6. Irwin RB, Greaves M, Schmitt M. Left superior vena cava: revisited. Eur Heart J Cardiovasc Imaging 2012 Apr;13(4):284–91.
7. Niikawa N, Kohsaka S, Mizumoto M, Hamada I, Kajii T. Familial clustering of situs inversus totalis, and asplenia and polysplenia syndromes. Am J Med Genet 1983 Sep;16(1):43–7.
8. Bharambe V, Arole V, Vatsalaswamy P. Left superior vena cava with associated venous variations. International Journal of Anatomical Variations 2013;6:9–12.

SUGGESTED READING

- S. Minniti, S. Visentini, C. Procacci. Congenital anomalies of the venae cavae: embryological origin, imaging features and report of three new variants, Eur Radiol 2002(12):2040–2055
- Webb WR, Gamsu G, Speckman JM, Kaiser JA, Federle MP, Lipton MJ. Computed Tomographic Demonstration of Mediastinal Venous Anomalies, Am J Roentgenol. 1982 Jul;139(1):157-161

ABOUT THE AUTHORS

Article citation: Lama N, Maniatis P, Antonatos DH, Fagkrezos D, Triantopoulou C, Papailiou I. A rare case of situs ambiguous in an adult. Int J Case Rep Images 2015;6(11):672–677.

Niki Lama is Resident, Radiology Department, Konstantopouleio General Hospital, Athens, Greece.

Petros Maniatis is Consultant, CT Department Konstantopouleio General Hospital, Athens, Greece.

Dionisios Haralambos Antonatos is Consultant, Cardiology Department, Konstantopouleio General Hospital, Athens, Greece.

Dimitrios Fagkrezos is Consultant, CT Department Konstantopouleio General Hospital, Athens, Greece.

Charikleia Triantopoulou is Head of the Radiology Department, Konstantopouleio General Hospital, Athens, Greece.

Ioannis Papailiou is Head of the CT Department, Konstantopouleio General Hospital, Athens, Greece.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Rare congenital cardiac anomaly presenting with predominant respiratory complaint: A case report

Sheetal Chaurasia, Ravi Kumar, Alamelu Haran, Srikanth Katare

ABSTRACT

Introduction: Coronary cameral fistula is a rare anomaly where there is a fistulous connection between coronary artery and one of the cardiac chambers. It generally presents with predominant cardiac complaints or as accidental finding in an asymptomatic individual. Our patient presented chiefly with respiratory complaint and was misdiagnosed as tuberculosis. Case Report: A 22-year-old female presented in chest OPD with complains of cough and fever since one month and was started on anti-tubercular treatment since one month. On examination there was continuous murmur, thrill and coarse crackles in right axillary area. On Chest X-ray there was a multi-lobulated mass in the right side with upper zone linear and cystic opacities. Computed tomography (CT) scan of Thorax showed right middle lobe bronchiectasis and a large fistula arising from right coronary artery and draining into right superior pulmonary vein and left atrium. Cardiac catheterization confirmed the diagnosis and coronary arteriovenous fistula closure was done by percutaneous route via lifetechcera vascular plug. Conclusion: Coronary cameral fistula despite being large in size may remain silent without causing any hemodynamic abnormality or any compromise in the cardiac function. The predominant complaint may be due to pressure effect of the aneurysmal vessel on adjacent bronchi and causing secondary changes in the pulmonary parenchyma fed by these bronchi. A thorough clinical examination may clinch the diagnosis.

Keywords: Arteriovenous fistula, Congenital anomaly, Coronary cameral fistula, Middle lobe bronchiectasis, Respiratory involvement

Sheetal Chaurasia[1], Ravi Kumar[2], Alamelu Haran[3], Srikanth Katare[4]

Affiliations: [1]Assistant Professor, Department of respiratory medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India; [2]Associate Professor, Department of Respiratory Medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India; [3]Professor and Head, Department of Respiratory Medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India; [4]Post graduate, Department of respiratory medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India.

Corresponding Author: Sheetal Chaurasia, Department of Pulmonary Medicine, Vydehi Institute of Medical Sciences # 82, EPIP Area, Whitefield, Bangalore, Karnataka, India - 560066; Ph: +919972949900; +9108028412956; E-mail: sheetal.utkalit@gmail. com

Received: 05 June 2015
Accepted: 01 July 2015
Published: 01 November 2015

How to cite this article

Chaurasia S, Kumar R, Haran A, Katare S. Rare congenital cardiac anomaly presenting with predominant respiratory complaint: A case report. Int J Case Rep Images 2015;6(11):678–681.

doi:10.5348/ijcri-2015107-CR-10568

INTRODUCTION

A sizable communication between one of the branches of coronary artery and a chamber of heart bypassing the myocardial capillary bed is called coronary cameral fistula. It is a rare congenital anomaly with incidence of 0.08–0.3% of patient undergoing routine diagnostic left heart catheterization [1, 2]. Most of the small fistulae

are clinically silent [1]. Large fistulas progressively enlarge over time and are more likely to cause cardiac complication like congestive heart failure, myocardial infarction, arrhythmias, aneurysm formation, rupture and death [1, 3, 4]. Majority of the symptomatic patients present with symptoms like exertional dyspnea, angina, fatigue, palpitations and syncope often pointing to the cardiac origin of symptoms.

Most of the cases ECG and chest X-rays are not helpful in diagnosis and Echocardiography and cardiac catheterization and angiography confirm the diagnosis. Chest X-ray findings are generally normal except in the presence of significant shunt flow when cardiomegaly may be evident [5]. In addition pulmonary venous congestion and interstitial edema may be seen. ECG may reveal effect of volume overload in presence of coronary steal, ischemic changes and/or arrhythmias. Herein, we report a case of coronary cameral fistula presenting chiefly with respiratory complaints and chest X-ray abnormality and was wrongly diagnosed as tuberculosis.

CASE REPORT

A 22-year-old female presented in chest outpatient department with chief complaints of cough with expectoration, intermittent fever and breathlessness on exertion since three months. Patient also gave history of palpitation and easy fatigability. Patient was multipara with two uneventful pregnancies and both kids were delivered at full term by normal delivery. She was started on anti-tubercular treatment since one month by general practitioner on the basis of chest X-ray abnormality. Patient had history of recurrent cough with expectoration since last two years which responded to antibiotics prescribed by general practitioner.

Physical examination was remarkable with presence of grade 4 continuous murmur over right mammary, axillary and infra axillary areas, moreover breath sounds were decreased in right lower inter scapular area and infra scapular area and coarse mid and late inspiratory crackles could be appreciated in the right axillary region.

On investigation chest X-ray showed multi lobulated opacities arising from the right hilar region and extending into right middle and lower zones. There was presence of linear and cystic opacities in right upper zone (Figure 1 and 2). ECG was normal. 2D echocardiography showed dilated right coronary artery draining into left atrium with dilated left ventricle, mild mitral regurgitation and mild aortic regurgitation. Cardiac multidetector computed tomography scan showed grossly dilated and tortuous right coronary artery having fistulous communication with the dilated venous sac which in turn drains into superior pulmonary vein and left atrium. One of the largest sac was measuring 7x5 cm in size (Figure 3). Venous sacs were seen compressing right middle lobe bronchus resulting in bronchiectasis of right middle lobe (Figure 4).

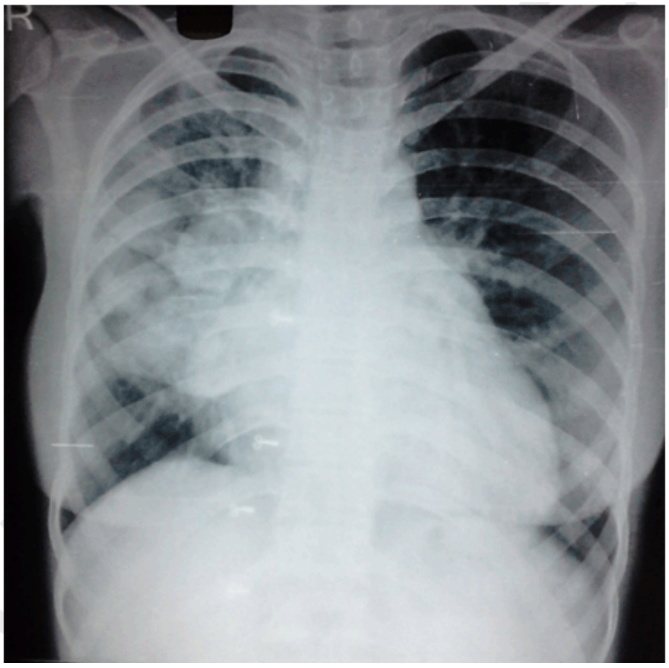


Figure 1: Chest X-Ray showing multi-lobulated opacity in right mid and lower zone. Cystic changes in right upper zone can be appreciated.

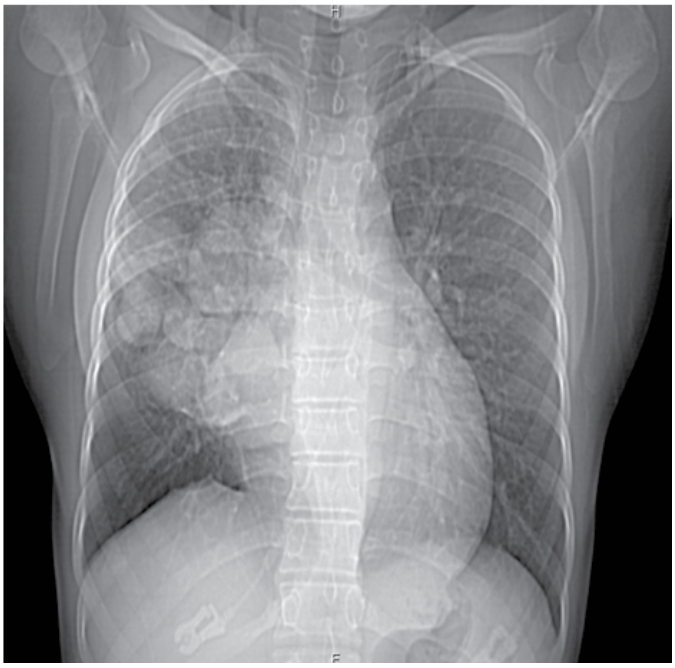


Figure 2: CT Scout Film - showing multi-lobulated mass in right lung.

Sputum was negative for acid-fast bacillus and Gram stain and culture sensitivity of sputum yielded *Pseudomonas aeruginosa*. Anti-tubercular treatment was stopped and was started on appropriate antibiotics, mucolytic agent and chest physiotherapy. Patient responded to treatment and was asymptomatic after 10 days of antibiotics. Follow-up culture was negative. Patient was referred to cardiologist for diagnostic cardiac catheterization which showed large coronary fistula

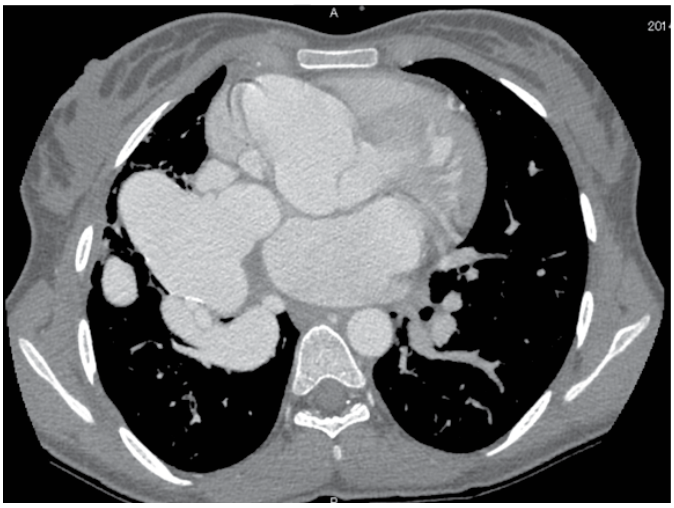


Figure 3: Contrast enhanced cardiac computed tomography In multidetector computed tomography scanner- grossly dilated right coronary atrery having fistulous communication with dilated venous sac draining into left atrium. Largest sac measures 7x5 cm. wall calcification can be appreciated suggesting long standing process.

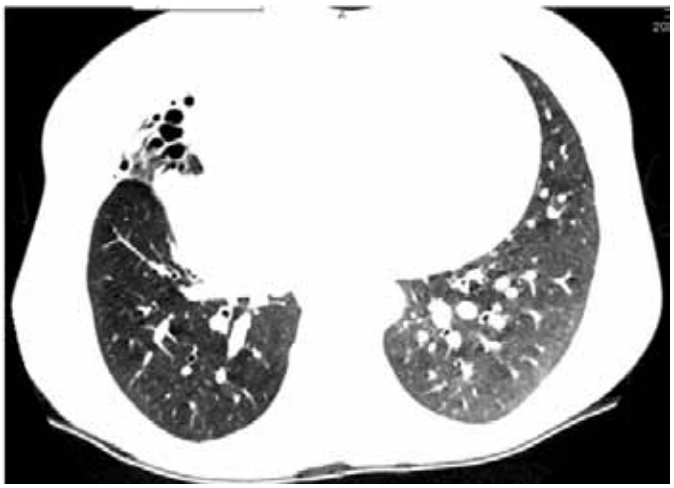


Figure 4: Venous sacs are compressing the right middle lobe bronchus resulting in bronchiatasis of the right middle lobe.

arising from right coronary sinus to left atrium through a long tortuous tunnel passing through superior pulmonary vein.

Coronary arteriovenous fistula closure was done by percutaneous route via lifetechcera vascular plug 16 mm, once the infection was controlled. Post deployment check angiogram showed mild residual shunt. Patient is asymptomatic after undergoing fistula closure.

DISCUSSION

A coronary cameral fistula is a rare vascular anomaly found in approximately 0.08–0.3% of patients undergoing diagnostic coronary angiography [1, 2]. Ninety percent of coronary cameral fistulas drain into right sided chambers of the heart [6]. Clinical presentation generally depend on the hemodynamic significance of the anomaly with majority of small fistulas found accidentally in asymptomatic individuals [1]. Patients with large shunts often present with symptoms arising due to myocardial steal causing angina, dyspnea, congestive heart failure and arrhythmias [1, 3, 4]. The cornerstone in establishing the diagnosis is 2D echocardiography and diagnostic cardiac catheterization and coronary angiography. In majority of cases, chest X-ray is normal or cardiomegaly is there, abnormal chest X-ray shadow is seen in approximately 4% of cases [5]. Our case is unique in many ways, firstly the predominant complaints of the patient was cough with expectoration and fever and chest X-ray was showing abnormal shadows in the right mid and lower zone without any obvious cardiomegaly, in view of above the patient was started on AKT by private practitioner. Secondly, the fistula was draining into the left side of the heart and despite there being huge aneurysmal dilatation of the right coronary artery there was no hemodynamic disturbance and the only complication was arising due to pressure effect of the aneurysmal sac over right middle lobe bronchus causing bronchiectasis. In our case physical examination gave a clue to the diagnosis which was later confirmed by more sophisticated investigations.

CONCLUSION

All abnormal shadows on chest X-ray in a patient with respiratory complaint need not be originating from the lung. A thorough clinical examination and investigations should be done before labeling abnormal shadows as tuberculosis. Coronary cameral fistula despite being large in size may remain silent without causing any hemodynamic abnormality or any compromise in the cardiac function. The predominant complaint may be due to pressure effect of the aneurysmal vessel on adjacent bronchi and causing secondary changes in the pulmonary parenchyma fed by these bronchi. A thorough clinical examination may clinch the diagnosis.

****

Author Contributions

Sheetal Chaurasia – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Ravi Kumar – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Alamelu Haran – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Srikanth Katare – Acquisition of the data, Drafting the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

Copyright

REFERENCES

1. Vavuranakis M, Bush CA, Boudoulas H. Coronary artery fistulas in adults: incidence, angiographic characteristics, natural history. Cathet Cardiovasc Diagn 1995 Jun;35(2):116–20.
2. Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Cathet Cardiovasc Diagn 1990 Sep;21(1):28–40.
3. Brooks CH, Bates PD. Coronary artery-left ventricular fistula with angina pectoris. Am Heart J 1983 Aug;106(2):404–6.
4. McLellan BA, Pelikan PC. Myocardial infarction due to multiple coronary-ventricular fistulas. Cathet Cardiovasc Diagn 1989 Apr;16(4):247–9.
5. Said SA. Current characteristics of congenital coronary artery fistulas in adults: A decade of global experience. World J Cardiol 2011 Aug 26;3(8):267–77.
6. Stierle U, Giannitsis E, Sheikhzadeh A, Potratz J. Myocardial ischemia in generalized coronary artery-left ventricular microfistulae. Int J Cardiol 1998 Jan 5;63(1):47–52.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Diarrhea and generalized weakness in a patient with metastatic melanoma and a lumbosacral mass, after initiation of therapy with a checkpoint inhibitor: A case report

Marija Cauchi, Nikitas Nikitas

ABSTRACT

Introduction: Checkpoint inhibitors are immunomodulatory antibodies against cytotoxic T-lymphocyte-associated antigen [Ipilimumab] and Programmed cell death-1 receptor [nivolumab, pembrolizumab] that have improved the prognosis of patients with melanoma and non-squamous cell lung carcinoma. Despite their clinical benefit, these agents are associated with the development of immune-related adverse events (irAEs) of varying morbidity. These irAEs are clinically challenging to be diagnosed and to be treated, as described in this case report. Case Report: A 58-year old male presented with radicular pain, weakness and loss of sensation in his right leg, eleven years after treatment for cutaneous melanoma. A large lumbosacral mass found on spinal MRI and patient underwent local palliative radiotherapy and he was initiated on systemic monotherapy with ipilimumab. Two doses of 3 mg/kg ipilimumab were administered intravenously within a 21-day interval. After ipilimumab administration, patient developed subsequently diarrhea and generalized weakness and treatment with corticosteroids initiated. Despite treatment, patient developed type 2 respiratory failure, intubated and admitted in general intensive care unit. Diagnostic workup suggested the presence of both ipilimumab associated severe colitis and Guillain-Barre syndrome (GBS). Ipilimumab was permanently discontinued and patient underwent treatment with infliximab and intravenous immunoglobulin for colitis and Guillain–Barre syndrome respectively. Prolonged recovery followed. Conclusion: To our knowledge, this is the first case report of concomitant development of both ipilimumab-induced severe colitis and life-threatening GBS, in the same patient. The choice of the optimal agent for treatment of these adverse events seems to be system and severity-specific.

Keywords: Colitis, Guillain-Barre syndrome, Ipilimumab, Melanoma

Marija Cauchi[1], Nikitas Nikitas[2]

Affiliations: [1]MD, Core Medical Trainee 2, Department of the Medicine of the Elderly, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, Cambridgeshire, United Kingdom; [2]MD, PhD, Clinical Fellow in Intensive Care Medicine and Neuro-Critical Care, The Neurosciences Critical Care Unit and Major Trauma Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, Cambridgeshire, United Kingdom.

Corresponding Author: Nikitas Nikitas MD, PhD., The Neurosciences Critical Care Unit and Major Trauma Unit, Box 1, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, Cambridgeshire, CB2 0QQ, United Kingdom; Ph: 01223216358 – 01223216297; Mob: 00447481187022; Email: nikitas.nikitas@addenbrookes.nhs.uk; nikitas.nikitas@outlook.com

Received: 09 June 2015
Accepted: 01 July 2015
Published: 01 November 2015

How to cite this article

Cauchi M, Nikitas N. Diarrhea and generalized weakness in a patient with metastatic melanoma and a lumbosacral mass, after initiation of therapy with a checkpoint inhibitor: A case report. Int J Case Rep Images 2015;6(11):682–685.

doi:10.5348/ijcri-2015108-CR-10569

INTRODUCTION

Immunotherapy is the primary systemic treatment for metastatic melanoma. Checkpoint inhibition with ipilimumab, is the preferred treatment option for most patients. Treatment with ipilimumab—an IgG1 monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)—has correlated with significantly improved progression-free survival and overall survival. However, treatment with ipilimumab is associated with a variety of clinically significant autoimmune side effects, which sometimes may be clinically challenging to be diagnosed and to be treated [1, 2].

CASE REPORT

A 58-year old male presented with radicular pain, weakness and loss of sensation in his right leg, 11 years after treatment for cutaneous melanoma. Spinal MRI scan revealed of a large lumbosacral mass (L5-S1 level), compressing the cauda equina, suggested the diagnosis of recurrent metastatic melanoma and 5 cycles of vemurafenib chemotherapy followed after histological confirmation. Despite chemotherapy, the mass increased in size and lower back pain worsened. At this stage, the patient underwent local palliative radiotherapy to improve his lower back pain and two months later he was initiated on monotherapy with ipilimumab (Yervoy©, Bristol-Myers Squibb Co., IMAGE study, NCT0511913). Two doses of 3 mg/kg ipilimumab were administered intravenously within a 21-day interval.

Two days after the second dose of ipilimumab, bloody diarrhea and fever developed. After exclusion of infectious causes of hemorrhagic colitis, the diagnosis of ipilimumab-induced colitis was considered as the most probable and treatment with 1 mg/kg intravenous prednisolone daily was commenced. After remission of symptoms within two days, the patient was discharged home on steroids.

However, thirteen days after the second ipilimumab dose, the patient was re-admitted with acute-onset weakness and paraesthesia in the left lower limb and a tingling sensation in his upper limbs. A new course of palliative radiotherapy was applied at the sacral mass but over the next 2 days he developed further neurologic deterioration with paraesthesia and weakness in all four limbs. Three days later, the patient's voice became hoarse and he failed a swallow test. He was found to have a power of 2 on the MRC grading score in all four limbs, with relative proximal sparing and absence of deep tendon reflexes. Ultimately, 19 days after the last ipilimumab administration, type 2 respiratory failure developed secondary to established airway compromise and deteriorating generalized muscle weakness. The patient was intubated and transferred to general intensive care unit (ICU) for mechanical ventilation. Autonomic dysfunction was also present initially. An urgent diagnostic workup for the cause of neurologic deterioration and acute respiratory failure was undertaken.

Computed tomography scan of the head was unremarkable. MRI scan showed no ascending infiltration of the spinal cord from the lumbosacral mass. A lumbar puncture, though necessary, could not be performed due to the large mass in the lumbar spine. Nerve conduction studies demonstrated severe sensory and motor poly-neuropathy, with no recordable motor potentials. Furthermore, needle electromyography showed an acute inflammatory neuropathy with conduction block, consistent with an acute inflammatory demyelinating polyneuropathy (AIDP). There was no axonal loss. Stool cultures were negative and campylobacter was not detected. An electro-encephalogram was normal. A paraneoplastic screen was negative. Based on clinical presentation and the results of neuro-physiological studies the diagnosis of Guillain-Barre syndrome (GBS) was established. After exclusion of all other possible causes, this GBS case was considered as directly related to the previous ipilimumab administration. Ipilimumab was permanently discontinued.

Given that GBS developed whilst the patient was on a high dose of prednisolone (1 mg/kg daily), a 5-day course of intravenous immunoglobulin (IVIg) was commenced at the recommended dose of 400 mg daily. Steroids were gradually tapered down. After completion of IVIg treatment, the patient's neurologic symptoms and muscular strength gradually improved over the course of the next 4 weeks. Due to prolonged weaning from mechanical ventilation and one failed extubation attempt, the patient underwent a tracheostomy.

During his ICU stay the patient experienced a recurrence of ipilimumab-induced colitis, confirmed on serial endoscopic studies and biopsies. Prednisolone tapering was held and high-dose treatment re-started but colitis proved resistant to steroid treatment. Infliximab treatment was therefore initiated, with satisfactory response and recovery starting within the next 72 hours.

After 26 days of treatment, the patient was decannulated and he was discharged from the ICU. Motor strength gradually improved. A minor swallowing defect remained present without, however, compromising his airway.

DISCUSSION

Ipilimumab is a new therapeutic human recombinant IgG1 antibody, currently used as second-line therapy in metastatic melanoma. It has been shown to result in sustained remission [1] of disease, with significantly improved overall survival rates demonstrated in two large phase III trials [2, 3]. Apart from its therapeutic effectiveness, ipilimumab has also been demonstrated to result in severe immune-related adverse events (irAEs), such as enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathy [4–6].

To our knowledge, this is the first case report of concomitant development of both ipilimumab-induced severe colitis and life-threatening GBS in the same patient, after treatment for metastatic melanoma. Both required intensive immunomodulatory treatment and permanent discontinuation of the drug. In phase III clinical trials, severe colitis was found to occur in 5% and life-threatening GBS in less than 1% of treated cases [4, 7, 8].

A previous case report of ipilimumab-induced GBS has some notable similarities and differences in comparison with our case [9]. Similarly to this case, the irAEs occurred after more than one dose of ipilimumab and progressed rapidly. However, our patient developed GBS four weeks after treatment initiation whilst the previously reported case occurred after 7 weeks. The two cases demonstrate a variable time onset of development and variable severity of the same irAE. In contrast to the previous case report, the case we present developed more severe GBS, with cranial nerve involvement and abolishment of swallowing and cough reflex for a prolonged period of time which led to patient's intubation, mechanical ventilation and prolonged ICU stay.

Our patient also developed severe colitis early after ipilimumab administration (day 2) and had already been on treatment with 1 mg/kg of prednisolone for 11 days prior to GBS onset. In view of that fact, GBS was treated with a 5-day course of IVIg instead of high-dose corticosteroids, with adequate and sustained response. Also, our patient finally required the addition of infliximab (as used in previous reports, i.e. 5 mg/kg once every two weeks [10]) due to the recurrence of colitis three weeks after his initial response. Despite the previously reported responsiveness of GBS [9] and colitis [11] to high dose corticosteroid treatment, in our case, GBS developed and colitis recurred whilst the patient was on high doses of prednisolone, and required treatment with IVIg and infliximab respectively for remission. That treatment response could be related to the severity of presentation and may indicate a refractoriness of ipilimumab–induced irAEs to corticosteroid treatment. Furthermore, our case would suggest that corticosteroid treatment is not protective against the development of ipilimumab–induced GBS and the established recommended therapies (IVIg and plasma-exchange) should be the first–line or mainstay of treatment of this life-threatening irAE.

Our case could be considered as clinically challenging for two reasons: first, the pre-existence of a large lumbosacral mass and right lower limb weakness was confusing and misled the diagnosis initially, until the involvement of upper limbs and cranial nerves became clinically evident. Second, in our case, lumber puncture was deferred due to the existence of the metastatic mass in the lumbar spine. Thus, the typical cerebrospinal fluid (CSF) albuminocytologic dissociation seen in GBS could not be demonstrated, and the exclusion of malignant CSF infiltration was not possible. However, the main diagnostic clinical features of GBS were met.

CONCLUSION

This case report showed that despite its therapeutic potential, ipilimumab may be associated with the development of more than one severe and life-threatening immune-related adverse events in the same patient. Therefore, physicians should have a low threshold for the suspicion and diagnosis of potentially severe or life-threatening ipilimumab-related adverse events. Early commencement of potent immunomodulatory therapies, along with the permanent discontinuation of ipilimumab, are necessary to halt their progression and treat them effectively. The choice of the optimal first-line and second-line immunomodulatory agent seems to be system and severity-specific, but further case-studies and clinical trials are warranted to clarify this clinically challenging decision.

****

Author Contributions

Marija Cauchi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Nikitas Nikitas – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

REFERENCES

1. Prieto PA, Yang JC, Sherry RM, et al. CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. Clin Cancer Res 2012 Apr 1;18(7):2039–47.
2. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010 Aug 19;363(8):711–23.
3. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic

melanoma. N Engl J Med 2011 Jun 30;364(26):2517–26.
4. Weber JS, Dummer R, de Pril V, et al. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013 May 1;119(9):1675–82.
5. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012 Jul 20;30(21):2691–7.
6. Corsello SM, Barnabei A, Marchetti P, De Vecchis L, Salvatori R, Torino F. Endocrine side effects induced by immune checkpoint inhibitors. J Clin Endocrinol Metab 2013 Apr;98(4):1361–75.
7. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010 Aug 19;363(8):711–23.
8. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010 Feb;11(2):155–64.
9. Wilgenhof S, Neyns B. Anti-CTLA-4 antibody-induced Guillain-Barré syndrome in a melanoma patient. Ann Oncol 2011 Apr;22(4):991–3.
10. Pagès C, Gornet JM, Monsel G, et al. Ipilimumab-induced acute severe colitis treated by infliximab. Melanoma Res 2013 Jun;23(3):227–30.
11. The YERVOY Immune-mediated Adverse Reaction Management Guide. The Food and Drug Administration (FDA) approved YERVOY Risk Evaluation and Mitigation Strategy (REMS). [available at: https://www.hcp.yervoy.com/pages/rems.aspx]

CASE REPORT PEER REVIEWED | OPEN ACCESS

Cardiac tamponade as the initial presentation of Hodgkin's lymphoma in a young female

Miguel Gonzalez, Amado Karduss-Urueta, Laura Gutiérrez, Juan Alejo Jimenez, Rosendo Perez

ABSTRACT

Introduction: Hodgkin's lymphoma can affect the heart both as primary and as a metastatic condition. Pericardial compromise is a common finding over the course of the disease, and the manifestations can range from pericarditis to pericardial tamponade. Pericardial tamponade is a life-threatening condition that requires immediate treatment, and is rarely the initial presentation of Hodgkin's lymphoma. We present a case of a young female with Hodgkin's lymphoma initially presenting as acute pericardial tamponade. Case Report: A 20-year-old female presented with acute shortness of breath. At presentation she was hypotensive, tachycardic, and tachypneic. Chest X-ray showed an enlarged mediastinum, without enlarged cardiac silhouette. Bedside transthoracic echocardiography demonstrated massive pericardial effusion with cardiac tamponade. The patient was in critical condition, and a pericardial window was performed. After the procedure she was hemodynamically stable. Positron emission tomography scan and computed tomography evidenced a ganglionar conglomerate in the mediastinum and supraclavicular area. An excisional biopsy of a neck lymph node confirmed classical Hodgkin's lymphoma. She was started with standard chemotherapy induction. At the time of the report the patient is doing well with favorable response to the treatment, and without any clinical evidence of systemic or cardiac recurrence. Conclusion: Pericardial involvement is frequent over the course of Hodgkin's lymphoma. Pericardial tamponade is rarely the initial presentation of Hodgkin's lymphoma. A team approach is necessary for favorable outcome. Treatment consists of stabilizing the patient by relieving the tamponade, followed by systemic chemotherapy treatment for the underlying malignancy and to prevent recurrence.

Keywords: Cardiac tamponade, Hodgkin's lymphoma, Malignant pericardial effusion, Pericardial window

Miguel González[1], Amado Karduss-Urueta[2], Laura Gutiérrez[3], Juan Alejo Jiménez[3], Rosendo Pérez[2]

Affiliations: [1]Internal Medicine Resident, Internal Medicine Department, Rutgers New Jersey Medical School, Newark, New Jersey, United States; [2]Bone Marrow Transplantation, Instituto de Cancerología-Clínica las Américas, Medellín, Colombia; [3]Instituto de Cancerología-Clínica las Américas, Medellín, Colombia.

Corresponding Author: Miguel González, MD, 40 Conger Street, Bloomfield, NJ, United States 07003; Ph: 01-718-610-9452; Email: mgonzalezvelez@gmail.com

Received: 15 July 2015
Accepted: 09 September 2015
Published: 01 November 2015

How to cite this article

Gonzalez M, Karduss-Urueta A, Gutiérrez L, Jimenez JA, Perez R. Cardiac tamponade as the initial presentation of Hodgkin's lymphoma in a young female. Int J Case Rep Images 2015;6(11):686–689.

doi:10.5348/ijcri-2015109-CR-10570

INTRODUCTION

Hodgkin's lymphoma (HL) is a hematologic malignancy that arises from germinal center or post-germinal center B cells. It accounts for approximately 10% of all lymphomas and approximately 0.6% of all cancers diagnosed in the developed world annually

[1]. Commonly, the initial clinical presentation is with painless localized peripheral lymphadenopathy, typically involving the cervical region. Over the course of disease Hodgkin's lymphoma can have different types of pericardial involvement. Manifestations can range from an asymptomatic mild effusion to acute pericardial tamponade [2, 3]. Pericardial tamponade is an acute condition that requires immediate treatment; and is rarely the initial presentation of Hodgkin's lymphoma [4–7]. Herein, we present a case of a young female with Hodgkin's lymphoma initially presenting as acute pericardial tamponade.

CASE REPORT

A previously healthy 20-year-old female presented to the emergency department with progressive shortness of breath. On clinical examination she was conscious, had fatigue, cough, swelling of the neck and evident respiratory distress. At presentation she was hypotensive (blood pressure 90/60 mmHg), tachycardic (pulse 125 beats/minute), and tachypneic (respiratory rate 27 respirations/minute), and temperature was 37°C. Electrocardiogram showed normal sinus rhythm with sinus tachycardia. Chest X-ray (Figure 1) showed an enlarged mediastinum, encompassing 60% of the internal transverse diameter of the thorax, without enlarged cardiac silhouette. Bedside transthoracic echocardiography demonstrated massive pericardial effusion with cardiac tamponade. The patient was in critical condition and was shifted emergently to the operating room where she was evaluated by cardiovascular surgery. A pericardial window was performed via subxiphoid incision. The pericardial sac was tense and the pericardium was opened anterior to the phrenic nerve. About 400 mL of bloody fluid was gradually suctioned from the pericardial cavity, and 300 mL from the right pleural space. The pericardium had normal appearance and no cardiac injuries could be identified. The pericardium was inspected and a large swelling was found in the middle mediastinum compressing the heart, the fluid was drained, fluid studies and a biopsy were performed and the bleeding was controlled by applying an absorbable hemostat. Pericardiopleural window was created posterior to the phrenic nerve and the chest was closed after inserting a thoracic drain. After the procedure she was hemodynamically stable. Chest computed-tomography scan evidenced a great ganglionar conglomerate in the anterior and medium mediastinum with a mediastinal mass of 150x100x130 mm with secondary stenosis of the superior vena cava. The cardiac biopsy and the fluid studies were negative for malignancy.

An excisional biopsy of an easily accessible neck lymph node was taken and sent for pathology and immunologic studies. The biopsy confirmed a lymphoproliferative disease consistent with classical Hodgkin's lymphoma of the nodular sclerosing subtype. Cytology evidenced the presence of large mononuclear cells and the classical Reed-Sternberg cells which were CD 30+. A staging positron emission tomography/computer tomography (PET/CT) scan (Figure 2) was performed and the patient was staged as a Hodgkin's lymphoma, stage III-2 (Both sides of diaphragm), A (No B symptoms), X (presence of bulky disease larger than 10 cm) according to Ann Arbor classification. She had compromise of retroperitoneal lymph nodes but without hepatic, splenic, or bone marrow compromise. The patient had three negative prognostic factors based on the International Prognostic Score (IPS); with a calculated 60% freedom from progression and 78% overall survival at five years. She was started with standard induction chemotherapy with adryamicin, bleomycin, vinblastine, and dacarbazine (ABVD). At the time of the report the patient has received the six cycles of chemotherapy and is doing well with favorable response

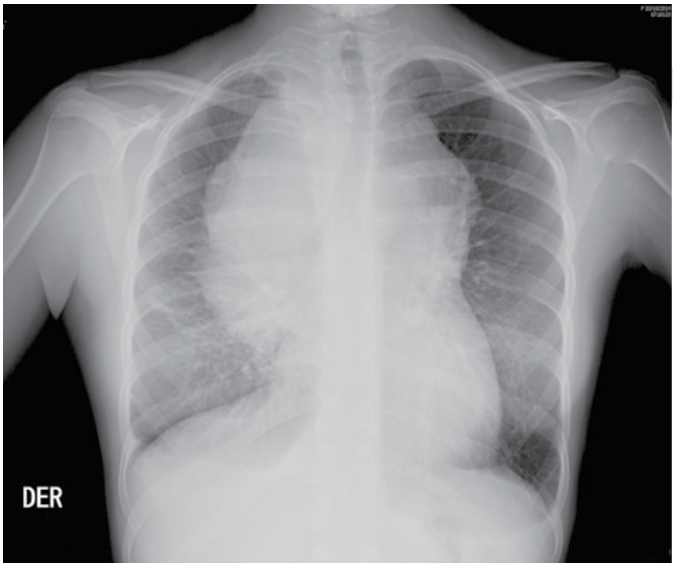


Figure 1: Chest X-ray with widened mediastinum at the initial presentation.

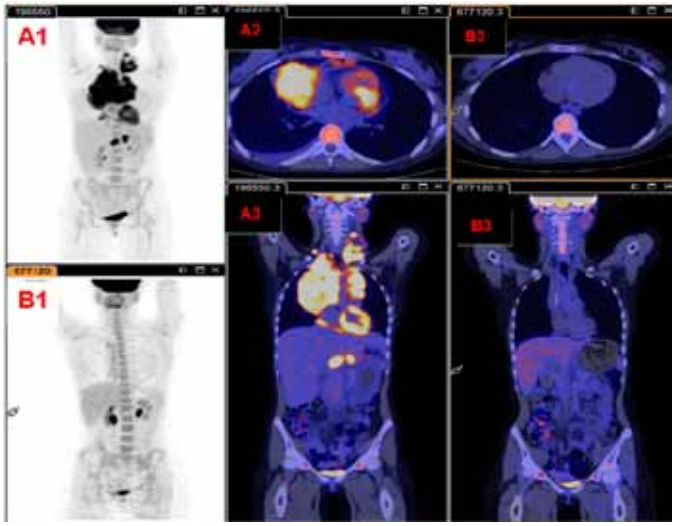


Figure 2: Comparison of initial staging PET/CT (Panels A1, A2, A3), scan showing non-FDG-avid pericardial effusion and the mediastinal mass, with a final PET/CT after six cycles of chemotherapy (Panels B1, B2, B3).

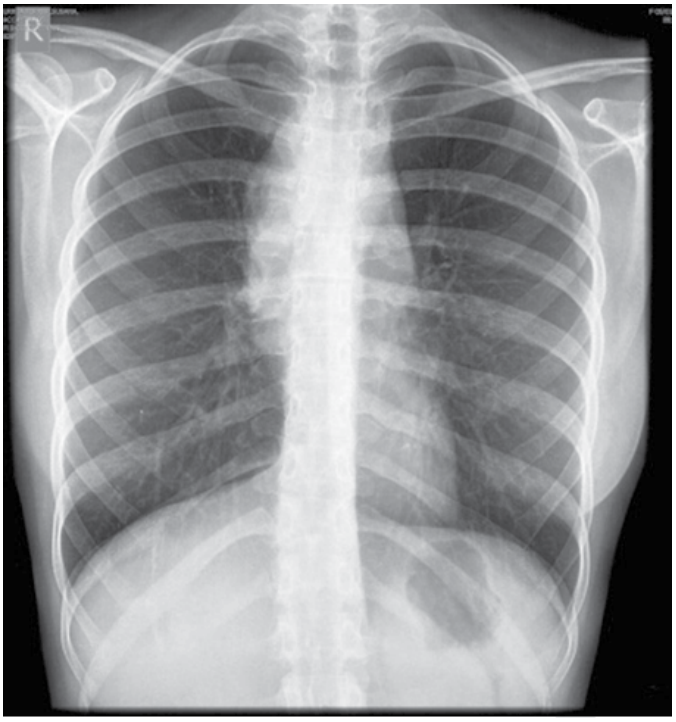


Figure 3: Chest X-ray after three cycles of chemotherapy.

to the treatment (Figures 2 and 3), and without any clinical or imagenological evidence of systemic or cardiac recurrence.

DISCUSSION

Hodgkin's lymphoma is a hematological malignancy with an incidence of 2–4 per 100,000 per year [1]. The most common presentation consists of a painless mass in >70% of the cases. Pericardial involvement is a common finding over the course of the disease, and it can present either as a primary or as a metastatic condition. Pericardial compromise can be asymptomatic or present with manifestations that range from pericarditis to pericardial tamponade [5, 7]. The clinical presentation of pericardial effusions depends upon whether the accumulation is acute or subacute.

Acute pericardial tamponade is a life-threatening condition that requires immediate diagnosis and treatment and is rarely the first presenting sign of Hodgkin's lymphoma [6, 8, 9]. The clinical presentation of acute pericardial tamponade includes: sudden dyspnea, chest pain, tachycardia, softening of heart sounds and echocardiographic signs of right heart compromise secondary to the acute rise in the pericardial pressure limiting the diastolic filling and leading to hemodynamic instability.

The diagnostic approach of pericardial tamponade includes a combination of electrocardiography, radiologic studies, and diagnostic/therapeutic pericardiocentesis. Chest X-ray can show an enlarged cardiac silhouette with clear lung fields. Echocardiography is the primary imaging tool to establish the diagnosis and quantify the amount of pericardial effusion and the hemodynamic impact on the patient. Imaging with computed tomography scan and positron emission tomography scan can provide additional information and can be useful in the evaluation of patients. Pericardial biopsy and examination of the pericardial fluid should be done to perform cytology studies and biomarkers and to rule out other diagnosis [2, 10].

Hodgkin's lymphoma has a good prognosis when treated promptly with chemotherapy. In patients presenting with acute symptoms of pericardial tamponade the mainstay of treatment is the removal of the fluid to obtain normal hemodynamic status and stabilize the patient by relieving the tamponade. A team approach including cardiologist, surgeon, anesthetist, radiologist and oncologist is necessary for favorable outcome. Following the stabilization of the hemodynamic parameters, staging should be completed and induction chemotherapy treatment initiated as soon as possible to treat the underlying disease and prevent reaccumulation of pericardial fluid. Our patient received appropriate acute management of the tamponade and received induction chemotherapy without recurrence of the pericardial fluid.

CONCLUSION

Pericardial involvement is a frequent finding in Hodgkin's lymphoma but is rarely the initial presentation. Given its rarity it is hard to give a specific recommendations regarding diagnosis, but clinical suspicion should remain high in an appropriate clinical context. Diagnosis and treatment should be directed depending on the presentation; with a team approach necessary for favorable outcomes. This atypical presentation should be suspected and promptly confirmed with imaging. Initial treatment consists of stabilizing the patient by relieving the tamponade, followed by systemic induction chemotherapy treatment for the underlying malignancy and to prevent fluid reaccumulation.

****

Acknowledgements

We wish to thank all the clinical staff at Clínicalas Americas in Medellin Colombia for their support in the care of the patient.

Author Contributions

Miguel Gonzalez – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Amado Karduss-Urueta – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Laura Gutiérrez – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Juan Alejo Jimenez – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Rosendo Perez – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

Copyright

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015 Jan-Feb;65(1):5–29.
2. Maisch B, Ristic A, Pankuweit S. Evaluation and management of pericardial effusion in patients with neoplastic disease. Prog Cardiovasc Dis 2010 Sep-Oct;53(2):157–63.
3. Elias MA. Mediastinal tumor causing cardiac tamponade. Middle East J Anaesthesiol 2000 Jun;15(5):569–74.
4. Atar S, Chiu J, Forrester JS, Siegel RJ. Bloody pericardial effusion in patients with cardiac tamponade: is the cause cancerous, tuberculous, or iatrogenic in the 1990s? Chest 1999 Dec;116(6):1564–9.
5. Retter A, Ardeshna KM, O'Driscoll A. Cardiac tamponade in Hodgkin lymphoma. Br J Haematol 2007 Jul;138(1):2.
6. Ben-Horin S, Bank I, Guetta V, Livneh A. Large symptomatic pericardial effusion as the presentation of unrecognized cancer: a study in 173 consecutive patients undergoing pericardiocentesis. Medicine (Baltimore) 2006 Jan;85(1):49–53.
7. Casey DJ, Kim AY, Olszewski AJ. Progressive pericardial effusion during chemotherapy for advanced Hodgkin lymphoma. Am J Hematol 2012 May;87(5):521–4.
8. Mumoli N, Cei M, Gambaccini L, Sabatini S, Vitale J. Hodgkin disease complicated by recurrent cardiac tamponade. QJM 2013 Sep;106(9):859–60.
9. Sagristà-Sauleda J, Mercé J, Permanyer-Miralda G, Soler-Soler J. Clinical clues to the causes of large pericardial effusions. Am J Med 2000 Aug 1;109(2):95–101.
10. García Vázquez E. Cardiac tamponade as clinical manifestation of neoplastic process: presentation of 11 cases and review of the literature. An Med Interna 2000 Jan;17(1):25–8.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Sarcoidosis associated with pseudopapillary pancreatic tumor

Elhadidy Tamer, Morsy Nesreen Elsayed, Abdelwahab Heba Wagih, Refky Basel, Zalata Khaled

ABSTRACT

Introduction: The sarcoidosis is an idiopathic multisystem inflammatory disease characterized by the presence of non-caseating granulomas in the affected organs. A clear association between sarcoidosis and malignancies has been reported. Cancer can occur in patients with an established diagnosis of sarcoidosis and sarcoidosis can subsequently develop in a cancer patient. Malignancy can also be associated with the occurrence of sarcoid reactions. Case Report: We report the case of sarcoidosis/sarcoid-like reaction associated with pseudopapillary pancreatic tumor. Conclusion: This case report emphasizes the need to add sarcoidosis in the differential diagnosis of lung lesions associated with pancreatic tumors.

Keywords: Pancreatic Neoplasms, Pseudo papillary neoplasm, Pseudopapillary neoplasm, Sarcoidosis

Elhadidy Tamer[1], Morsy Nesreen Elsayed[1], Abdelwahab Heba Wagih[2], Refky Basel[3], Zalata Khaled[4]

Affiliations: [1]Chest Medicine department, Mansoura University, Mansoura, Egypt; [2]Chest Medicine department, Mansoura University, Mansoura, Egypt; [3]Oncology surgery. Oncology center .Mansoura University, Mansoura, Egypt; [4]Pathology department, Mansoura University, Mansoura, Egypt.

Corresponding Author: Heba Wagih Abdelwahab, Mansoura, Chest Medicine department, Mansoura University Egypt; Ph: 00201011930335; Email: Wagihheba84@gmail.com

Received: 14 August 2015
Accepted: 14 September 2015
Published: 01 November 2015

How to cite this article

Tamer E, Elsayed MN, Wagih AH, Basel R, Khaled Z. Sarcoidosis associated with pseudopapillary pancreatic tumor. Int J Case Rep Images 2015;6(11):690–693.

doi:10.5348/ijcri-2015110-CR-10571

INTRODUCTION

Solid pseudopapillary neoplasia of the pancreas is an extremely rare epithelial tumor of low malignant potential and accounts for less than 1–2% of exocrine pancreatic tumors [1]. This tumor was described by using various names including 'solid cystic tumor', 'papillary cystic tumor', 'papillary epithelial neoplasia', 'solid and papillary epithelial neoplasia', 'papillary epithelial tumor' and 'Frantz's tumor', 'solid and papillary tumor', 'solid-cystic papillary epithelial neoplasm', 'benign or malignant papillary tumor of the pancreas' until it was defined by the World Health Organization in 1996 as 'solid pseudopapillary tumor' of the pancreas [2]. Sarcoidosis is a multisystem inflammatory disease that mainly affects the intrathoracic lymph nodes, the lungs, the skin and the eyes. The clinical pictures include systemic and organ-specific symptoms. However, in the majority of cases it is diagnosed in asymptomatic patients, based on the finding of hilar adenopathy on chest radiography performed for other reasons [3]. Malignancy can be associated with the occurrence of sarcoid reactions. Problems may also arise in distinguishing between tumor-related sarcoidosis and true systemic sarcoidosis. In this study, we report, to our knowledge, the first case of sarcoidosis associated with pseudopapillary pancreatic tumor.

CASE REPORT

A 44-year-old female presented to oncology center Mansoura University with a one month history of vague abdominal pain and bilateral edema lower limbs. Abdominal ultrasound revealed well defined soft tissue mass at splenic and left renal area with area of cystic degenerations. Further etiological investigations were performed, including abdominal computed tomography (CT) scan which showed large enhanced soft tissue mass in left hypochondriac region with cystic degeneration and foci of calcifications inside. Anteriorly it was seen in contact with greater curvature of the stomach with no clear fat plane in between. Medially, it is seen contacting and displacing pancreatic tail. Chest CT scan showed multiple enlarged pretracheal, aortopulmonary, subcarinal and hilar lymph nodes. The largest seen was subcarinal lymph node measuring 3.5x2.8 cm. Both lung parenchymas showed bilateral perilymphatic nodules. A metastatic cancer was initially suspected then ultrasound-guided Tru-cut biopsy of the abdominal mass showed sheets of small uniform tumor cells surrounding delicate hyalinized fibrovascular stroma forming pseudopapillae. Some cells have eosinophilic others have vacuolated cytoplasm with grooved nuclei. Infrequent mitosis was detected. No significant immunohistochemical staining was observed for CD10PR picture consistent with pseudopapillary pancreatic tumor (Figure 1). The surgical removal of pancreatic mass was done and sent for pathological evaluation which confirms the result of previous tru-cut biopsy. She was discharged and transferred to chest department Mansoura University for assessment of CT chest. Fiber optic bronchoscopy was done from which bronchoalveolar lavage and transcarinal needle aspiration was taken but showed inflammatory cells without atypical or giant cells.

Follow-up CT scan of chest 10 months later showed bilateral perilymphatic nodules with disappearance of previously described lymphadenopathy (Figure 2). Thoracoscopic lung biopsy then taken and histological examinations revealed non-caseating epithelioid granuloma.

DISCUSSION

A solid pseudopapillary neoplasm (SPN) of the pancreas was described firstly by Dr. Frantz in 1959. It is a rare pancreatic tumors which have a relatively low malignant potential and are mostly diagnosed in young women. The treatment is surgical resection; the prognosis is favorable after resection [4, 5]. Sarcoidosis is a multisystem disease of unknown etiology that can affect any organ. It is characterized by non-caseating granulomatous lesions involving the lungs, skin, eyes, salivary glands and internal organs [6]. The question of whether there is a causal relationship between sarcoidosis and cancer has been debated for years. Sarcoidosis is associated with malignancy more than can be explained by chance. Cancer can occur in patients with an established diagnosis of sarcoidosis and sarcoidosis can subsequently develop in a cancer patient. Malignancy can also be associated with the occurrence of sarcoid reactions. Problems may also arise in distinguishing between tumor-related sarcoid reactions and true systemic sarcoidosis [7]. So, in this study revision of pathological specimen was then carried out in order to make a differential diagnosis between pancreatic tumor associated with sarcoidosis, or the presence of a pancreatic granuloma as a part of a systemic sarcoidosis. Pathological revision showed epithelioid granuloma of thoracoscopic biopsy and solid pseudopapillary pancreatic tumor of pancreatic mass biopsy. The strongest association between sarcoidosis and solid tumors is described with adenocarcinoma of the lung, although other cancers have also been reported. In most cases, the diagnosis of sarcoidosis preceded the detection of neoplasm, leading to the hypothesis that the immune system dysfunction and the tissue chronic inflammation characterizing sarcoidosis can facilitate cancer development. However, it has been also reported cases in which diagnosis of cancer precedes the development of sarcoidosis, as well as cases of concomitant diagnosis. Sarcoid-like reaction occurs more frequently in regional lymph nodes of neoplasm ("typical sarcoid-like reaction"), and is believed to represent a T cell-mediated immune response to soluble antigenic factors shed by the tumoral cells.

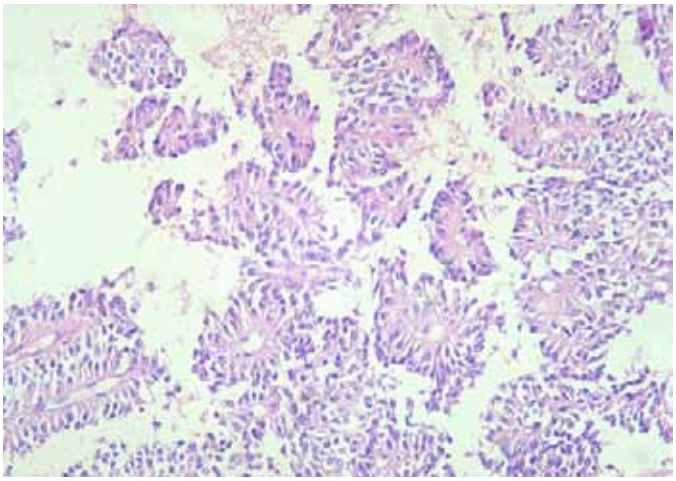


Figure 1: Pancreatic mass biopsy revealing Pseudopapillary pattern formed of multiple layers of bland looking cells arranged around blood vessels (H&E stain, x100).

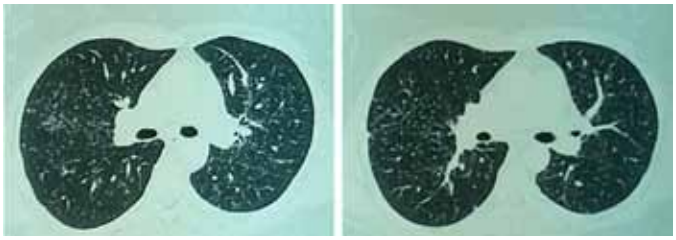


Figure 2: Computed tomography scan of chest revealing bilateral perilymphatic nodules in lung parenchyma.

However, cases of ("atypical sarcoid-like reaction") in distant lymph nodes have been observed [3]. Other studies such as Mastroroberto et al. reported the first case of association of sarcoidosis and pancreatic neuroendocrine tumor [3] and Zambrana et al. also reported a case with both sarcoidosis and pancreatic cancer [7]. In this study, we report, to our knowledge, the first case of sarcoidosis associated with pseudopapillary pancreatic tumor.

CONCLUSION

This case report summarizes the association between sarcoidosis and pancreatic tumors to be one of the differential diagnoses in our mind while dealing with pancreatic cancer in addition to metastatic lesions.

****

Acknowledgements
We wish to thank all the clinical staff at Clínicalas Americas in Medellin Colombia for their support in the care of the patient.

Author Contributions
Elhadidy Tamer – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Morsy Nesreen Elsayed – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Abdelwahab Heba Wagih – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Refky Basel – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Zalata Khaled – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

REFERENCES

1. Martin RC, Klimstra DS, Brennan MF, Conlon KC. Solid-pseudopapillary tumor of the pancreas: a surgical enigma? Ann Surg Oncol 2002 Jan-Feb;9(1):35–40.
2. Kloppel G, Solcia E, Longnecker DS, Capella C, Sobin LH. Histological typing of tumors of the exocrine pancreas. In: World Health Organization International Histological Classification of Tumours. 2ed. Berlin, Heidelberg, New York: Springer; 1996:8452/1.
3. Mastroroberto M, Berardi S, Fraticelli L, et al. Sarcoidosis and sarcoid-like reaction associated with pancreatic malignancy: are you able to read a riddle? JOP 2012 Jul 10;13(4):454–7.
4. Frantz VK. Papillary tumors of the pancreas: Benign or malignant? Tumors of the pancreas. In: Atlas of Tumor Pathology, Section 7, Fascicles 27 and 28. Washington, DC, USA: Armed Forces Institute of Pathology; 1959:32–3.
5. Guo N, Zhou QB, Chen RF, et al. Diagnosis and surgical treatment of solid pseudopapillary neoplasm of the pancreas: analysis of 24 cases. Can J Surg 2011 Dec;54(6):368–74.
6. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007 Nov 22;357(21):2153–65.
7. Zambrana F, Antúnez A, García-Mata J, Mellado JM, Villar JL. Sarcoidosis as a diagnostic pitfall of pancreatic cancer. Clin Transl Oncol 2009 Jun;11(6):396–8.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Severe hyponatremia: A physician's nightmare

Michele Carron, Mariarosa Meneghetti, Giuseppe Gagliardi, Carlo Ori

ABSTRACT

Introduction: Osmotic demyelination syndrome is an uncommon neurological disease that may complicate the treatment of severe hyponatremia [1–4]. In case of osmotic demyelination syndrome, the computed tomography and the magnetic resonance imaging scans are used for diagnosis. The experience with positron emission tomography with ^{18}Fluoro-fluorodeoxyglucose is limited. Case Report: We report the case of a 32-year-old female who presented to the emergency department with signs and symptoms of severe hyponatremia (104 mmol/L). Treatment with hypertonic saline allowed to increase her serum sodium level to 132 mmol/L in the following three days with initial clinical benefit. On the 3rd day, the patient showed neurological deterioration complicated by seizures requiring intensive care. The computed tomography and magnetic resonance imaging scans of her brain obtained in the first fifteen days from hospital admission were normal. Instead, positron emission tomography with ^{18}Fluoro-fluorodeoxyglucose revealed an overall reduction in ^{18}Fluoro-fluorodeoxyglucose uptake in the cortical area attributable to diffuse brain damage, confirmed by a subsequent third magnetic resonance imaging scan taken twenty days after the hospitalization. Osmotic demyelination syndrome was diagnosed. The patient did not recover neurologically as confirmed by a second positron emission tomography with ^{18}Fluoro-fluorodeoxyglucose performed ninety days after hospitalization. Conclusion: Great attention should be placed on treatment of severe hyponatremia. In case of osmotic demyelination syndrome, the use of positron emission tomography with ^{18}Fluoro-fluorodeoxyglucose may be considered for diagnosis and for assessment of the degree and extent of cerebral damage over time.

Keywords: ^{18}Fluoro-fluorodeoxyglucose, Hyponatremia, Osmotic demyelination syndrome, Positron emission tomography

Michele Carron[1], Mariarosa Meneghetti[2], Giuseppe Gagliardi[2], Carlo Ori[3]

Affiliations: [1]Anesthesiologist and Intensivist, Assistant Professor, Department of Medicine, Anesthesiology and Intensive Care, University of Padova, Padova, Italy; [2]Anesthesiologist and Intensivist, Intensive Care Unit, St. Antony Hospital, Via Jacopo Facciolati, 71 - 35127 Padova, Italy; [3]Anesthesiologist and Intensivist, Professor and Chief, Department of Medicine, Anesthesiology and Intensive Care, University of Padova, Padova, Italy

Corresponding Author: Michele Carron, Via C. Battisti, 267, Padova, Italy, 35121, Ph: +39 049 8213090; Fax: +39 049 8755093 Email: michele.carron@unipd.it

Received: 17 June 2015
Accepted: 13 August 2015
Published: 01 November 2015

How to cite this article

Carron M, Meneghetti M, Gagliardi G, Ori C. Severe hyponatremia: A physician's nightmare. Int J Case Rep Images 2015;6(11):694–697.

doi:10.5348/ijcri-2015111-CR-10572

INTRODUCTION

Osmotic demyelination syndrome (ODS) is an uncommon neurological disease characterized by demyelination of areas of the central nervous system that may complicate the treatment of severe hyponatremia

[1–4]. Lesions can occur at central pons (central pontine myelinolysis) and/or outside the pons (extrapontine myelinolysis) [1–4]. Damage is often permanent [1–4]. In case of ODS, the use of adequate imaging is important for diagnosis and early treatment [4–6]. The computed tomography (CT) scan and the magnetic resonance imaging (MRI) scan are used for diagnosis [4, 5]. In particular, MRI scan is considered the radiological modality of choice for earlier detection of ODS lesions [4, 5]. However, in highly suspect ODS, the radiological evidence of lesions may be not found at the beginning and a further MRI scan may be necessary [4, 5]. The role of positron emission tomography (PET) scan with ^{18}Fluoro-fluorodeoxyglucose (^{18}F-FDG) in case of ODS is not well established.

CASE REPORT

A 32-year old female presented to the hospital with severe confusion, weakness, and vomiting. She had a history of hypertension and kidney hypoplasia. Upon admission her serum sodium concentration was 104 mmol/L. Treatment with hypertonic saline allowed to increase her serum sodium level to 118 mmol/L on first day, 125 mmol/L on second day, and 132 mmol/L on third day after admission. On the 3rd day, the patient experienced neurological deterioration complicated by seizures, requiring medical treatment and tracheal intubation. The computed tomography (CT) scan and the magnetic resonance imaging (MRI) scan of her brain were initially normal. A second MRI scan was obtained fourteen days after hospitalization and did not reveal significant abnormalities. There were no anoxic or hypoxic episodes during the time in which the patient was being followed. However, her brain function did not recover. A ^{18}F-FDG PET scan taken one day later the second MRI scan revealed an overall reduction in ^{18}F-FDG uptake in the cortical area with two regions of increased metabolic activity (Figure 1). A third MRI scan performed twenty days after hospitalization showed diffuse brain damage. The ODS was, then, diagnosed. Similarly to other neurological disorders, general care were applied, including adequate nutrition, good skin care, passive joint exercises, airways suctioning, careful management of the bladder and bowel. Percutaneous tracheostomy and endoscopic gastrostomy were performed for manage secretions and feeding, respectively. An indwelling urinary catheter was also necessary. The ICU care was complicated by occurrence of ventilator-associated pneumonia. Once weaned from mechanical ventilation and stabilized her clinical condition, the patient was transferred to neurological ward for neuro-rehabilitation. The patient did not recover neurologically as confirmed by a second ^{18}F-FDG PET scan performed ninety days after hospitalization (Figures 2 and 3). The patient was able to spontaneously open and close her eyes, but she was unable to follow instructions or track movements, and speak or communicate in any forms. Three months after the diagnosis of ODS, she was still in a vegetative state and was, then, transferred to a neuro-rehabilitation centre for the care of case.

DISCUSSION

The ODS remains a feared complication of the treatment of severe hyponatremia [1–4]. It is not clear the best rate of correction of hyponatremia [1–3]. Depending on the severity of the patient's symptoms, the serum sodium was suggested to be corrected at a rate of 0.5 mmol/L/h or 1 mmol/L/h [2, 3]. However, the revision of published reports on patients with very severe hyponatremia (serum sodium <106 mmol/L) revealed that neurologic sequelae were associated with correction of hyponatremia by more than 12 mmol/L per day [1]. So that, the more recent recommendations are to limit the increase in serum sodium concentration to a total of 10 mmol/L during the first 24 h and an additional 8 mmol/L during every 24 h thereafter until the serum sodium concentration reaches 130 mmol/L [4].

In case of ODS, uncertainty regarding the optimal approach still exists [5–8]. Reinduction of hyponatremia by using desmopressin, intravenous 5% dextrose solution or a combination of both, is recommended in high risk patients [6, 7]. Corticosteroids, plasmapheresis and intravenous immunoglobulin have been successfully proven in selected patients [7]. Besides pharmacological therapy, the treatment of ODS is supportive and includes physical therapy, similarly to other neurological disorders [7]. Outcome is variable. Patients who survive ODS are likely to require extensive and prolonged neuro-rehabilitation [5, 8].

The CT and the MRI scans are used for diagnosis. In particular, MRI scan is the radiological modality of choice for detection of ODS lesions [5, 8]. Typically,

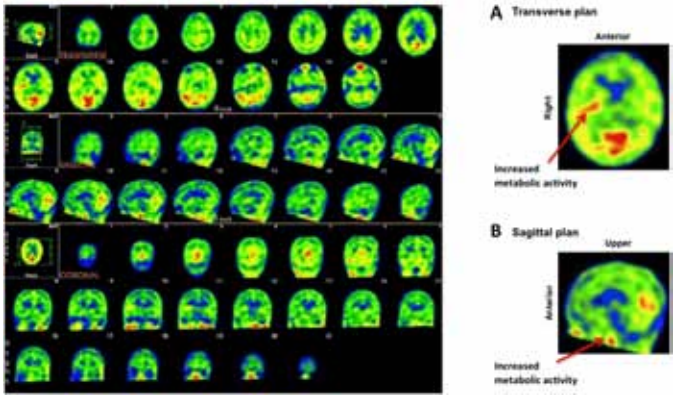


Figure 1. ^{18}F-FDG PET scan of the brain of a female patient affected by osmotic demyelination syndrome obtained fifteen days after hospitalization. It shows an overall reduction in ^{18}F-FDG uptake in the bilateral frontotemporal cortex because of a reduced brain function mainly due to a diffuse brain damage. Two increased metabolic activity were found in the temporal area (A) and in hypothalamic region (B).

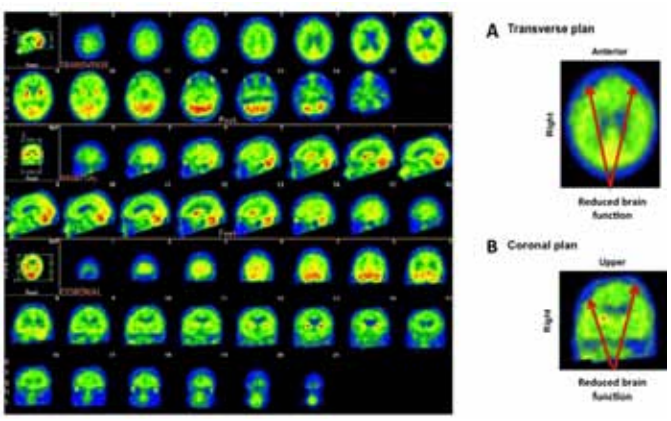


Figure 2. ^{18}F-FDG PET scan of the brain of a female patient affected by osmotic demyelination syndrome obtained ninety days after hospitalization. It shows an overall reduction in ^{18}F-FDG uptake in the bilateral frontotemporal cortex because of a reduced brain function due to a diffuse brain damage. The residual brain function was established in absence of medical treatment and metabolic disorders.

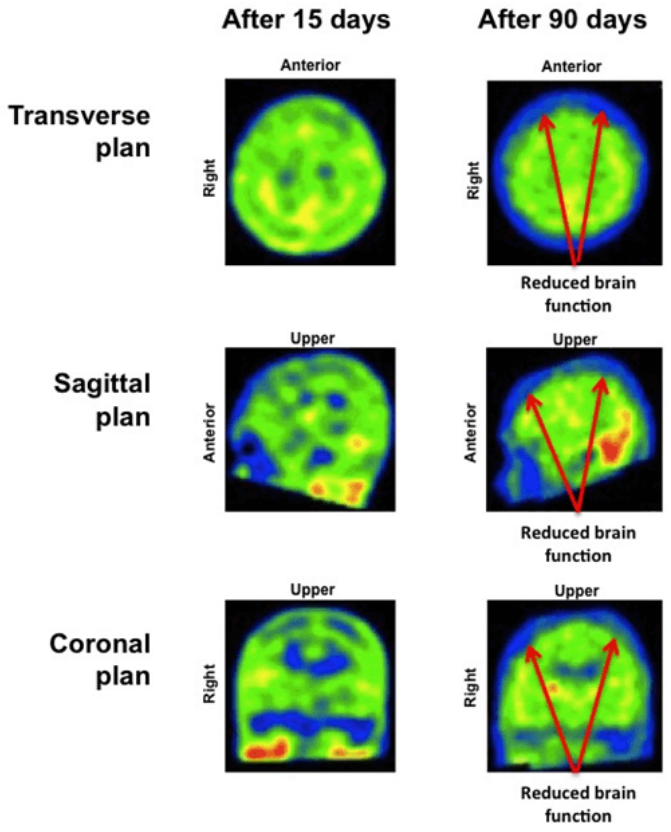


Figure 3. Comparison of ^{18}F-FDG PET scan of the brain of a female patient affected by osmotic demyelination syndrome obtained fifteen days and ninety days after hospitalization. The overall reduction in ^{18}F-FDG uptake in the bilateral frontotemporal cortex is related to reduced brain function, due to a diffuse brain damage. It appears greater after ninety days than after fifteen days from hospitalization. Frames are from transverse, sagittal and coronal planes.

T2-weighted and fluid attenuated inversion recovery (FLAIR) MRI images show increased signal intensity where demyelination has occurred [5, 8]. Sometimes, however, radiological evidence of lesions in case of ODS may be not found. If ODS is highly suspected, but there is no evidence on imaging, it is recommended to repeat the MRI scan after 2–3 weeks (following the onset of symptoms or correction of hyponatremia) being able, at this time, to reveal lesions not apparent on early scans [5, 8]. The radiological findings may not improve over time, even in case of complete clinical recovery [7].

^{18}F-FDG is a glucose analog used in the medical imaging modality PET. The uptake of ^{18}F-FDG by high-glucose-using cells, such as brain cells, is a marker for the tissue uptake of glucose, which in turn is closely correlated with tissue glucose metabolism [9–11]. In case of brain damage, ^{18}F-FDG PET scan may provide earlier information than CT or MRI scan [10, 11]. In case of ODS, ^{18}F-FDG PET may demonstrate hypermetabolism in some brain regions, probably due to increased glucose activity of the phagocytic microglial cells and astrocytes [9], and a progressive hypometabolism owing to the destructive demyelination, as seen in our case. Furthermore, ^{18}F-FDG PET has not only an important role in establishing the degree, and extent of cerebral damage, but also in providing information on the residual brain function in patients with ODS [10, 11].

CONCLUSION

Great attention should be placed on treatment of severe hyponatremia. It is necessary to follow strictly the more recent recommendations on treatment of severe hyponatremia. In case of osmotic demyelination syndrome, the use of adequate imaging is important for diagnosis and early treatment and for assessment of the degree and extent of cerebral damage over time.

****

Author Contributions

Michele Carron – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Mariarosa Meneghetti – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Giuseppe Gagliardi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Carlo Ori – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

REFERENCES

1. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 1986 Jun 12;314(24):1535–42.
2. Abbott R, Silber E, Felber J, Ekpo E. Osmotic demyelination syndrome. BMJ 2005 Oct 8;331(7520):829–30.
3. Snell DM, Bartley C. Osmotic demyelination syndrome following rapid correction of hyponatraemia. Anaesthesia 2008 Jan;63(1):92–5.
4. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med 2014 Mar;40(3):320–31.
5. Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. J Neurol Neurosurg Psychiatry 2004 Sep;75 Suppl 3:iii22–8.
6. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013 Oct;126(10 Suppl 1):S1–42.
7. Corona G, Simonetti L, Giuliani C, Sforza A, Peri A. A case of osmotic demyelination syndrome occurred after the correction of severe hyponatraemia in hyperemesis gravidarum. BMC Endocr Disord 2014 Apr 11;14:34.
8. Mascarenhas JV, Jude EB. Central pontine myelinolysis: electrolytes and beyond. BMJ Case Rep 2014 Mar 28;2014. pii: bcr2013203516.
9. Roh JK, Nam H, Lee MC. A case of central pontine and extrapontine myelinolysis with early hypermetabolism on 18FDG-PET scan. J Korean Med Sci 1998 Feb;13(1):99–102.
10. Hattori N, Huang SC, Wu HM, et al. Correlation of regional metabolic rates of glucose with glasgow coma scale after traumatic brain injury. J Nucl Med 2003 Nov;44(11):1709–16.
11. Yilmaz K, Yilmaz M, Mete A, Celen Z. A correlative study of FDG PET, MRI/CT, electroencephalography, and clinical features in subacute sclerosing panencephalitis. Clin Nucl Med 2010 Sep;35(9):675–81.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Cervical paraspinal chordoma with left vertebral artery encasement

Chi-Man Yip, Ping-Hong Lai, Hui-Hwa Tseng, Shu-Shong Hsu

ABSTRACT

Introduction: Chordomas are slow-growing, low-grade malignant but locally invasive tumors which originate from embryonic remnants of the primitive notochord. Chordomas are principally midline tumors. In the neuraxis, chordomas are most commonly located in the sacrococcygeal region (50–55%), followed by the cranio-occipital region (25–30%). Case Report: A 71-year-old male has a left paraspinal tumor extending from C2 to C6 with bone erosion and left vertebral artery encasement. The tentative diagnosis before surgery was lymphoma or metastatic tumor. He underwent posterior cervical decompression with surgical debulking of the tumor to release the cord compression and posterior lamina screw fixation from C2 to C7 with allograft fusion and pathology confirmed the tumor to be chordoma. Conclusion: Due to the rare occurrence of chordomas extra-axially, these lesions have not earned a great deal of consideration in the clinical and radiographic differential diagnoses of extra-axial paraspinal lesions. An accurate preoperative diagnosis of chordoma is crucial, as survival is optimal when radical en bloc resection is performed at primary surgery.

Keywords: Cervical paraspinal, Chordoma, Extra-axial paraspinal lesions, Radical en bloc resection

Chi-Man Yip[1] Ping-Hong Lai[2], Hui-Hwa Tseng[3], Shu-Shong Hsu[1]

Affiliations: [1]Division of Neurosurgery, Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [2]Department of Radiology, Section of Neuroradiology Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [3]Department of Pathology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan.

Corresponding Author: Dr. Chi-Man Yip, MD, Division of Neurosurgery, Department of Surgery, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1 st Road, Kaohsiung 813, Taiwan; Ph: +886-7-3422121 ext 3017; Fax: +886-7-346-8367; E-mail: yip_chiman@yahoo.com

Received: 22 July 2015
Accepted: 14 September 2015
Published: 01 November 2015

How to cite this article

Chi-Man Y, Ping-Hong L, Hui-Hwa T, Shu-Shong H. Cervical paraspinal chordoma with left vertebral artery encasement. Int J Case Rep Images 2015;6(11):698–701.

doi:10.5348/ijcri-2015112-CR-10573

INTRODUCTION

Chordomas are slow-growing, low-grade malignant but locally invasive tumors which originate from embryonic remnants of the primitive notochord. These tumors account for approximately 1% of all intracranial tumors, 4% of primary bone tumors and 2% of spinal tumors [1–3]. Chordomas are principally midline tumors. In the neuraxis, chordomas are most commonly located in the sacrococcygeal region (50–55%), followed by the cranio-occipital region (25–30%) and then in the mobile spine vertebral bodies (10–15%) [1, 3–6]. For extra-axial paraspinal lesions, the common pathology are metastatic tumor, neurogenic tumor (schwannoma or neurofibroma) and lymphoma [2]. Extra-axial chordomas are rare but important consideration in the diagnosis of extra-axial lesions of the central nervous system. We would like to share a case of cervical paraspinal chordoma with others in order to increase clinical experience.

CASE REPORT

A 71-year-old male having past medical history of hypertension, herb-related chronic renal insufficiency and Parkinsonism who presented to us in December 2014 with the chief complains of progressive weakness of four extremities and unsteady gait for more than one year. On admission, he was conscious clear and his neurological examination revealed motor weakness of his bilateral upper limbs and bilateral lower limbs with muscle power grade 4; clumsy hands and unsteady gait; positive Hoffmann's sign and Babinski's sign on his left side; fine hand tremor; evident spasticity on his four limbs and rigidity on his upper limbs.

C-spine plain film showed degenerative change, but magnetic resonance imaging (MRI) scan of C-spine (Figures 1A and 1B) demonstrated a mildly enhancing mass lesion involving left side spinal canal from C2 to C6, left neuroforamina of C2/3, C3/4, C4/5, C5/6, erosion of vertebral body, left pedicle, lamina and transverse foramina of C3 to C5, encasement of left vertebral artery (yellow arrow), and spinal cord compression at C3 level. Computed tomography (CT) scan of C-spine (Figure 2) showed multiple foci of radiolucent and osteolytic lesions over left lateral mass of C3, C4 and C5, as well as narrowing was found over left C3/C4, C4/C5 and C5/C6 neuroforamina. Based on the imaging finding, lymphoma or metastatic tumor was the tentative diagnosis, but the tumor markers checked before operation were within normal limits. Under general anesthesia, this patient was put in prone position with his neck was in neutral position. He underwent posterior cervical decompression with surgical debulking of the tumor to release the cord compression and posterior lamina screw fixation from C2 to C7 with allograft fusion.

Histology examination of the specimen (Figure 3) revealed individual cells, cords and lobules of physaliferous cells and cells with eosinophilic cytoplasm in a prominent myxoid background. Nucleoli was inconspicuous and mitoses was absent. The immunohistochemistry results of neoplastic cells reveal positive for brachyury, EMA, S100, CKAE1/AE3, and negative for GFAP immunohistochemistry. Chordoma was diagnosed based on the tumor cells morphology and immunohistochemistry results. Followed-up C-spine MRI scan (Figure 4) showed that the spinal cord was free from the compression, however, residual tumor was present. Postoperative radiotherapy was arranged and the dosage was 45 Gy on the tumor bed in 25 fractions. He recovered well from the surgery and postoperative radiotherapy. He is regularly follow-up at our out-patient department in a stable condition.

DISCUSSION

Notochord is an embryonic structure which subsequently develops as vertebral column. During the second month of embryonic development, the notochord is restricted to the intervertebral residues. In adults, it gives rise to the nucleus pulposus of the intervertebral disks. Remnants of the notochord may persisted and give rise to a chordoma which can occur at any level along the neural axis [4, 7].

The radiological features of chordoma on MRI scan include hypointense or isointense on T1-weighted image (T1WI), hyperintense on T2-weighted image (T2WI), with heterogeneous enhancement. Low signal intensity fibrous septae on T2WI is detected in 70% cases [3–5, 7]. However, these MRI findings are very nonspecific and the differential diagnosis includes neurofibroma, metastasis, lymphoma, and chondrosarcoma [7]. Computed tomography (CT) scan is helpful to assess the degree of bone involvement or destruction and detect patterns of calcifications within the lesion in 30–70% of cases. Imaging differential diagnosis of spinal extradural

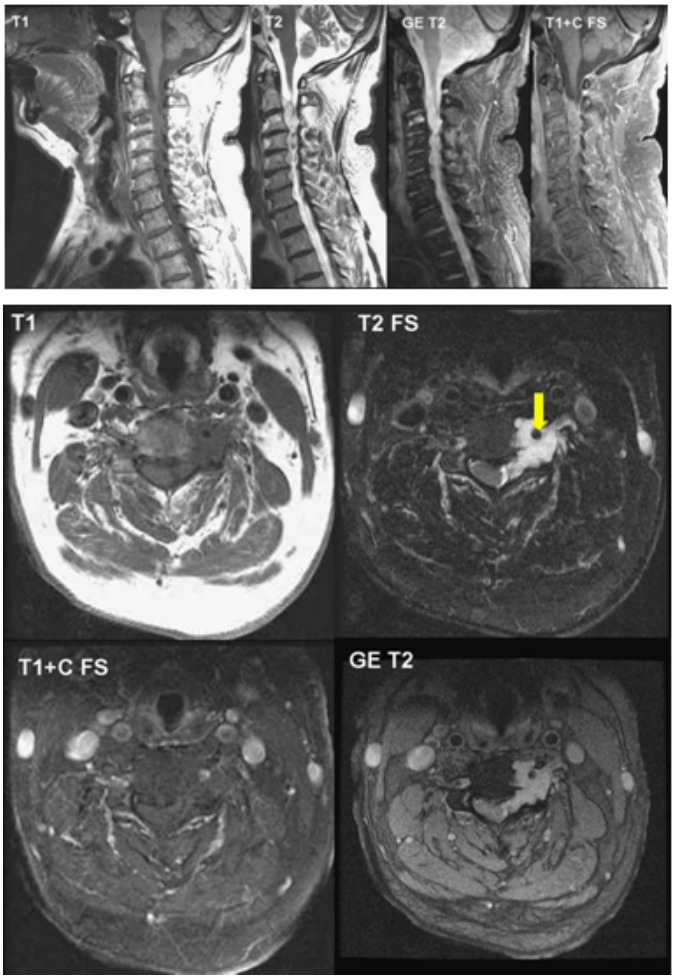


Figure 1: Preoperative C-spine MRI scan. (A) sagittal view, (B) Axial view demonstrating a mildly enhancing mass lesion hyperintensity in T2-weighted image involving the left side spinal canal and the left neuroforamina from C2 to C6 with erosion of adjacent vertebral body and encasement of the left vertebral artery (yellow arrow) and significant cord compression at the level of C3.

and foraminal/extraforaminal mass lesions includes neurogenic tumor (schwannoma, neurofibroma), metastasis, lymphoma and chordoma which is a very rare entity [2]. An accurate preoperative diagnosis of chordoma is crucial, as survival is optimal when radical en bloc resection is performed at primary surgery if possible [5, 8].

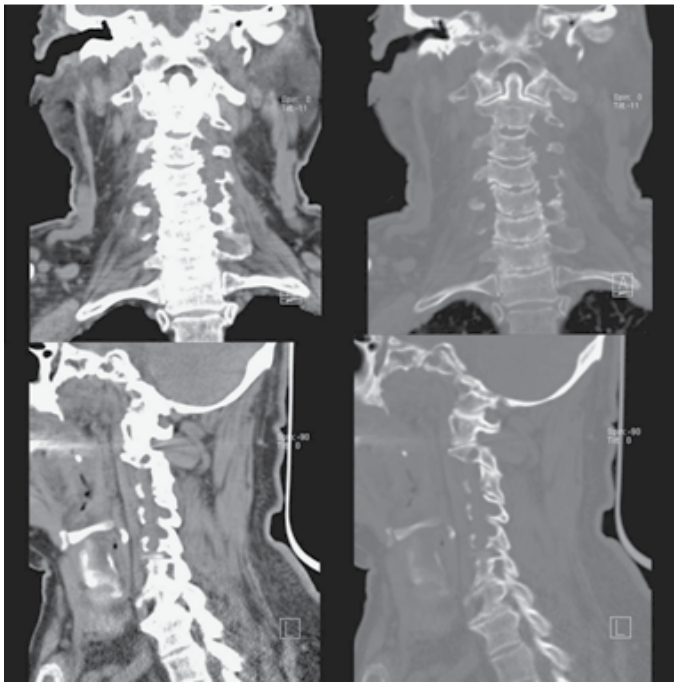


Figure 2: Preoperative C-spine computed tomography scan. Multiple foci of radiolucent and osteolytic lesions are noted over left lateral mass of C3, C4 and C5, as well as narrowing is found over left C3/C4, C4/C5 and C5/C6 neuroforamina.

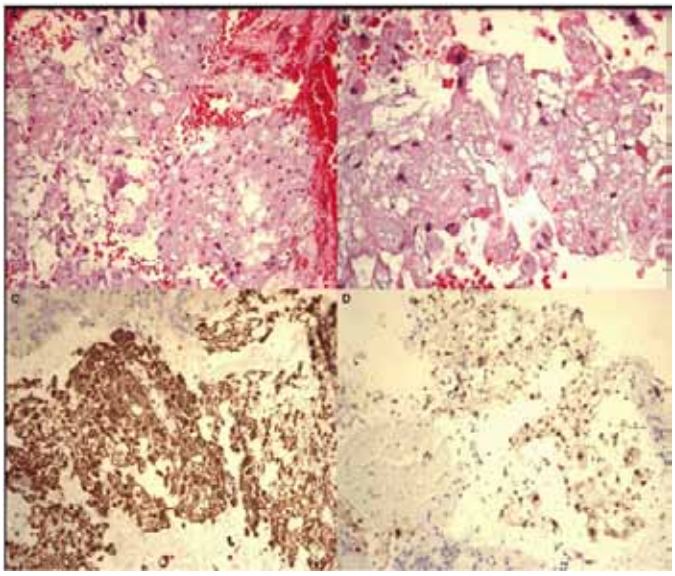


Figure 3: Histology of the tumor. (A, B) The tumor is consisting individual cells, cords and lobules of physaliferous cells and cells with eosinophilic cytoplasm in a prominent myxoid background (H&E stain, x200). Nucleoli is inconspicuous and mitoses is absent CKAE1/AE3 stain (C), brachyury stain (D) showing positive stain of the neoplastic cells.

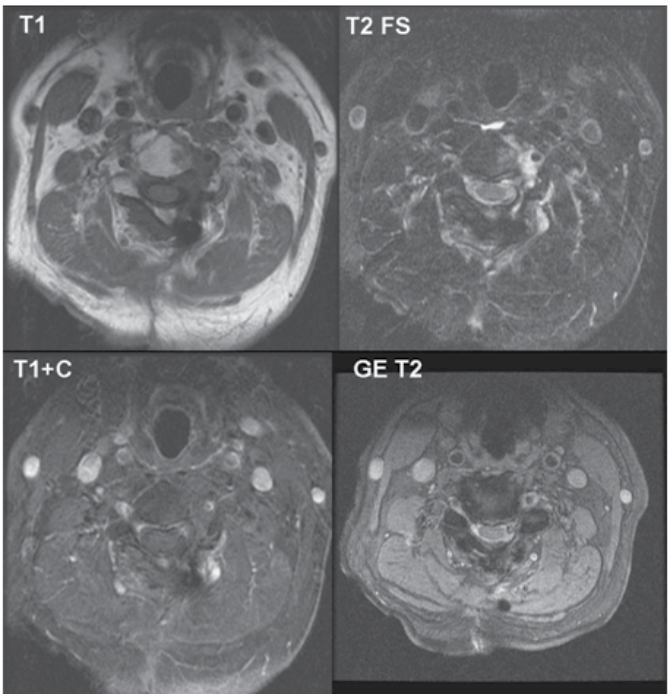


Figure 4: Postoperative C-spine MRI (axial view)The spinal cord was free from the compression, however, residual tumor was present.

Spinal extraosseous chordoma arises from ectopic notochordal rests outside the vertebrae and it should be in the differential diagnosis when a soft tissue mass with dumbbell morphology, vertebral artery encasement, vertebral body bone erosion, high signal on T2WI and varied enhancement. Nuclear staining for brachyury represents a unique specific diagnostic marker for chordoma [9]. Aggressive resection is the treatment of choice, followed by adjuvant treatments (radiation and sometimes chemotherapy). Proton beam radiation has been used to treat chordomas recently [8].

CONCLUSION

Spinal extraosseous chordoma should be in the differential diagnosis when a soft tissue mass showing dumbbell morphology, vertebral artery encasement, vertebral body bone erosion, and hyperintense on T2WI image with varied enhancement. An accurate preoperative diagnosis of chordoma is crucial, as survival is optimal when radical en bloc resection is performed at primary surgery.

****

Author Contributions

Chi-Man Yip – Substantial contributions to conception and design, Acquisition of data, Drafting the article,

Revising it critically for important intellectual content, Final approval of the version to be published
Ping-Hong Lai – Substantial contributions to conception and design, Analysis and interpretation of data, Revising the article critically for important intellectual content, Final approval of the version to be published
Hui-Hwa Tseng – Substantial contributions to conception and design, Analysis and interpretation of data, Revising the article critically for important intellectual content, Final approval of the version to be published
Shu-Shong Hsu – Substantial contributions to conception and design, Revising the article critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

Copyright

REFERENCES

1. Brennan PM, Summers DM, Ironside J, Fitzpatrick MO. Chordoma masquerading as a nerve root tumour -- a clinical lesson. Br J Radiol 2009 Nov;82(983):e231–4.
2. Lang SS, Thawani JP, Sayah A, et al. Chordomas and Their Consideration in the Radiographic Differential of Extra-Axial Lesions of the Central Nervous. Open Journal of Modern Neurosurgery 2012;2:58–62.
3. Sciubba DM, Chi JH, Rhines LD, Gokaslan ZL. Chordoma of the spinal column. Neurosurg Clin N Am 2008 Jan;19(1):5–15.
4. Smolders D, Wang X, Drevelengas A, Vanhoenacker F, De Schepper AM. Value of MRI in the diagnosis of non-clival, non-sacral chordoma.Skeletal Radiol 2003 Jun;32(6):343–50.
5. Kotnis N, Goepel J. Paraspinal chordoma mimicking a neurofibroma: a rare but important radiological pitfall. Skeletal Radiol 2013 Mar;42(3):443–6.
6. Khong P, Milross J, Cherukuri RK. Lumbar chordoma mimicking a neurogenic tumour. J Clin Neurosci 2011 Feb;18(2):302–4.
7. Mortelé B, Lemmerling M, Mortelé K, et al. Cervical chordoma with vertebral artery encasement mimicking neurofibroma: MRI findings Eur Radiol 2000;10(6):967–9.
8. Kohli A, Chaddha R, Vatchha SP. Chordomas of cervical spine: surgical management strategies and outcome. Coluna/Columna 2008;7:71–5.
9. Walcott BP, Nahed BV, Mohyeldin A, Coumans JV, Kahle KT, Ferreira MJ. Chordoma: current concepts, management, and future directions. Lancet Oncol 2012 Feb;13(2):e69–76.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Cryptococcus gattii meningitis in a young adult in South India: A case report

Alagiri Sivaranjini, Sekar Uma, Kindo Anupma Jyoti, V. Shankar

ABSTRACT

Introduction: Cryptococcus species is one of the leading causes of invasive fungal infections in the world today. The clinical differences between the two *Cryptococcus* species, namely, *Cryptococcus neoformans* and *Cryptococcus gattii* depends on the ecology, epidemiology, virulence of the strain and immune status of the host. *Cryptococcus gattii* is an environmental fungus of the tropics and subtropics but is now known to cause sporadic infections in non-endemic regions as well. Case Report: This paper reports a case of cryptococcal meningoencephalitis in a young, immunocompetent male, in South India, which is deemed a non-endemic region for *Cryptococcus gattii* infections. The patient presented with sub acute symptoms of headache and visual disturbances of two months duration. Cerebrospinal fluid was sent for investigation. Diagnosis was done by demonstration of capsule by microscopy, culture, detection of capsular antigen by latex agglutination and further confirmed by gene sequencing. In spite of intensive therapy, the disease progressed rapidly and the patient succumbed to the infection. Conclusion: *Cryptococcus gattii*, which was reported as a fungal pathogen of the endemics, is no longer considered as an accidental pathogen. Prompt detection and timely intervention is of utmost importance in treating this serious infection.

Keywords: *Cryptococcus gattii*, *Cryptococcus neoformans*, Invasive fungal infections, Meningitis

Alagiri Sivaranjini[1], Sekar Uma[2], Kindo Anupma Jyoti[3], V. Shankar[4]

Affiliations: [1]MBBS, Final year post graduate in MD Microbiology, Department of Microbiology, Sri Ramachandra Medical College & Research Institute, Chennai, India; [2]Professor and Head, Department of Microbiology, Sri Ramachandra Medical College & Research Institute, Chennai, India; [3]Professor, Department of Microbiolgy, Sri Ramachandra Medical College & Research Institute, Chennai, India; [4]Professor of Neurology, Sri Ramachandra Medical College & Research Institute, Chennai, India.

Corresponding Author: Dr. Anupma Jyoti Kindo, Professor, Department of Microbiology, Sri Ramachandra Medical College & Research Institute, Porur, Chennai, Tamilnadu. India- 600116; Ph: 91- 9884839196; Email: anupmalakra@gmail. com

Received: 02 July 2015
Accepted: 22 August 2015
Published: 01 November 2015

How to cite this article

Sivaranjini A, Uma S, Jyoti KA, Shankar V. *Cryptococcus gattii* meningitis in a young adult in South India: A case report. Int J Case Rep Images 2015;6(11):702–706.

doi:10.5348/ijcri-2015113-CR-10574

INTRODUCTION

Invasive fungal infections are a significant threat to immunocompromised patients. Recently, reports of systemic mycosis in previously healthy individuals are on the rise [1]. This may be attributed to the evolution of the fungal pathogens with increased virulence. This necessitates a high index of suspicion for fungal infections with atypical presentations.

Cryptococcus neoformans species complex belongs to the phylum Basidiomycota. These group of yeasts can cause fatal infections of the central nervous system, lung and skin not only in humans but also in animals.

C. neoformans var. grubii (serotype A) and *C. neoformans* var. neoformans (serotype D) have been isolated worldwide, causing disease in immunocompromised hosts. *C. neoformans* var. gattii (serotype B and C), has been recently elevated to species level as *Cryptococcus gattii,* due to its phenotypic and molecular differences [2, 3]. Moreover, *C. gattii* infects mainly immunocompetent hosts. It is an environmental fungus, first isolated in Vancouver Islands, British Columbia in 1970. By two decades, it has been associated with 176 cases and 8 deaths worldwide [3, 5]. This fungi is generally restricted geographically to the tropical and subtropical climates [6]. It spreads through the inhalation of spores. It is known to produce large space occupying lesions. The sequencing of the genomes of the two species reveals distinct functional differences in similar genes. The microevolution in the genome of *C. gattii* has lead to a change in its ecological niche and its virulence factors, which explains reports of sporadic cases of *C. gattii* infections in non-endemic regions [6]. *C. gattii* meningitis requires a more aggressive and longer duration of therapy when compared to *Cryptococcus neoformans*. Though reported rarely, prevalence of *C. gattii* infections is now on the rise [7].

This paper describes a case of primary central nervous system (CNS) cryptococcosis caused by *C. gattii*. The infection was diagnosed by detection of Cryptococcal capsular antigen and demonstration of capsulated yeast cells in negative staining microscopy and further confirmed by culture and gene sequencing.

CASE REPORT

A 24-year-old unmarried male presented to our hospital with chief complaints of headache, bilateral visual disturbance (diplopia), photosensitivity and intermittent fever. He was an engineering graduate by profession, with no history of travel in the previous 5 years. He gave no history of association with animals. His residence was not in proximity to any vegetation which might serve as a source of Cryptococcus infection. He was seronegative for retroviral infection and had no overt immunodeficiency state. It was later found that his CD4 count was below normal (292 cells/mm^3). On admission, his systemic examination revealed no abnormalities. Ocular examination showed bilateral lateral rectus palsy and papilledema. Computed tomography (CT) scan and magnetic resonance imaging (MRI) scan of brain were normal. As the patient developed increasing drowsiness and restlessness, he was admitted in the ICU with a provisional diagnosis of meningoencephalitis.

Lumbar puncture was done in which cerebrospinal fluid pressure was high. *The* CSF parameters showed: sugar-3 mgs/dl, protein 73mg/dl, white blood cells 63 cells/cm^3. red blood cells 26 cells/cm^3. Gram staining of CSF revealed occasional pus cells and plenty of yeast cells with a clear halo, suggestive of capsule (Figure 1). Negative staining with India ink showed plenty of capsulated yeasts, compatible with *Cryptococcus* species (Figure 2). Fungal culture of the CSF sample on Sabouraud's dextrose agar yielded cream colored, mucoid colonies, which were identified as *Cryptococcus gattii* by VITEK 2 (BioMerieux, Inc, Durham NC, USA. panel YST 21 343) (Figure 3). The identification was further confirmed by gene sequencing. The sequence has been submitted to the databank. The accession number is Banklt1828989 Cryptococcus KT027381.

The patient was started on Injection amphotericin B for treatment of meningitis, but since he developed anaphylactic reaction to it, the medication was discontinued. Fluconazole 400 mg per day plus flucytosine100 mg/kg/d in 4 divided doses was given since this patient was unable to tolerate amphotericin B. He was put on mechanical ventilation. A therapeutic lumbar puncture was done to decrease the raised intracranial pressure. A repeat CT brain, done at this point of time, revealed diffuse cerebral edema (Figure 4). A repeat MRI could not be performed. The patient's condition deteriorated through a period of 16 days. Cardiopulmonary decompensation and superadded bacterial infections worsened his condition.

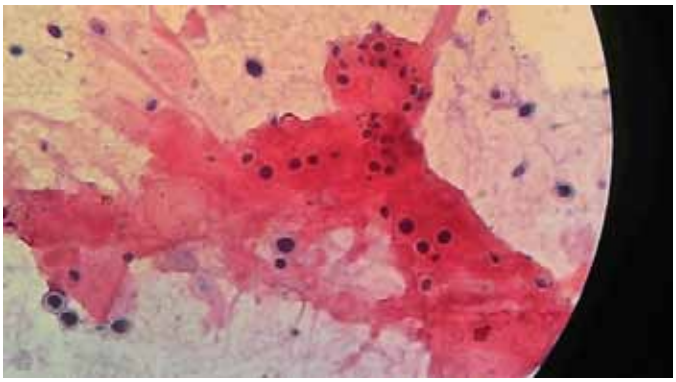


Figure 1: Gram stain of the cerebrospinal fluid showing round to oval budding yeast cells ranging from 5–20 μm in size, with clearing around them suggestive of capsule (Magnification x100).

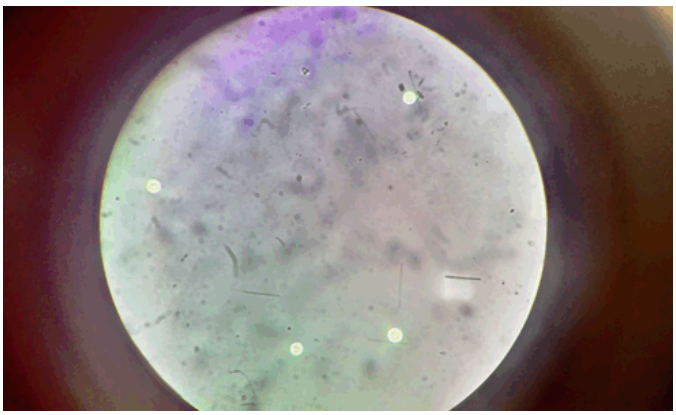


Figure 2: Direct microscopy of cerebrospinal fluid with 10% Nigrosin showing round to oval yeast cells ranging from 5–20 μm in size with a distinct halo, suggestive of capsule (Magnification, x100).

Figure 3: 48 hr old culture of *Cryptococcus gattii* on Sabouraud Dextrose agar without actidione showing mucoid, cream colored colonies.

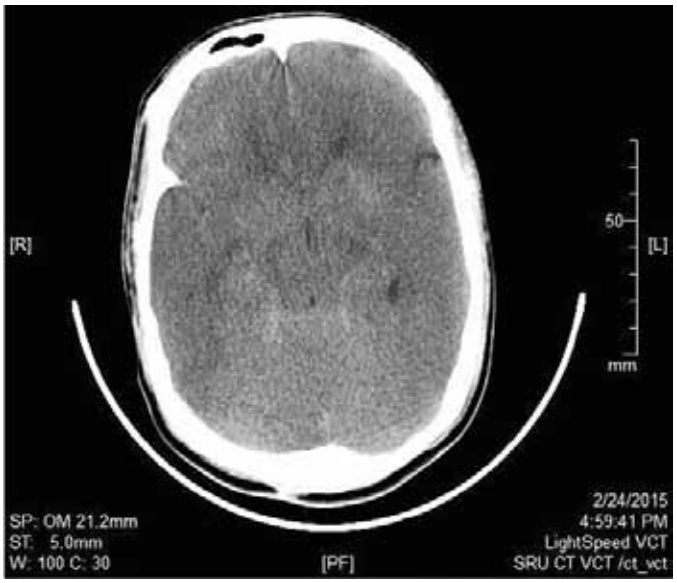


Figure 4: Computed tomography scan of brain (plain study) showing diffuse cerebral edema.

After three weeks of intensive therapy, he succumbed to the infection.

DISCUSSION

Being an environmental fungus of the tropics and subtropics, *Cryptococcus gattii* has been reported as an accidental infection in apparently immunocompetent individuals, with history of residing in or recent travel to an endemic area like British Columbian Islands and North West Pacific Coast of America. It has a specialized ecological niche in eucalyptus and almond trees [4, 7]. *C. gattii* more frequently causes pulmonary infections while *C. neoformans* has increased cerebral tropism [8]. *C. gattii* meningitis is characterized by larger space occupying lesions than *C. neoformans,* and associated with more neurological complications increased incidence of neurosurgical intervention and delayed response to therapy [1, 9]. Radiographic imaging is used to identify mass lesions, which may be the primary finding in this indolent infection. Phenotypically, *C. gattii* is differentiated from *C. neoformans* by L-Canavanine-glycine-bromothymol blue agar. Serotypic determination can be by slide agglutination tests. Molecular methods like PCR and gene sequencing aid in the confirmation of the isolate to species level. Cryptococcal meningitis is treated in 3 phases: Induction (AmpB plus Flucytosine for 2 weeks), Consolidation (Fluconazole for 8 weeks) and Maintenance (Fluconazole for 6 months to 1 year).

The first report of *C. gattii* as a pathogen was in 1896 by pathologist, Ferdinand Curtis. First case of human meningitis by *C. gattii* was reported in 1999 in Vancouver Islands, British Columbia, Canada [5]. Nearly 60 cases of *C. gattii* infection have been reported in United States during the outbreak in 2006–2010. Between 2004 and 2011, 96 cases of *C. gattii* infections were reported from Pacific Northwest. In India, the first case of *C. gattii* infection in an AIDS patient was documented by Abraham et al. [8]. Chakrabarti et al. reported five isolates of *C. gattii* from eucalyptus trees in Northern India, and traced the origin of these trees to Australia, thus validating spread of *C. gattii* infection in nonendemic areas [10]. Marriott et al. recorded five cases of *C. gattii* meningitis among seven HIV patients with cryptococcal infection [11]. Few reports of *C. gattii* meningitis among immunocompetent population of India and other countries are tabulated (Table 1) [12]. It is inferred that though there have been sporadic cases of *C. gattii* infections in immunocompetent individuals, isolated primary cerebral cryptococcosis is found to be rare.

Table 1: Few Reports of cerebral *Cryptococcus gattii* infections in immunocompetent patients globally.

Reported By	Year	Site	Geographical Area
Zahra et al.	2003	Cerebral	Malta, Southern Europe
Georgi et al.	2009	Cerebral	Zurich, Switzerland
Shu Hao Chang	2009	Disseminated (Cerebral & Cutaneous)	Taichung, Taiwan
Manoj Kumar Pranigrahi et al.	2010	Disseminated (Pulmonary & Cerebral)	Tamilnadu, India
Suchitha et al.	2012	Disseminated (Cutaneous, Pulmonary & Cerebral)	Mysore, India
Rajesh T Patil et al.	2013	Cerebral	Uttarakhand, India
Olivia Cometti et al.	2014	Cerebral	Cuiaba, Brazil

The present report is a case of *C. gattii* meningitis in a young adult who was seronegative for HIV infection and apparently immunocompetent. He presented with indolent signs of meningitis like intensifying headaches and diplopia of two months duration, which later progressed to acute cryptococcal meningitis. Further, anaphylaxis to amphotericin B posed a hurdle in clearing the cryptococcal infection. Hence, the patient was started on fluconazole combined with flucytosine. However, the combination of fluconazole and flucytosine is clinically inferior to amphotericin B–based therapy. The patient expired after 23 days of stay in the intensive care unit.

CONCLUSION

This case report heralds the need for suspicion of *Cryptococcus gattii* infection even in non-endemic regions. It contradicts the popular belief that invasive cryptococcosis is usually caused by *Cryptococcus neoformans* and not by *Cryptococcus gattii*. Environmental and clinical surveillance of cryptococcosis is important in preventing under reporting of *C. gattii* infections in non-endemic areas.

****

Author Contributions

Sivaranjini Alagiri – Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published
Uma Sekar – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Anupma Jyoti Kindo – Substantial contributions to conception and design, Analysis of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
V. Shankar – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

REFERENCES

1. Perfect JR. The triple threat of cryptococcosis: it's the body site, the strain, and/or the host. MBio 2012 Jul 10;3(4). pii: e00165–12.
2. Smith RM, Mba-Jonas A, Tourdjman M, et al. Treatment and outcomes among patients with Cryptococcus gattii infections in the United States Pacific Northwest. PLoS One 2014 Feb 19;9(2):e88875.
3. Kwon-Chung KJ, Boekhout T, Fell JW, Diaz M. Proposal to conserve the name Cryptococcus gattii against C. hondurianus and C. bacillisporus (Basidiomycota, Hymenomycetes, Tremellomycetidae). Taxon 2002;51(4):804–6.
4. McLaughlin J. Cryptococcus gattii-An Emerging Infectious Disease in the Pacific Northwest. State of Alaska Epidemiology-Bullettin 2010;27.
5. Galanis E, Waters S, Li M, Hoang L, MacDougall L, Phillips P. Cryptococcus gattii in BC: Update on an emerging disease. BCMJ 2007;49(7):7374–5.
6. Kidd SE, Hagen F, Tscharke RL, et al. A rare genotype of Cryptococcus gattii caused the cryptococcosis outbreak on Vancouver Island (British Columbia, Canada) Proc Natl Acad Sci U S A. 2004 Dec 7;101(49):17258–63.
7. Springer DJ, Chaturvedi V. Projecting global occurrence of Cryptococcus gattii. Emerg Infect Dis 2010 Jan;16(1):14-20.
8. Heitman J. Clinical perspectives on Cryptococcus neoformans and Cryptococus gattii: implications for diagnosis and management. ASM; 2012. p. 595–606.
9. Cogliati M. Global Molecular Epidemiology of Cryptococcus neoformans and Cryptococcus gattii: An Atlas of the Molecular Types. Scientifica (Cairo) 2013;2013:675213.
10. Chakrabarti A, Jatana M, Kumar P, Chatha L, Kaushal A, Padhye AA. Isolation of Cryptococcus neoformans var. gattii from Eucalyptus camaldulensis in India. J Clin Microbiol. 1997 Dec;35(12):3340–2.
11. Nagarathna S, Kumari HB, Arvind N, Prevalence of Cryptococcus gattii causing meningitis in a tertiary neurocare center from south India: a pilot study. Indian J Pathol Microbiol. 2010 Oct-Dec;53(4):855–6.
12. da Costa MM, Teixeira FM, Schalcher TR, Mioni Thielli Figueiredo Magalhães de Brito, Valério ES, Monteiro MC. Cryptococcosis, A Risk for Immunocompromised and Immunocompetent Individuals. The Open Epidemiology Journal 2013;6:9–17.

CASE REPORT PEER REVIEWED | OPEN ACCESS

A case of pericardial angiosarcoma with refractory pericardial tamponade treated with multidisciplinary therapy with pericardial fenestration, radiotherapy and chemotherapy

Hirano Satoshi, Yamanaka Kyoko, Ichinose Shuji, Ikeda Atsushi, Hayama Noriko, Shimizu Shinichiro, Aruga Takashi, Uchida Osamu, Nakamura Sukeyuki

ABSTRACT

Introduction: Outcomes for patients with pericardial angiosarcoma, especially with metastatic disease are very poor, even when these patients are treated with chemotherapy or radiotherapy. Case Report: This report describes a case of a 50-year-old male with pericardial angiosarcoma presenting with cardiac tamponade. Repeat pericardiocentesis showed bloody fluid with cytopathology negative for malignant cells. Pericardial fenestration was performed to prevent recurrent pericardial tamponade due to poor drainage. A diagnosis of cardiac angiosarcoma was made based on the resected pericardium and a biopsied specimen from gluteus medius muscle. The patient responded to combination therapy with docetaxel and radiotherapy. However, the patient died four months after diagnosis due to intraperitoneal bleeding from liver metastases. The patient was not dependent on a chest tube or a pericardial drain before he died. At autopsy, only a small amount of residual tumor was revealed around the heart. Conclusion: There is a possibility that palliative local control against refractory cardiac tamponade could be obtained via multidisciplinary therapy with pericardial fenestration, radiotherapy, and chemotherapy.

Keywords: Cardiac tamponade, Multidisciplinary therapy, Pericardial angiosarcoma, Pericardial fenestration, Radiotherapy

Hirano Satoshi[1], Yamanaka Kyoko[2], Ichinose Shuji[3], Ikeda Atsushi[4], Hayama Noriko[5], Shimizu Shinichiro[6], Aruga Takashi[7], Uchida Osamu[8], Nakamura Sukeyuki[9]

Affiliations: [1]Manager, Department of Medical Oncology, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan; [2]Senior resident, Division of Cardiology, Funabashi Municipal Medical Center Heart and Vascular Institute, Funabashi, Chiba, Japan; [3]Assistant manager, Department of Thoracic Surgery, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan; [4]Assistant manager, Division of Cardiology, Funabashi Municipal Medical Center Heart and Vascular Institute, Funabashi, Chiba, Japan; [5]Chief physician, Department of Respiratory Medicine, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan; [6]Manager, Laboratory Division of Pathology, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan; [7]Manager, Department of Radiation Oncology, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan; [8]Manager, Department of Thoracic Surgery, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan; [9]Manager, Department of Respiratory Medicine, Funabashi Municipal Medical Center, Funabashi, Chiba, Japan.

Corresponding Author: Satoshi Hirano, 1-21-1 Kanasugi, Funabashi, Chiba, Japan, 273-8588; Ph: +81-4-38-3321; Fax: +81-4-38-7323; Email: shirano@mmc.funabashi.chiba.jp

Received: 04 August 2015
Accepted: 15 September 2015
Published: 01 November 2015

How to cite this article

Satoshi H, Kyoko Y, Shuji I, Atsushi I, Noriko H, Shinichiro S, Takashi A, Osamu U, Sukeyuki N. A case of pericardial angiosarcoma with refractory pericardial tamponade treated with multidisciplinary therapy with pericardial fenestration, radiotherapy and chemotherapy. Int J Case Rep Images 2015;6(11):707–711.

doi:10.5348/ijcri-2015114-CR-10575

INTRODUCTION

Pericardial angiosarcoma is extremely rare, but this entity should still be included in the differential diagnosis of bloody pericardial effusion, even when cytopathology is negative for malignant cells. Outcomes for patients with metastatic disease are very poor, even when these patients are treated with chemotherapy or radiotherapy. This report describes a case of a patient with pericardial angiosarcoma presenting with recurrent pericardial tamponade and illustrates that palliative local control against cardiac tamponade can be obtained via multidisciplinary therapy with pericardial fenestration, radiotherapy, and chemotherapy.

CASE REPORT

A 50-year-old male with a history of gout treated with febuxostat was referred for the evaluation for a three-day history of dyspnea and pericardial effusion. He admitted to heavy alcohol consumption and 28 pack-years of former smoking. On physical examination, his pulse was 108 bpm, blood pressure was 128/ 88 mmHg, and oxygen saturation was 98% on room air. His body temperature was 37.4°C. Heart murmurs and lung rales were not heard. The rest of the physical examination was unremarkable. His basic laboratory findings were unremarkable except for elevation of hepatocellular enzymes (aspartate aminotransferase of 42 IU/L and alanine aminotransferase of 50 IU/L) and C-reactive protein (3.03 mg/dL). Electrocardiogram showed sinus rhythm and low voltage tracings. Chest X-ray showed cardiac enlargement (Figure 1A). Echocardiography demonstrated massive pericardial effusion (Figure 1B).

Pericardiocentesis was performed, and 1600 mL of bloody fluid was aspirated. Repeat fluid cytologic examination revealed no malignant cells. The results of examinations for tuberculosis and other bacterial agents were negative. A pericardial drain was placed, and drain output was 600 to 800 mL of bloody fluid every other day. Contrast-enhanced computed tomography (CT) scan of the chest showed large pericardial effusion and swelling of mediastinal lymph nodes (Figure 1C). There was no evidence of intracardiac abnormality. ^{18}F-labeled deoxyglucose (FDG) positron emission tomography scan showed increased FDG uptake in mediastinum nodules, pericardium, gluteus medius muscle, and cervical vertebrate (Figure 1D). About two weeks later, the pericardial drain was removed to prevent infection. However, two weeks after removal of pericardial drain, the patient developed syncope with massive pericardial effusion. A pericardial drain was placed but was not effective due to the high viscosity of the pericardial fluid. Therefore, pericardial fenestration was performed to prevent recurrent cardiac tamponade.

From the resected pericardium and the specimen from a gluteus medius muscle biopsy, a diagnosis of pericardial angiosarcoma was made. Proliferation of atypical short spindle or oval or epithelioid cells with hyperchromatic irregular nuclei and eosinophilic cytoplasm arranged in papillary structures or situated around variably gaping organization was demonstrated. Immunohistochemically, many atypical cells were positive for CD31, CD34, and Fli-1 (Figure 2). Desmin, S-100, D2-40, cytokeratins (CAM5.2, AE1/AE3), EMA, calretinin, and STAT6 were negative.

The patient was treated with concomitant chemoradiotherapy using a total dose of 40 Gy (2 Gy/ fraction) for 4 weeks and docetaxel at a dose of 25 mg/ m^2 weekly after administration of 300 mg of carboplatin into the pericardial space. The pericardial drain was removed after administration of carboplatin, and the chest drainage tube was also removed two weeks later.

After 1 month, multiple brain, pulmonary, and liver metastases were demonstrated. Therefore, treatment with docetaxel was stopped, and pazopanib was initiated.

Two months later, he presented to our hospital with palpitations, dyspnea on exertion, and new-onset dizziness. Laboratory work was performed and showed severe anemia with a hemoglobin of 5.6 g/dL. He received 2 units of red blood cells, but his condition did not improve. Two days later, he was readmitted to our hospital for further evaluation. His heart rate was 101 bpm, blood pressure was 93/65 mmHg, and oxygen saturation

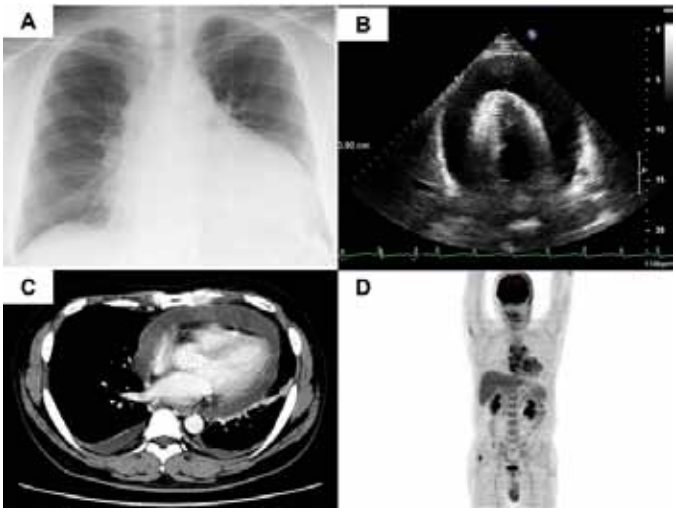


Figure 1:(A) Chest radiograph, at the time of admission, showing cardiac enlargement, (B) Two-dimensional echocardiogram showing large pericardial effusion with tamponade physiology, (C) Axial computed tomography section through the chest after intravenous contrast, mediastinal window showing a massive pericardial effusion without any evidence of intracardiac abnormality, and (D) ^{18}F-labeled deoxyglucose (FDG) positron emission tomography scan, showing increased FDG uptake in mediastinum nodules, pericardium, gluteus medius muscle, and cervical vertebrate.

was 96% on room air. On initial laboratory evaluation, his hemoglobin level was 5.6 g/dL. He also complained of right upper abdominal pain. Contrast-enhanced CT scan of the abdomen showed intraperitoneal hemorrhage due to multiple liver metastases (Figure 3A).

Unfortunately, the patient died four days after readmission due to intraperitoneal bleeding.

At autopsy, fatal massive intraperitoneal hemorrhage arising from liver metastases was demonstrated (Figure 3B). Although multiple nodular tumors remained within the pericardium, only a small pericardial effusion was demonstrated (Figure 4). Microscopically, most of the pericardial tumors were necrotic. Multiple lung metastases were also demonstrated, but pleural effusion was mild (about 300 mL in each thoracic cavity).

DISCUSSION

Primary cardiac angiosarcoma is extremely rare but is the most common primary cardiac malignancy. Therefore, cardiac angiosarcoma should be included in the differential diagnosis of cardiac tamponade. Unfortunately, this tumor is not easy to diagnosis due to its minimal incidence and difficult location to approach. Pericardiocentesis and tissue biopsy are often used for diagnosis. However, pericardial fluid cytology analysis is unreliable and should not be used, because malignant cells are very rarely found in the bloody fluid, even when the tumor has invaded into the pericardium, as in the present case. For accurate diagnosis, surgical exploration and intraoperative frozen sections are needed [1].

Outcomes associated with these tumors are very poor due to their aggressive character and due to late diagnosis, with 80% of patients already presenting with metastases at the time of diagnosis [2]. Surgical resection of primary tumor should be attempted when feasible, as

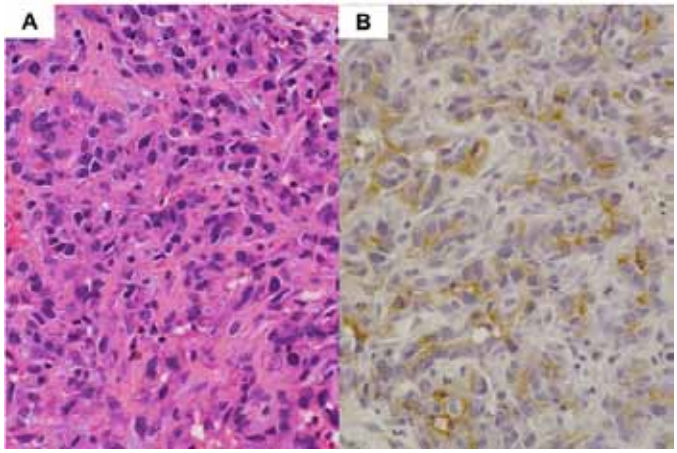


Figure 2: (A) Histological examination of the pericardial biopsy, showing proliferation of atypical short spindle or oval or epithelioid cells with hyperchromatic irregular nuclei and eosinophilic cytoplasm arranged in papillary structures (H&E stain, x200), (B) Immunohistochemistry demonstrating the endothelial nature of the cells expressing CD34 antigen (x200).

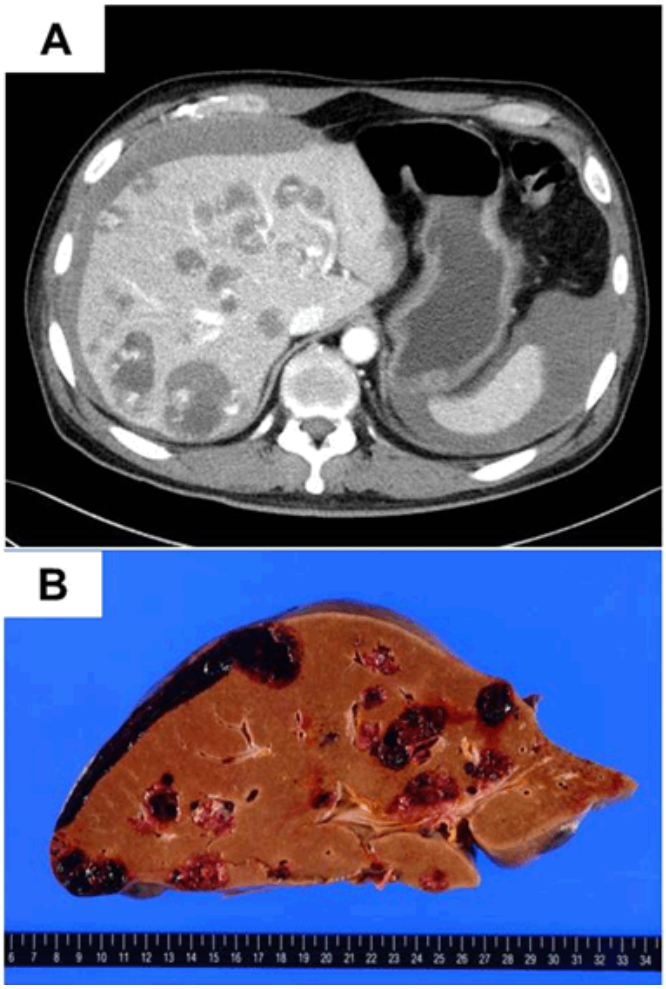


Figure 3: (A) Contrast-enhanced computed tomography scan of the abdomen, showing intraperitoneal hemorrhage due to multiple liver metastases, (B) At autopsy, fatal massive intraperitoneal hemorrhage arising from liver metastases was demonstrated.

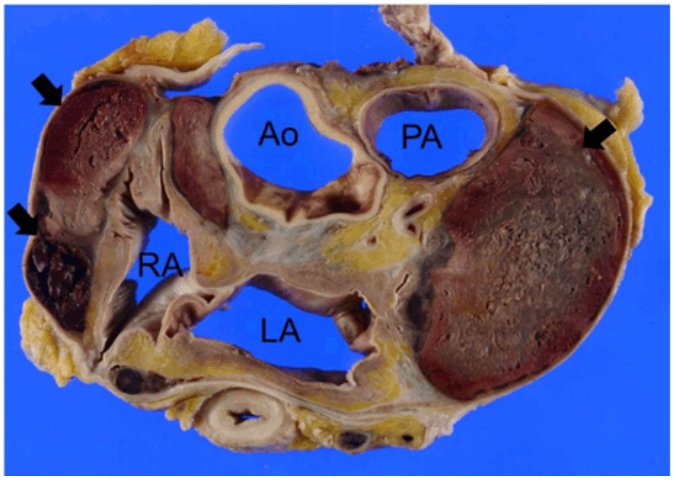


Figure 4: At autopsy, multiple residual tumors (arrow) are seen within the pericardium space, without intracardiac abnormality. Abbreviation: PA pulmonary artery, Ao aorta, LA left atrium, RA right atrium.

overall survival (OS) may be improved. Few studies have characterized survival outcomes in patients with cardiac angiosarcoma and metastatic disease. Hong et al. analyzed 10 patients who presented with metastatic disease and reported a median OS of only six months [3].

The optimal chemotherapy regimen for these aggressive tumors has not been established. Recently, Okiyama et al. reported that low-dose docetaxel therapy was effective for treatment of angiosarcoma of the skin [4]. On the other hand, Nakamura-Horigome et al. reported that docetaxel and radiotherapy was an effective treatment for cardiac angiosarcoma [5]. Their patient was treated with standard fractionated radiotherapy with a total dose of 42 Gy (2 Gy/fraction) for 4 weeks. The patient received docetaxel, 25 mg/m^2 weekly. With this treatment, the radiation dosage was reduced, using docetaxel as a radiosensitizer to decrease the adverse effects of high-dose standard fractionated radiotherapy. Subsequent cycles docetaxel were administered as maintenance therapy (2 weeks of treatment, 1 week of rest) until disease progression. Suderman et al. described a case of cardiac angiosarcoma treated with the same method. Their patient survived for more than 16 months [6].

Pazopanib is a synthetic imidazolyl pyrimidine that functions as a multi-targeted tyrosine kinase inhibitor with a high affinity for vascular endothelial growth factor receptors. The median length of progression-free survival and overall survival of patients with angiosarcoma treated with pazopanib after one or more cytotoxic regimens was reported as 3.2 months and 8.0 months, respectively [7]. A recent case report noted a durable response of more than 10 months when using pazopanib for treatment of pericardial angiosarcoma [8].

In our patient, multiple metastases were demonstrated at the time of diagnosis, and recurrent pericardial effusion was hard to resolve. Therefore, multidisciplinary therapy with pericardial fenestration, radiotherapy, and chemotherapy with docetaxel followed by pazopanib was performed. The treatment was effective for local tumor control and for maintenance of quality of life. The patient was not dependent on a chest tube or a pericardial drain until the time of his death.

CONCLUSION

We conclude that multidisciplinary approaches involving palliative surgery, radiotherapy, and chemotherapy may offer better quality of life in cases of cardiac angiosarcoma even in patients with metastatic disease.

****

Acknowledgements
We thank Dr. Hisaoka Masanori for his diagnostic expertise.

Author Contributions
Satoshi Hirano – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Kyoko Yamanaka – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Shuji Ichinose – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Atsushi Ikeda – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Noriko Hayama – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Shinichiro Shimizu – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Takashi Aruga – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Osamu Uchida – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Sukeyuki Nakamura – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

REFERENCES

1. Patel SD, Peterson A, Bartczak A, et al. Primary cardiac angiosarcoma - a review. Med Sci Monit 2014 Jan 23;20:103–9.
2. Oshima K, Ohtaki A, Kano M, et al. Primary cardiac angiosarcoma associated with cardiac tamponade: case report. Jpn Circ J 1999 Oct;63(10):822–4.
3. Look Hong NJ, Pandalai PK, Hornick JL, et al. Cardiac angiosarcoma management and outcomes: 20-year single-institution experience. Ann Surg Oncol 2012 Aug;19(8):2707–15.

4. Okiyama N, Miyazaki Y, Watanabe K, Yokozeki H, Nishioka K. 3 Cases of Angiosarcoma Cured by Docetaxel/Paclitaxel. [in Japanese] Jpn J Dermatol 2003;113(12):1827–33.
5. Nakamura-Horigome M, Koyama J, Eizawa T, et al. Successful treatment of primary cardiac angiosarcoma with docetaxel and radiotherapy. Angiology 2008 Jun-Jul;59(3):368–71.
6. Suderman D, Cooke A, Wong R, Klein J. Treatment of cardiac angiosarcoma with radiation and docetaxel: a case report with partial response and prolonged stable disease. J Thorac Oncol 2011 Apr;6(4):834–5.
7. Yoo KH, Kim HS, Lee SJ, et al. Efficacy of pazopanib monotherapy in patients who had been heavily pretreated for metastatic soft tissue sarcoma: a retrospective case series. BMC Cancer 2015 Mar 19;15:154.
8. Ong P, Greulich S, Schumm J, et al. Favorable course of pericardial angiosarcoma under paclitaxel followed by pazopanib treatment documented by cardiovascular magnetic resonance imaging. Circulation 2012 Oct 30;126(18):e279–81.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Compound heterozygous deletions presenting as infantile chylomicronemia

Susanna Felsenstein, Geesje Dallinga-Thie, Shankar Kanumakala

ABSTRACT

Introduction: Monogenic disorders affecting the lipid metabolism are rare, but early diagnosis is important to ensure prompt initiation of management. Case Report: A three-week old neonate presenting with rectal bleeding was found to have blood of an unusual cream-like appearance. Significant lipemia was confirmed, with massive increase in triglyceride and cholesterol levels. Centrifugation confirmed chylomicronemia. Primary chylomicronemia is extremely rare and most commonly caused by a lipoprotein lipase (LPL) gene mutation. The infant was a compound heterozygous for two deletions in the LPL gene: p. Thr45HisfsX3, and the here for the first time described p. Phe189X, both leading to a premature stop codon the absence of a mature protein. Subsequent change to medium chain triglyceride feed resulted in near-normal blood lipid levels. Conclusion: Novel mutations affecting chylomicron metabolism continue to be identified and may affect patients of ethnic background considered low-risk. This case illustrates that adequate treatment and dietary management is highly effective in symptomatic management, and in preventing serious complications in both infancy and later in life.

Keywords: Child, Chylomicronemia, Hyperlipidemia, Infant, Lipoprotein lipase gene mutation, Neonate, Ultracentrifugation

How to cite this article

Felsenstein S, Dallinga-Thie G, Kanumakala S. Compound heterozygous deletions presenting as infantile chylomicronemia. Int J Case Rep Images 2015;6(11):712–716.

doi:10.5348/ijcri-2015115-CR-10576

Susanna Felsenstein[1], Geesje Dallinga-Thie[2], Shankar Kanumakala[3]

Affiliations: [1]Great Ormond Street Hospital, London, United Kingdom; [2]Academisch Medisch Centrum Universiteit van Amsterdam. Department of Vascular Medicine, Amsterdam, Netherlands; [3]Royal Alexandra Children's Hospital, Brighton, United Kingdom.

Corresponding Author: Susanna Felsenstein, Great Ormond Street Hospital, London, United Kingdom; E-mail: sfelsenstein@hotmail.com

Received: 05 June 2015
Accepted: 12 August 2015
Published: 01 November 2015

INTRODUCTION

Infantile presentation with gross hyperlipidemia is rare, and may pose a challenge to the front-line pediatrician in differential diagnosis, therapeutic management and follow-up [1]. The diagnosis will rarely be straightforward, as manifestations are not diagnostic, but can be as diverse and severe as liver failure, pancreatitis, coagulopathy or fat emboli formation including the possibility of infantile stroke or other vascular complications. Herein, we present a case of infantile chylomicronemia illustrating these points as well as reviewing current diagnostic and treatment concepts.

CASE REPORT

Presentation and Diagnostic workup

A three-week-old female infant was referred for evaluation of rectal bleeding for three days. There were

no ante- or perinatal concerns and the baby had been fully breastfed. Apart from passing a small amount of fresh blood with every bowel motion she showed no other clinical signs or symptoms of bleeding tendency. Upon venipuncture, the infant's blood was noted to be grossly lipemic on inspection (Figure 1).

Coagulation profile was normal, though results were difficult to obtain because of the severe hyperlipidemia.

The initial fasting lipid profile showed a triglyceride level of 243.3 mmol/L (normal range: 0.8–1.7 mmol/L). Measurements taken of other blood lipids were not valid due to the degree of hypertriglyceridemia. Hemogram, renal and liver function tests including amylase were within normal range (hemoglobin 10.7 g/dL, white blood cell count 21.2x10^9/L, platelet 299x10^9/L, hematocrit 0.3, MCV 98 fL, MCH 35.1 pg, neutrophils 11.2x10^9/L, lymphocytes 7.7x10^9/L, monocytes 1.8x10^9/L, eosinophils 0.5x10^9/L. Na 142 mmol/L, K 5.0 mmol/L, urea 1.6 mmol/L, creatinine 27 umol/L, albumin 41 g/L, total protein 62 g/L, ALT 17 IU/L, blood glucose 5.3 mmol/L (normal range: 4.4–6.1 mmol/L), amylase 46 IU/L (normal range: 28–100 IU/L)).

Thyroid function tests demonstrated a TSH of 2.39 mU/L (normal range: 0.3–4.2 mU/L), and free thyroxine of 17.5 pmol/L (normal range: 12–22 pmol/L), excluding hypothyroidism.

A blood sample after three days of breastmilk feeds revealed near-normal lipid profile following removal of the chylomicron fraction by ultracentrifugation, establishing presence of chylomicronemia.

A fundoscopy at this point illustrated classical lipemia retinalis (Figure 2A).

Genetic work-up:

Genetic analysis showed compound heterozygosity for two different deletions in LPL, resulting in premature stop codons in Exons 2 and 5. Genetic work-up was also done for both parents. Whilst the father is a heterozygous carrier of the deletion in exon 2 (c.133-143del; p.Thr45HisfsX3), a mutation described previously [1], the mother was heterozygous for a deletion in exon 5 (c.566-567del, p.Phe189X) also resulting in a premature stop codon, which to our knowledge has not been described before.

The patient's father showed a slightly raised triglyceride level at 2.4 mmol/L (Reference: 0.8-1.7 mmol/L), her mother had marginally elevated cholesterol at 5.7 mmol/L (Reference range: 2.8–5.0 mmol/L). Both parents are thus clinically asymptomatic carriers of one recessive allele with mild derangement of their lipid profile.

Management

Upon diagnosis, milk feeds were stopped and Monogen (Nutrica, Schipohl, Netherlands), an MCT feed containing predominantly medium chain fatty acids, introduced, as avoidance of long chain- and supplementation with medium- and short chain fatty acids results therefore in an improvement of the hypertriglyceridemia phenotype. Figure 3 illustrates the rapid decrease in plasma cholesterol and triglycerides following introduction of exclusive Monogen® feed.

This diagnosis entails a lifelong condition, with complex management challenges throughout life.

Through the first year of life the patient maintained near-normal levels of both Cholesterol and triglycerides (TGs) on Monogen® to date. The necessity of avoiding long chain fatty acids was expected to make weaning onto a solid diet and nutrition challenging and is therefore closely supervised by a dietician. Weaning has been successful so far and the patient is on to a largely fat free solid diet, rich in protein and carbohydrates.

As a result of the strict restriction on fat intake, the infant receives 66% of her energy from protein, 26% from carbohydrate intake, and only 8% of her energy from fat, compared to the normally recommended 30% of energy derived from fat intake in this age group (Table 1).

Careful planning of the diet with additional Monogen® feeds ensures the patient's micronutrient requirements were met in infancy. Supplementation with Walnut oil (0.1 ml/56 kcal energy requirement) will provide the appropriate ratio of essential fatty acids. Close dietary monitoring will be necessary throughout to ensure all her macronutritional and micronutritional needs are met.

Repeat fundoscopy at six months of age showed complete resolution of lipemia retinalis (Figure 2B). The patient's cholesterol and TG levels have successfully

Figure 1: Appearance of venous blood taken on day of admission

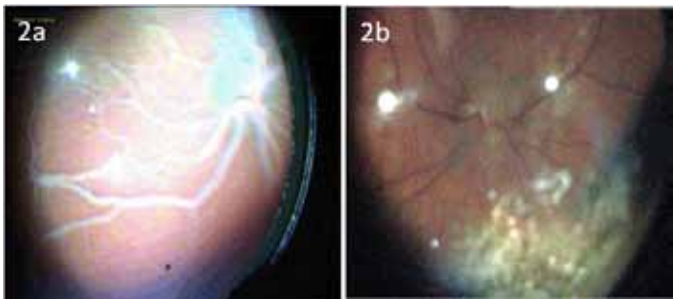


Figure 2: (A) Fundoscopy on admission whilst on breastfeeds, and (B) illustrating lipemia retinalis and following introduction of Monogen feeds and normalization of lipemia

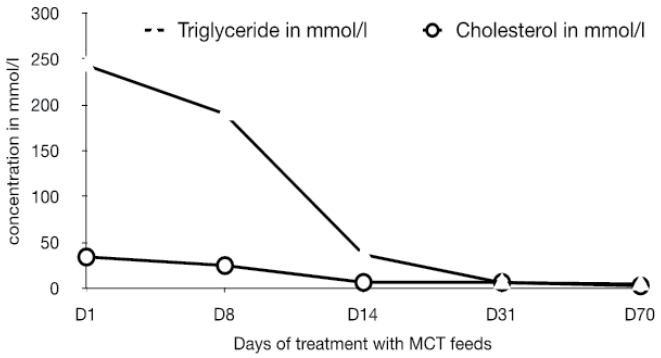


Figure 3: Cholesterol and triglyceride levels after introduction of exclusive Monogen® feed

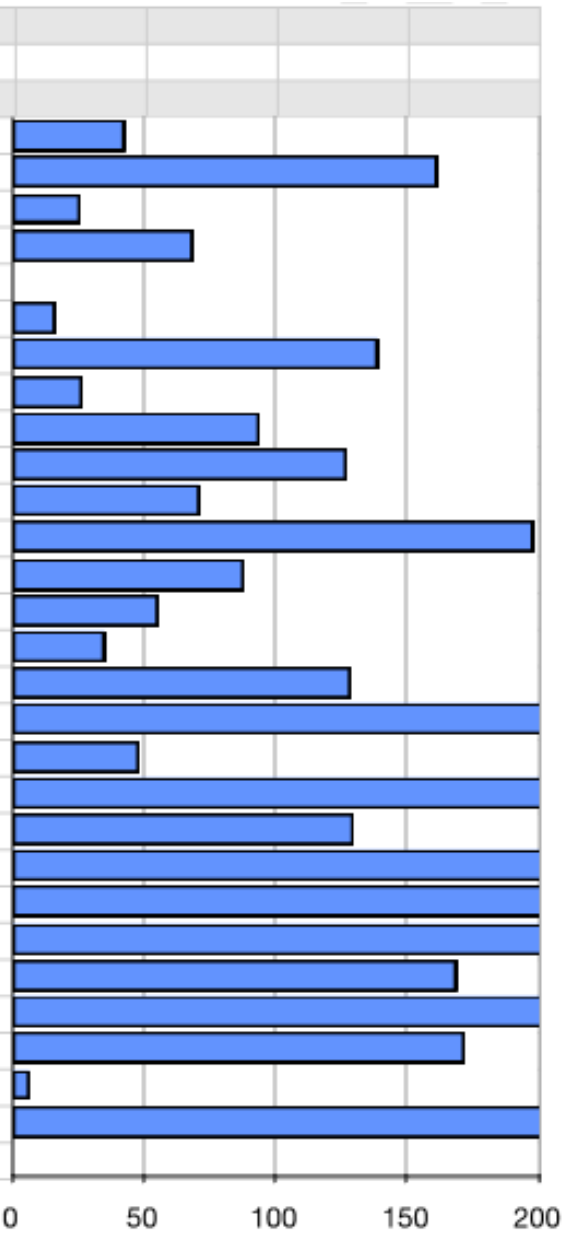
been maintained at near-normal levels following the introduction of a solid diet, and she continues to thrive and develop normally.

DISCUSSION

Primary chylomicronemia (also known as familial hypertriglyceridemia type I) is a rare autosomal recessively inherited disorder. The estimated prevalence rate of chylomicronemia is reported at around 1 in 1 million [1]. A founder effect results in a slightly higher prevalence in Quebecois Canadians. It is most commonly caused by a mutation in LPL, a key enzyme in TG metabolism

Table 1: Dietary analysis (not including monogen® feeds) highlighting deficiencies in many micronutrients, when following a strict fat restricted diet DRV (dietary recommended values)

Nutrients with UK DRV's				
Female, 10-12 months				
Nutrient	unit	Amount	RNI	%age
Energy	kcal	370.4	865	42.8
Protein	g	24.07	14.9	161.5
Fat, total	g	3.53	13.58	26
Polyunsaturates	g	1.7	2.47	68.7
Monounsaturates	g	0.5		
Saturates	g	0.68	4.12	16.4
Carbohydrate	g	64.49	46.42	138.9
Calcium	mg	139.96	525	26.7
Phsphorus	mg	376.04	400	94
Magnesium	mg	101.7	80	127.1
Sodium	mg	249.51	350	71.3
Potassium	mg	1385.2	700	197.9
Chloride	mg	440.08	500	88
Iron	mg	4.33	7.8	55.5
Zinc	mg	1.76	5	35.2
Copper	mg	0.39	0.3	128.6
Selenium	mcg	20.43	10	204.3
Iodine	mcg	28.97	60	48.3
Thiamin (B1)	mg	0.44	0.11	395.1
Riboflavin (B2)	mg	0.52	0.4	129.7
Nicotinic Acid eq	mg	14.21	2.44	581.3
Vitamin B6	mg	0.84	0.31	268.6
Vitamin B12	mcg	1.02	0.4	255.5
Folate	mcg	84.36	50	168.7
Vitamin C	mg	77.03	25	308.1
Vitamin A	mcg	601.61	350	171.9
Vitamin D	mcg	0.47	7	6.7
Vitamin E eq	mg	4.24	0.68	625.1
Cholesterol	mg	34.44		



located on the luminal surface of endothelium [2]. It aids the absorption of free fatty acids in peripheral tissues, catalyzing the hydrolysis of chylomicron-TGs and VLDL-TGs, thus delivering free fatty acids to peripheral tissues either for direct energy delivery or storage. Lack of or malfunction of LPL results in the inability to hydrolyze triglycerides from chylomicron and VLDL particles and leads to a massive rise in plasma levels of chylomicron and VLDL particles and accumulation of TGs in the plasma compartment [2, 3]. In this case, the patient was found to be heterozygous for two LPL mutations resulting in premature stop codons.

LPL requires a cofactor, apolipoprotein CII (APOC2), which resides on TG-rich particles and on HDL. Deficiency in apolipoprotein CII (APOC2) is very rare, but affected patients develop a similar phenotype, as LPL cannot function properly resulting in absence of TG hydrolysis and accumulation of TGs in plasma.

Two more proteins play an essential role in LPL homeostasis: Lipase Maturation Factor 1 (LMF1) and glycosylphosphatidylinositol (GPI)-anchored HDL binding protein 1 (GPIHBP1). Deficiencies in LMF1 and GPIHBP1 result in a similar clinical phenotype as LPL deficiency, with severe chylomicronemia at a young age [3–5].

LMF1 is an intracellular protein involved in the maturation of LPL. In the absence of functional LMF1 no active LPL will be secreted, again leading to severe hypertriglyceridemia similar to LPL deficiency. GPIHBP1 acts as the platform at the endothelial cell surface that provides LPL and TG rich lipoprotein particles to meet and subsequently allow TG hydrolysis [6]. The phenotype of these patients is similar to LPL deficiency. Deficiency of apolipoprotein A5 (APOA5) does not lead to hypertriglyceridemia but requires a secondary, yet unknown factor to fully express the hypertriglyceridemia phenotype.

Severe hypertriglyceridemia also occurs secondary to other conditions including hypothyroidism and diabetes, however, usually not as severe. More importantly, in secondary hyperchylomicronemia the elevation in plasma VLDL remnant particles contributes to the hypertriglyceridemia phenotype.

Patients are often diagnosed when the lactescent, grossly lipemic appearance of their blood raising the suspicion of chylomicronemia. The largest cohort of infants with familial chylomicronemia investigating presenting symptoms in these patients was done in Quebec [7]. 7/16 patients presented with irritability, 5 with anemia and/or splenomegaly, 2 had a rectal bleed and 2 cases were incidentally discovered. Another cohort of patients in South Africa of 29 individuals included adult patients. Here, the majority of patients presented with pancreatitis [8]. Patients who develop hypertriglyceridemia at a later age had less deleterious LPL mutations.

If untreated, the massively increased TGs in the plasma leads to recurrent attacks of acute pancreatitis (the most common cause of early death in this population), hepatosplenomegaly, abdominal pain, eruptive xanthomata, and psychiatric manifestations [9, 10].

The only therapeutic intervention for patients with primary hyperchylomicronemia at present is a drastic reduction of fat in the patient's diet. For infants, milk feeds are substituted with MCT feeds. The fasting lipid levels in these patients respond usually within days to fat restriction. The mainstay of controlling the plasma concentration of lipids is dietary management, aiming at a daily intake of fat of less than 20 g equivalent to two glasses of whole milk.

Compliance with this diet is difficult to maintain for the patient especially later in childhood and adolescence. In the young age, ensuring normal calorie intake from alternate sources to promote adequate growth is important, as is to ensure a balanced diet, especially in view of a restricted diet with vitamins, minerals and essential fatty acids. Supplementation with walnut oil is helpful as a source of essential fatty acids, compared to other edible oils. Exogenous factors such as alcohol, oral contraceptives, or retinoids may aggravate hyperlipidemia and should be avoided [9, 10]. Statins and other medications used in hyperlipidemias of other etiologies are not helpful and thus not indicated in patients with primary chylomicronemia.

CONCLUSION

Chylomicronemia is rare, but its inclusion in the differential diagnosis of the unwell infant is important for the general pediatrician, especially because once recognized, the condition can be managed effectively by dietary intervention and potential serious complications can thus be avoided. Attempts to target monogenic chylomicronemia with gene therapy may alter the management approach in the future.

****

Acknowledgements
We wish to thank Chris Smith, pediatric dietician at the Royal Alexandra Children's Hospital in Brighton, for critical revision of the manuscript.

Author Contributions
Susanna Felsenstein – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for intellectually important content, Final approval of the version to be published
Geesje Dallinga-Thie – Substantial contributions to analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Shankar Kanumakala – Substantial contributions to analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the

version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

Copyright

REFERENCES

1. Rahalkar AR, Hegele RA. Monogenic pediatric dyslipidemias: classification, genetics and clinical spectrum. Mol Genet Metab 2008 Mar;93(3):282–94.
2. Merkel M, Eckel RH, Goldberg IJ. Lipoprotein lipase: genetics, lipid uptake, and regulation. J Lipid Res 2002 Dec;43(12):1997–2006.
3. Beigneux AP, Franssen R, Bensadoun A, et al. Chylomicronemia with a mutant GPIHBP1 (Q115P) that cannot bind lipoprotein lipase. Arterioscler Thromb Vasc Biol 2009 Jun;29(6):956–62.
4. Franssen R, Young SG, Peelman F, et al. Chylomicronemia with low postheparin lipoprotein lipase levels in the setting of GPIHBP1 defects. Circ Cardiovasc Genet 2010 Apr;3(2):169–78.
5. Péterfy M, Ben-Zeev O, Mao HZ, et al. Mutations in LMF1 cause combined lipase deficiency and severe hypertriglyceridemia. Nat Genet 2007 Dec;39(12):1483–7.
6. Young SG, Davies BS, Fong LG, et al. GPIHBP1: an endothelial cell molecule important for the lipolytic processing of chylomicrons. Curr Opin Lipidol 2007 Aug;18(4):389–96.
7. Feoli-Fonseca JC, Lévy E, Godard M, Lambert M. Familial lipoprotein lipase deficiency in infancy: clinical, biochemical, and molecular study. J Pediatr 1998 Sep;133(3):417–23.
8. Pouwels ED, Blom DJ, Firth JC, Henderson HE, Marais AD. Severe hypertriglyceridaemia as a result of familial chylomicronaemia: the Cape Town experience. S Afr Med J 2008 Feb;98(2):105–8.
9. Brunzell JD. Familial Lipoprotein Lipase Deficiency. In: Pagon RA, Adam MP, Ardinger HH, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
10. Wilson CJ, Priore Oliva C, Maggi F, Catapano AL, Calandra S. Apolipoprotein C-II deficiency presenting as a lipid encephalopathy in infancy. Ann Neurol 2003 Jun;53(6):807–10.

CASE REPORT PEER REVIEWED | OPEN ACCESS

Hypertrophic obstructive cardiomyopathy in the setting of systemic scleroderma

Robert Sogomonian, Hassan Alkhawam, Feras Zaiem, Sunyoung Lee, M. Umair Bakhsh, Emma A. Moradoghli Haftevani, Dennis Chang

ABSTRACT

Introduction: The association of systemic sclerosis (SS) with restrictive cardiomyopathy has well been established, but that with hypertrophic obstructive cardiomyopathy (HOCM) is not clearly understood. Herein, we report a case of a patient with SS, identified to have both HOCM and myocardial fibrosis. Case Report: A 54-year-old female with systemic sclerosis, idiopathic lung disease with moderate pulmonary hypertension, presented with fatigue, decreased appetite and shortness of breath. Cardiac magnetic resonance imaging (CMRI) was significant for both hypertrophic and restrictive cardiomyopathy. Cardiac biopsy revealed evidence of diffuse fibrosis. Conclusion: Our case report describes an interesting association between SS and HOCM, as well as restrictive cardiomyopathy. However, more evidences are needed to clarify whether this unique affiliation is a coincidental random finding or a causative association.

Robert Sogomonian[1], Hassan Alkhawam[1], Feras Zaiem[2] Sunyoung Lee[1], M. Umair Bakhsh[3], Emma A. Moradoghli Haftevani[4], Dennis Chang[5]

Affiliations: [1]Department of Medicine, Icahn School of Medicine at Mount Sinai, Elmhurst Hospital Center, New York, USA; [2]Mayo Evidence Based Practice Center- Mayo Clinic, Rochester, MN; [3]Department of Medicine, Mount Sinai St. Luke's Hospital, NYC, NY, USA; [4]Ross University School of Medicine; [5]Department of Medicine, Icahn School of Medicine at Mount Sinai, NYC, USA.

Corresponding Author: Robert Sogomonian, MD, Department of Medicine, Elmhurst, Hospital, Center Icahn School of Medicine at Mount Sinai, 7901 Broadway, Elmhurst, New York 11373, USA; Email: Robert.sogomonian@mssm.edu

Received: 22 August 2015
Accepted: 09 September 2015
Published: 01 November 2015

Keywords: Cardiac biopsy, Cardiomyopathy, Hypertrophic obstructive cardiomyopathy (HOCM), Lung disease, Pulmonary hypertension, Systemic sclerosis (SS)

How to cite this article

Sogomonian R, Alkhawam H, Zaiem F, Lee S, Bakhsh MU, Haftevani EAM, Chang D. Hypertrophic obstructive cardiomyopathy in the setting of systemic scleroderma. Int J Case Rep Images 2015;6(11):717–719.

doi:10.5348/ijcri-2015116-CR-10577

INTRODUCTION

Restrictive cardiomyopathy has been a common variant seen in systemic sclerosis (SS) with myocardial fibrosis. An uncommon entity of hypertrophic obstructive cardiomyopathy (HOCM) has been described previously in only a very few cases of patients with systemic sclerosis. The association of SS with restrictive cardiomyopathy has well been established, but that with HOCM is not clearly understood. Herein, we report a case of a patient with SS, identified to have both HOCM and myocardial fibrosis. This singular case suggests that SS could be associated with HOCM, as well as restrictive cardiomyopathy.

CASE REPORT

A 54-year-old female with systemic sclerosis, idiopathic lung disease with moderate pulmonary hypertension, presented with fatigue, decreased appetite and shortness of breath. On admission, the patient became hypoxic with O_2 saturation of 86% on room air, tachycardic to 117 bpm, blood pressure of 110/53 mmHg.

Physical examination was significant for diffuse rhonchi in all lung fields, systolic murmurs, malar rash and skin excoriation in bilateral lower extremities without edema. Laboratory studies were significant for fingerstick glucose of 20 mg/dL with normal serum glucose, indicative of pseudohypoglycemia due to Raynaud's phenomenon, and elevated brain natriuretic peptide (858 pg/mL). Transthoracic echocardiography revealed evidence of diastolic heart failure with a left ventricular ejection fraction of 78%. Electrocardiography illustrated left ventricular hypertrophy and sinus tachycardia.

Cardiac magnetic resonance imaging (CMRI) was significant for severe left ventricular cardiac asymmetric septal hypertrophy with outflow obstruction caused by anterior motion of mitral valve and pericardial effusion (Figure 1). Cardiac biopsy revealed evidence of diffuse fibrosis, but did not show iron, glycogen, or amyloid deposition (Figure 2).

She was initially treated for pneumonia and presumptive pulmonary embolism. She was aggressively diuresed with intravenous furosemide given clinical signs of hypervolemia followed by dehydration and hypotension to 89/54 mmHg. Intravenous normal saline hydration was provided with resolution of blood pressure.

Subsequently, initiated bosentan for presumptive concerns of pulmonary hypertension causing the symptoms however, symptoms worsened as patient was preload dependent and HOCM was exacerbated. Methylprednisolone was initiated, yet patient developed severe proteinuria and renal crisis in the setting of scleroderma. Patient was maintained on mycophenolate mofetil, lower dose of methylprednisolone, morphine, clonazepam and transferred to hospice care with risks, benefits and prognosis of further treatment explained.

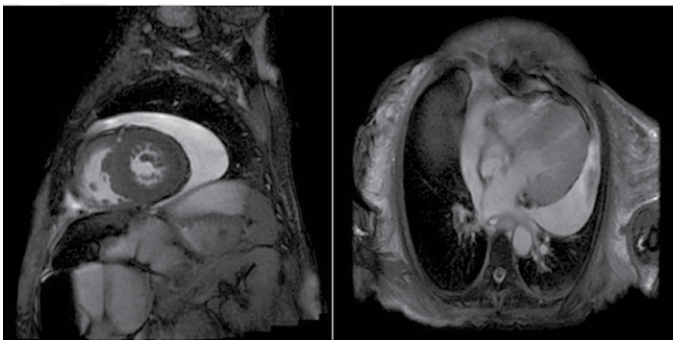


Figure 1: Cardicc MRI images showing the hypertrophied vwntricle with fibrosis. These images demonstrate features of both hypertropic and restrictive cardiomyopathy.

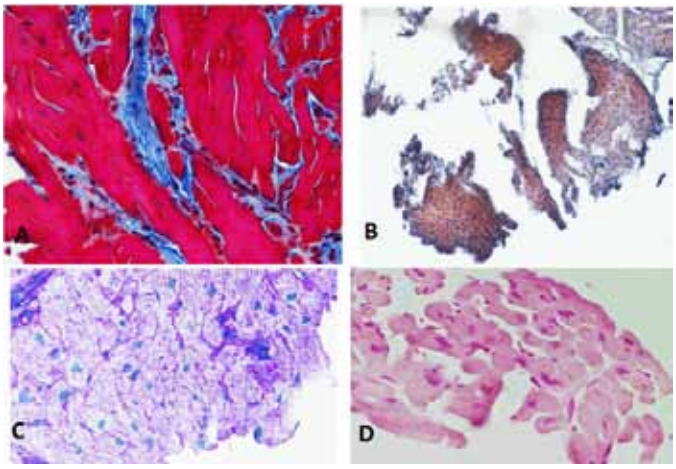


Figure 2: (A)-Masson'a trichrome stain reveals a large degree of collagen infiltrate and fibrosis demonstrating evidence of restrictive cardiomyopathy. (B)- Congo red stain shows no evidence of collagen storage disease.(D) Peels' Prussian blue stain does not show iron infiltration, ruling out hemochromatosis as a cause of restrictive cardiomyopathy.

DISCUSSION

Hypertrophic obstructive cardiomyopathy (HOCM) is the most common cardiac genetic disorder with an autosomal dominant transmission pattern. It is characterized by asymmetric left ventricular hypertrophy (LVH) out of proportion of systemic after load. The most common cardiac involvement in systemic sclerosis (SS) is myocardial fibrosis [1, 2]. while HOCM is rarely seen in SS.

Genetically, a predisposition for HOCM with human lymphocyte antigen (HLA)-DR3 has been reported, and this may provide a possible link with SS as reported [3]. A possible autoimmune mechanism might be a good explanation of the unique association between HOCM and SS supported by the fact that HOCM has also been reported in many chronic hepatitis C virus infection; a disease with multiple extra-hepatic autoimmune manifestations [4].

Although myocardial fibrosis is the hallmark of primary myocardial involvement in SS, few previous studies reported an increased incidence of LVH or septal hypertrophy in patients with SS [2, 5]. A study of serial echocardiography for thirty patients with SS and 48 control objects had concluded that patients with SS have an increased LV wall thickness with impaired diastolic dysfunction, which may attribute to myocardial fibrosis [5]. Another study correlated the findings of echocardiography, electrocardiography, and autopsy in 95 patients with SS, who were monitored up to eight years [2]. Three patients have septal hypertrophy on autopsies. Echocardiography along with electrocardiography detects septal hypertrophy in 12 patients, six of whom had asymmetric septal hypertrophy. Out of these 12, ten had limited cutaneous SS involvement and only two was noted in the diffuse cutaneous SS pattern.

CONCLUSION

The association of systemic sclerosis (SS) with restrictive cardiomyopathy has been well established, but with hypertrophic obstructive cardiomyopathy (HOCM), is rarely reported. Our case report describes an interesting association between SS and HOCM, as well as restrictive cardiomyopathy. However, more evidences are needed to clarify whether this unique affiliation is a coincidental random finding or a causative association.

****

Author Contributions

Robert Sogomonian – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Hassan Alkhawam – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Feras Zaiem – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Sunyoung Lee – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
M. Umair Bakhsh – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Emma A. Moradoghli Haftevani – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Dennis Chang – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

REFERENCES

1. Champion HC. The heart in scleroderma. Rheum Dis Clin North Am 2008 Feb;34(1):181–90; viii.
2. Murata I, Takenaka K, Shinohara S, Suzuki T, Sasaki T, Yamamoto K. Diversity of myocardial involvement in systemic sclerosis: an 8-year study of 95 Japanese patients. Am Heart J 1998 Jun;135(6 Pt 1):960–9.
3. Fiorito S, Autore C, Fragola PV, Purpura M, Cannata D, Sangiorgi M. HLA-DR3 antigen linkage in patients with hypertrophic obstructive cardiomyopathy. Am Heart J 1986 Jan;111(1):91–4.
4. Matsumori A, Ohashi N, Sasayama S. Hepatitis C virus infection and hypertrophic cardiomyopathy. Ann Intern Med 1998 Nov 1;129(9):749–50.
5. Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in patients with systemic sclerosis. J Intern Med 1990 Aug;228(2):183–92.

CASE REPORT PEER REVIEWED | OPEN ACCESS

A case of acute megakaryocytic leukemia associated with a nonseminomatous primary mediastinal germ cell tumor diagnosed through elevation of serum lactate dehydrogenase

Emi Noguchi, Yasushi Omuro, Yoshiharu Maeda, Tsuneo Sasaki

ABSTRACT

Introduction: Hematologic malignancies are seen in a small percentage of patients with primary mediastinal germ cell tumors (PMGCT). Case Report: A 29-year-old male patient with a nonseminomatous primary mediastinal germ cell tumor was diagnosed with acute megakaryocytic leukemia. Serum lactate dehydrogenase (LDH) elevation was a diagnostic clue. We discussed our case with a review of literature. Conclusion: Oncologists should be aware of the association of PMGCT with hematologic malignancies and consider this phenomenon as a differential diagnosis when LDH elevation is present in patients with PMGCT.

Keywords: Primary mediastinal germ cell tumor, Acute megakaryocytic leukemia, Hematologic malignancy, Differential diagnosis

Emi Noguchi[1], Yasushi Omuro[2], Yoshiharu Maeda[3], Tsuneo Sasaki[5]

Affiliations: [1]Department of Medical and Breast Oncology, National Cancer Center Hospital, Tokyo, Japan; [2]Department of Chemotherapy, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; [3]Director, Department of Chemotherapy, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; [4]Honorary Director, Department of Chemotherapy, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan.

Corresponding Author: Emi Noguchi, 5-1-1 Tsukiji, Chuo-ku, Tokyo, Japan, 104-0045; Ph: +81-3-3542-2511; Fax: +81-3-3542-3815; Email: enoguchi@ncc.go.jp

Received: 09 July 2015
Accepted: 28 August 2015
Published: 01 November 2015

How to cite this article

Noguchi E, Omuro Y, Maeda Y, Sasaki T. A case of acute megakaryocytic leukemia associated with a nonseminomatous primary mediastinal germ cell tumor diagnosed through elevation of serum lactate dehydrogenase. Int J Case Rep Images 2015;6(11):720–723.

doi:10.5348/ijcri-2015117-CR-10578

INTRODUCTION

The association of germ cell tumors (GCT) with hematologic malignancies is rare and has been described mostly in case reports and case series for more than 30 years [1–6]. It has a separate etiology from treatment-related leukemia. In most cases, it affects patients with nonseminomatous primary mediastinal GCT (PMGCT). Megakaryocytic leukemia has been described to be more common in this setting.

Herein, we report a case of acute megakaryocytic leukemia associated with a nonseminomatous primary mediastinal germ cell tumor whose diagnosis was challenging. Elevated serum lactate dehydrogenase (LDH) was a diagnostic clue.

CASE REPORT

A 29-year-old male was referred to our hospital with complaints of chest pain and exercise-induced dyspnea. The results of physical examination were unremarkable. Chest X-ray imaging revealed a mass in the hilum of the left lung. Computed tomography (CT) scan demonstrated a 9x8 cm tumor in the left anterior mediastinum (Figure 1). Serum concentration of human chorionic gonadotropin (hCG) was 1.2 mIU/mL (normal

range <0.7), the β subunit of hCG (β-hCG) was 0.4 ng/mL (<0.1), α-fetoprotein (AFP) was 111.9 ng/mL (<10.0), and serum lactate dehydrogenase (LDH) was 468 IU/l (115 to 245). Ultrasonography showed no lesions in the testes. A CT-guided biopsy was performed, and a few clusters of malignant tumor cells were obtained, with ambiguous histological features. Based on the tumor location (predominant midline distribution), relatively young age of the patient, male sex, and elevated serum β-hCG, AFP, and LDH levels, we diagnosed this condition as a primary mediastinal germ cell tumor; T1N0M0S2, Stage IIIB. The patient received four cycles of standard chemotherapy with cisplatin, etoposide, and bleomycin (BEP). The levels of tumor markers decreased as expected and normalized after two cycles of BEP chemotherapy. After the completion of four cycles of BEP chemotherapy, the tumor markers remained within the reference range, but a CT scan showed an increase in the tumor size. The patient underwent surgical resection of the tumor. Histopathological examination revealed viable nonseminomatous tumor cells in the resected specimen. The patient was then scheduled to receive two additional cycles of BEP chemotherapy.

Approximately one month post-operatively, just when one of the additional cycles of the chemotherapy was initiated, the serum LDH level suddenly rose to 420 IU/L. HCG and AFP remained within their reference ranges. A CT scan showed no evidence of recurrence of germ cell tumors. There were no aberrations in the results of blood tests except for elevated LDH. Since the serum LDH kept increasing up to 1,270 IU/L for three weeks, we surmised hematopoietic abnormalities and performed a bone marrow aspiration; the result was a dry tap. We also performed a bone marrow biopsy, which resulted in the diagnosis of acute megakaryocytic leukemia (AML) M7 according to the French–American–British (FAB) classification. Eventually, large atypical cells appeared in peripheral blood (Figure 2); this change happened approximately a month after the serum LDH level started to increase. The patient referred to hematologist to receive induction chemotherapy (idarubicin plus cytarabine) for the leukemia. Later, the chromosome 12 abnormality was detected in repeated bone marrow test.

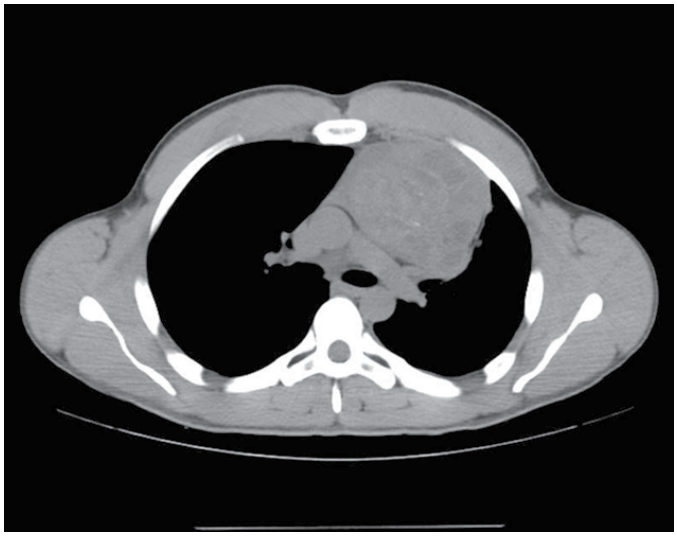


Figure 1: Computed tomography scan of the mediastinal mass.

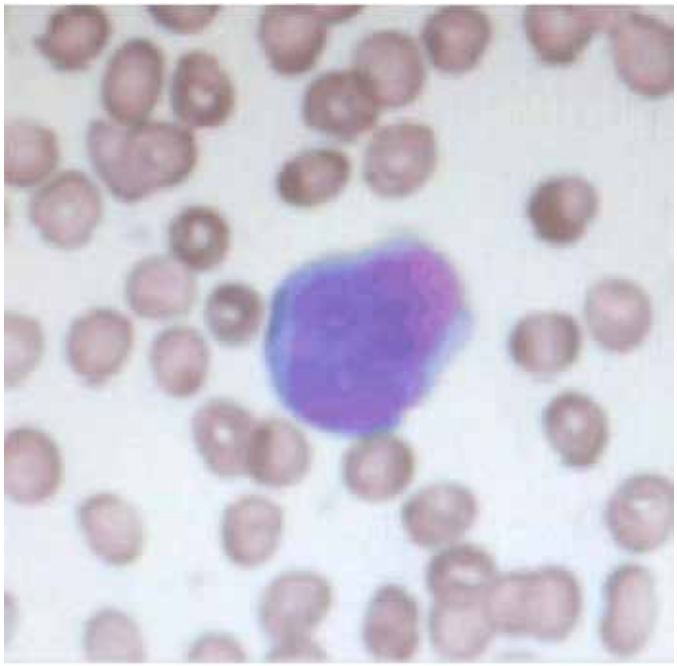


Figure 2: Bone marrow smear showing megakaryocytic leukemia cell (May-Giemsa stains, ×400).

DISCUSSION

It is well known that somatic teratomatous component of GCT leads to aggressive non-germ cell malignancies, such as rhabdomyosarcoma, acute myeloid leukemia, carcinoma, and primitive neuroectodermal tumors [7]. WHO classification also defines GCT accompanied by leukemia or lymphoma as “germ cell tumors with somatic-type malignancy”, which are synonyms of “teratoma with malignant transformation” [8]. The leukemic transformation has been exclusively observed in patients with nonseminomatous PMGCT except for a few cases [5]. In a large, international, database-based study, the incidence rate of hematologic malignancies was found to be 2.0% among patients with nonseminomatous PMGCT [6]. Those researchers also reported that these hematologic malignancies mostly affect the megakaryocyte lineage as AML M7, whereas it is a rare type of de novo AML. In patients with AML M7, a bone marrow aspiration frequently yields a dry tap, which is consistent with our case. Some cases showed elevated serum GCT markers (AFP and/or β-hCG), and others did not [8]. The presence of an isochromosome 12p (i(12p)), which is found in more than 80% of GCT, may suggest the clonal relationship between PMGCT and hematologic malignancies [3–8]. In our case, it was challenging to

detect AML M7 because the patient initially showed high levels of LDH only.

The differential diagnosis is treatment-induced leukemia. A time to leukemia development from GCT diagnosis differs between leukemia associated with GCT and treatment-induced leukemia. Treatment-induced leukemia usually develops approximately 2–3 years after treatment with topoisomerase II inhibitors and approximately five years after treatment with alkylating agents, whereas leukemia associated GCT develops shorter from or simultaneously with diagnosis of GCT [6]. Chromosomal translocations involving 11q are also characteristic of etoposide-related acute leukemia [9].

The prognosis of hematologic malignancies associated with PMGCT is very poor, while some cases would survive after intensive treatment with allogenic hematopoietic stem-cell transplantation [10].

CONCLUSION

Oncologists should be aware of the association of primary mediastinal germ cell tumors (PMGCT) with hematologic malignancies and consider this phenomenon as a differential diagnosis when serum lactate dehydrogenase (LDH) elevation is present in patients with PMGCT. Periodic monitoring blood tests will help diagnosing this phenomenon as well as potential treatment-induced leukemia.

****

Author Contributions

Emi Noguchi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Yasushi Omuro – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Yoshiharu Maeda – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Tsuneo Sasaki – Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

REFERENCES

1. DeMent SH, Eggleston JC, Spivak JL. Association between mediastinal germ cell tumors and hematologic malignancies. Report of two cases and review of the literature. Am J Surg Pathol. 1985 Jan;9(1):23–30.
2. Nichols CR, Hoffman R, Einhorn LH, Williams SD, Wheeler LA, Garnick MB. Hematologic malignancies associated with primary mediastinal germ-cell tumors. Ann Intern Med 1985 May;102(5):603–9.
3. Nichols CR, Roth BJ, Heerema N, Griep J, Tricot G. Hematologic neoplasia associated with primary mediastinal germ-cell tumors. N Engl J Med 1990 May 17;322(20):1425–9.
4. Orazi A, Neiman RS, Ulbright TM, Heerema NA, John K, Nichols CR. Hematopoietic precursor cells within the yolk sac tumor component are the source of secondary hematopoietic malignancies in patients with mediastinal germ cell tumors. Cancer 1993 Jun 15;71(12):3873–81.
5. Menon R, Twardowski P, Forman SJ, Huang Q, Slovak ML, Krishnan A. Primary gonadal germ cell tumor associated with acute leukemia with common cytogenetics. J Clin Oncol 2010 Feb 20;28(6):e96–8.
6. Hartmann JT, Nichols CR, Droz JP, et al. Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. J Natl Cancer Inst 2000 Jan 5;92(1):54–61.
7. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. N Engl J Med 1997 Jul 24;337(4):242–53.
8. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. Pathology & Genetics of Tumours of Lung, Pleura, Thymus & Heart, World Health Organization Classification of Tumours. 3ed. Lyon, France: IARC Press; 2004. p. 216–8.
9. Kollmannsberger C, Beyer J, Droz JP, et al. Secondary leukemia following high cumulative doses of etoposide in patients treated for advanced germ cell tumors. J Clin Oncol 1998 Oct;16(10):3386–91.
10. Hiramatsu H, Morishima T, Nakanishi H, et al. Successful treatment of a patient with Klinefelter's syndrome complicated by mediastinal germ cell tumor and AML(M7). Bone Marrow Transplant 2008 May;41(10):907–8.

CLINICAL IMAGES PEER REVIEWED | OPEN ACCESS

A case of rhino-orbital-cerebral mucormycosis

Aishwarya Venkataraman, Bridget Callaghan

CASE REPORT

A 16-year-old, neutropenic boy on treatment for acute lymphoblastic leukemia developed acute onset fever and swelling of the left eye. The initial differential diagnoses were periorbital cellulitis and orbital cellulitis. Ophthalmological examination showed no eye movements, no pupillary reaction, no perception of light and a swollen retina. An urgent computed tomography (CT) scan of head with orbits was suggestive of orbital cellulitis and broad spectrum antibiotics (piperacillin/ tazobactam and amikacin) were commenced. A detailed ENT examination on the same day revealed possible spores or hyphae along the nasal septum on the left side 2 cm from the nostril. Mucormycosis was suspected and he was started on antifungals (amphotericin B and posaconazole) in addition to the antibiotics. Magnetic resonance imaging (MRI) scan of the brain and orbits performed the next day, showed extensive infiltration consistent with infection of the left orbit, left maxillary antrum and ethmoidal sinus, extending to the right medial nasal region (Figure 1A, arrow and Figure 1B, arrow). Subsequently, he underwent debridement and enucleation of the left eye with radical bilateral frontoethmoidectomy to salvage the right eye. Histology

Aishwarya Venkataraman[1], Bridget Callaghan[2]
Affiliations: [1]Paediatric Registrar, International and Private Patients, Great Ormond Street Hospital NHS Trust, London, United Kingdom; [2]Lead Consultant for International and Private Patients, Great Ormond Street Hospital NHS Trust, London, United Kingdom.
Corresponding Author: Dr. Aishwarya Venkataraman, International and Private Patients, Great Ormond Street Hospital, Great Ormond Street, London, United Kingdom, WC1N 3JH; Ph: 0044 7877278031; Fax: 0044 2078298635; Email: Aishwarya.Venkataraman@gosh.nhs.uk

Received: 15 July 2015
Accepted: 24 September 2015
Published: 01 November 2015

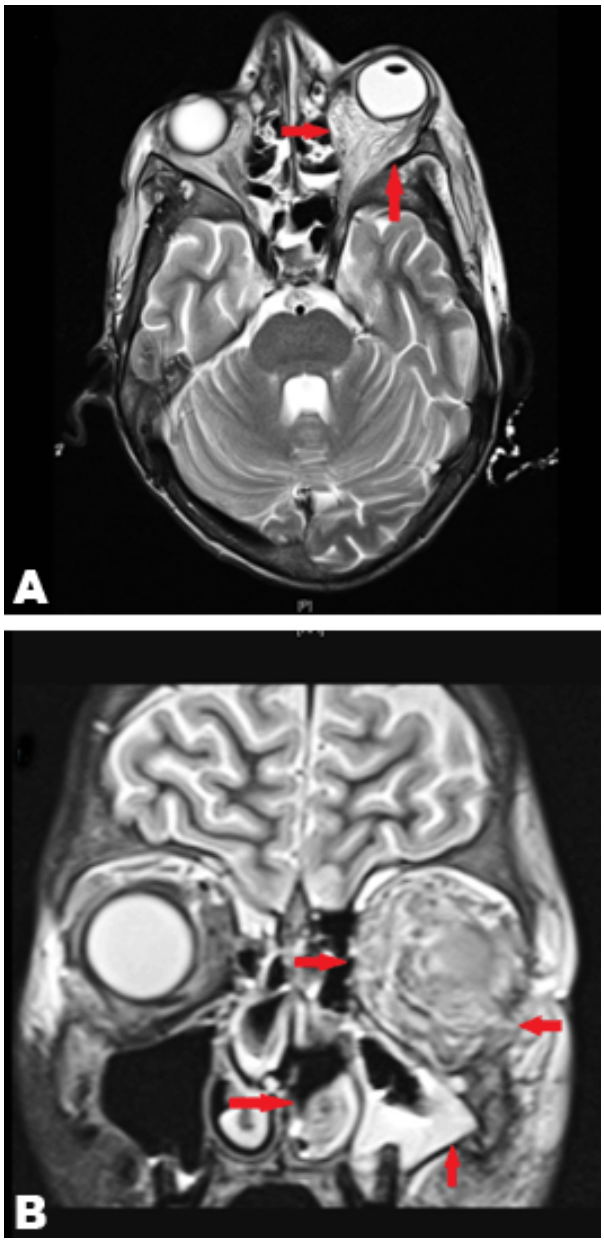


Figure 1: (A, B): Magnetic resonance imaging scan of brain and orbits showing extensive involvement of left orbit and some involvement of right orbit, left maxillary antrum and ethmoidal sinus.

confirmed widespread necrotizing, angioinvasive and perineural fungal infection with involvement of sclera, choroid and dura. Culture grew *Rhizopus microsporus, Staphylococcus aureus* and *Acinetobacter* species. Despite optimum treatment, he succumbed to extensive central nervous system disease 40 days after initial presentation.

DISCUSSION

Mucormycosis is a rare, rapidly destructive fungal infection most commonly affecting immunocompromised and diabetic patients [1–4]. Depending on the anatomical site involved, it can be broadly classified as rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous or disseminated disease [1, 2]. The fungus is angioinvasive, causing severe thrombosis and tissue necrosis [1]. Underlying predisposing conditions are major risk factors for the disease [1–4]. In our case, chemotherapy-induced neutropenia (ANC of the patient remained $<1.0x10^9$/l throughout) was one of the risk factors. Steroids, used in treatment of ALL, may also increase the risk of fungal infection [2, 3]. The initial symptoms of rhino-orbital-cerebral mucormycosis is similar to either sinusitis or periorbital cellulitis. If untreated, infection can spread to the orbit from the ethmoid sinuses, resulting in loss of extraocular muscle function and proptosis. Progressive vision loss and ultimately blindness may result either from involvement of the optic nerve or from cavernous sinus thrombosis. Extensive central nervous system involvement can present with signs and symptoms of cerebral infarctions secondary to internal carotid artery and cavernous sinuses thrombosis [1].

Diagnosis of rhino-orbito-cerebral mucormycosis is challenging. Initial CT scan findings can be negative or have findings suggestive of sinusitis. MRI scans are more sensitive than CT scans for detecting disease beyond the sinuses [5]. Confirmatory diagnosis is made by histopathological examination and positive microbiology culture. Unfortunately, this is time consuming and *Mucorales* species often fail to grow in fungal culture [1].

Antifungal therapy alone is usually insufficient to control the rapidly spreading disease. It is important to treat or reverse the underlying cause and immunosuppressive medications should be dose reduced or stopped if possible [1–3]. Angioinvasion, thrombosis, and tissue necrosis result in poor penetration of anti-fungal agents to the site of infection. Surgical excision of the infected sinuses and appropriate debridement of the retro-orbital space is often required and can prevent the spread of infection into the eye, resulting in improved cure rates [1]. Unfortunately, mortality and morbidity remains high despite appropriate medical and surgical treatment [1, 6]. The patient described in the case report developed extensive cerebral and brain stem infarction due to the rapidly spreading disease despite prompt diagnosis and treatment.

CONCLUSION

Rhino-orbital-cerebral mucormycosis is rare but potentially fatal in immunocompromised patients. Diagnosis is often difficult and surgical debridement, prompt use of antifungal agents and reversal of predisposing factors, if possible remains the mainstay of treatment. Despite optimum treatment, the mortality remains high; more than 50%. Newer tools are urgently needed to diagnose and treat mucormycosis.

Keywords: Angio-invasive, Anti-fungal, Fungal infection, Mucormycosis, Posaconazole

How to cite this article

Venkataraman A, Callaghan B. A case of rhino-orbital-cerebral mucormycosis. Int J Case Rep Images 2015;6(11):724–726.

doi:10.5348/ijcri-201534-CL-10089

****

Author Contributions

Aishwarya Venkataraman – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Bridget Callaghan – Substantial contributions to conception and design, Revising the article critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

REFERENCES

1. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005 Jul;18(3):556–69.

2. Dehority W, Willert J, Pong A. Zygomycetes infections in pediatric hematology oncology patients: a case series and review of the literature. J Pediatr Hematol Oncol 2009 Dec;31(12):911–9.
3. Kara IO, Tasova Y, Uguz A, Sahin B. Mucormycosis-associated fungal infections in patients with haematologic malignancies. Int J Clin Pract 2009 Jan;63(1):134–9.
4. Thomas S, Singh VD, Vaithilingam Y, Thayil SC, Kothari R. Rhinocerebral mucormycosis--a case report. Oral Maxillofac Surg 2012 Jun;16(2):233–6.
5. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis 2008 Aug 1;47(3):364–71.
6. Spellberg B, Ibrahim AS. Recent advances in the treatment of mucormycosis. Curr Infect Dis Rep 2010 Nov;12(6):423–9.

CLINICAL IMAGES PEER REVIEWED | OPEN ACCESS

101 spots: Find the primary site

Geraldine Bera, Gabriel Malouf, Nathanaëlle Yeni, Charlotte Lepoutre-Lussey

CASE REPORT

A 57-year-old male was presented to the emergency department with acute dysphagia and severe hypercalcaemia. He had a history of a locally advanced oral squamous cell carcinoma (OSCC) of the base of the tongue and a localised pleomorphic pulmonary sarcomatoid carcinoma (PSC) of the upper lobe of the right lung, treated five years and eighteen months ago, respectively. Clinical examination revealed a bleeding epiglottic lesion, cervical lymphadenopathies and scattered subcutaneous nodules. ^{18}Fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}[F]-FDG PET/CT) scan highlighted intense whole-body disseminated uptake (Figure 1A), in particular from the oral cavity to pyriform sinus (Figure 1B), in the subcutaneous tissues (Figure 1C), on bone, pancreas (Figure 1D) and a moderate uptake on the right upper lung lobe probably corresponding to a pleomorphic PSC recurrence (Figure 1E, 1F). Thus these findings have suggested a distant metastatic relapse of the PSC associated with a loco-regional recurrence of OSCC. Surprisingly, histological analysis of subcutaneous biopsies (Figure 1G) concluded a well-differentiated SCC and immunostaining for thyroid transcription factor-1 (TTF-1) was negative.

Geraldine Bera[1], Gabriel Malouf[2], Nathanaëlle Yeni[3], Charlotte Lepoutre-Lussey[4]

Affiliations: [1]University Medical Assistante, Department of Nuclear Medicine, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital 75651 Paris Cedex 13 France and Departement of Biophysic UPMC Paris VI, 91 Bd de l'hôpital 75651 Paris Cedex 13 France; [2]Clinical University Hospital Asssitant, Department of Medical Oncology, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital 75651 Paris Cedex 13 France and Laboratoire de la Fondation AVEC and Institut Universitaire de Cancérologie, GRC5, UPMC, Paris, France; [3]Contractual Hospital Practitioner, Department of Nuclear Medicine, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital 75651 Paris Cedex 13 France and Department of Biophysic UPMC Paris VI, LIB, INSERM UMR 678, 91 Bd de l'hôpital 75651 Paris Cedex 13 France; [4]Practitioner Attached, Department of Biochemistry INSERM 0970, AP-HP European Hospital Georges-Pompidou, 56 rue Leblanc 75015 Paris, France ; Department of Nuclear Medicine, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital 75651 Paris Cedex 13 France.

Corresponding Author: Geraldine Bera, Department of Nuclear Medicine, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital Paris Cedex 13 France 75651; Ph: +33.1.42.17.62.81; Fax: +33.1.42.17.62.92; E-mail: berageraldine@gmail.com

Received: 03 August 2015
Accepted: 17 September 2015
Published: 01 November 2015

DISCUSSION

Pulmonary sarcomatoid carcinoma is a rare, poorly differentiated subtype of non-small cell lung cancer accounting for 0.1-0.4% of all lung malignancies. They

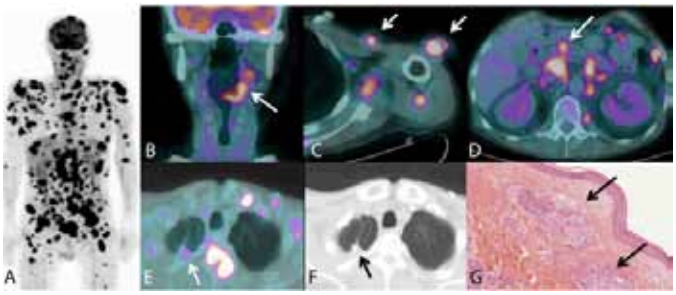


Figure 1: (A) Maximum intensity projection of whole-body ^{18}[F]-FDG PET scan suggesting multisystem and profuse metastatic relapse of a cancer, (B) Uptake of the left epiglottic lesion (white arrow), head and neck coronal slice, (C) Disseminated uptakes of cutaneous, subcutaneous (whites arrows) and muscular nodules, left shoulder axial slice, (D) Pathological uptake of the head of the pancreas (white arrow) and abdominal lymphadenopathies, (E , F) Moderate uptake on a lesion of the right upper lung lobe (white arrow on ^{18}[F]-FDG PET/CT and black arrow on CT), and (G) Histopathological slice of a cutaneous lesion biopsy showing a dermal metastasis of a well differentiated carcinoma with vascular embols (blacks arrows) and a healthy epidermis (magnification x10).

occur mostly in smoking males, at an average age of 60 years. With a high frequency of local recurrence and distant metastatio, they are responsible of an aggressive clinical course. Microscopically, this poor prognostic disease is the result of a biphasic proliferative malignant cells with both carcinoma and sarcomatoid components. Immunohistochemically, TTF-1, a specific marker of thyroid and pulmonary tumors such as adenocarcinoma and small cell carcinoma, is find to be positive in more than 50% of PSCs [1]. Head and neck squamous cell carcinoma (HNSCC), as far as they are concerned, preferentially metastasise to cervical lymph nodes. They have an uncommon hematogenous spread varying from 4.2–23.8%, up to 57% at autopsies on the lungs (80%), mediastinal nodes (34%), bone (31%) and liver (31%). Distant metastatic clearly affect the prognosis of HNSCCs and if not present at initial presentation it usually becomes apparent within two years [2]. Even so their clinicopathological predictive factors of occurrence are the site of the primary tumor (oropharynx, hypopharynx and larynx), multilevel nodal involvement in neck and primary tumor invasion into muscular, bone or cartilage ; metastatic screening by ^{18}[F]-FDG PET/CT can detect them early, before the onset of medical complications [3]. Detection of occult disseminated disease without curative options allow avoiding all futile treatment, counseling patients about prognosis and optimizing their quality of life [4]. Cancer-related hypercalcemia is most common in patients with lung, breast, head and neck and kidney cancer. It could be related either to osteolysis of the severe bone metastases -that was probably the reason for this atypical patient- or a paraneoplastic syndrome. Having a strong correlation with the stage of the primary tumor and the development of recurrence or metastasis, hypercalcemia has an adverse impact on survival of OSCC. Its early recognition could help to recognize occult neoplasms leading to a proper therapeutic strategy and so prolong survival with a better quality of life [5].

CONCLUSION

This atypical case illustrates the utility of whole-body ^{18}Fluorine-fluorodeoxyglucose positron emission tomography computed tomography (^{18}[F]-FDG PET/CT) scan in the follow-up of head and neck squamous cell carcinoma (HNSCC) that can have a fatal issue due to distant metastatic and their resulting metabolic disorders such as hypercalcemia, more than their common local aggressive growth. Screening progression in these patients may help to anticipate the complications that are difficult to be managed.

Keywords: Cancer, Distant metastasis, Pulmonary sarcomatoid carcinoma, Head and neck squamous cell carcinoma

How to cite this article

Bera G, Malouf G, Yeni N, Lepoutre-Lussey C. 101 spots: find the primary site. Int J Case Rep Images 2015;6(11):727–729.

doi:10.5348/ijcri-201535-CL-10090

****

Acknowledgements
Professor Aurelie KAS MD. PhD., Department of Biophysic UPMC Paris VI, LIB, INSERM UMR 678, 91 Bd de l'hôpital 75651 Paris Cedex 13 France and Department of Nuclear Medicine, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital 75651 Paris Cedex 13 France.

Pathology Department, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital 75651 Paris Cedex 13 France.

Head and neck Oncology concertation meeting, AP-HP Hospital Pitié-Salpêtrière, 47-83 Bd de l'hôpital 75651 Paris Cedex 13 France.

Author Contributions
Geraldine Bera – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Gabriel Malouf – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Nathanaëlle Yeni – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Charlotte Lepoutre-Lussey – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

REFERENCES

1. Rossi G, Cavazza A, Sturm N, et al. Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements: a clinicopathologic and immunohistochemical study of 75 cases. Am J Surg Pathol 2003 Mar;27(3):311–24.
2. Takes RP, Rinaldo A, Silver CE, et al. Distant metastases from head and neck squamous cell carcinoma. Part I. Basic aspects. Oral Oncol 2012 Sep;48(9):775–9.
3. Ferlito A, Buckley JG, Rinaldo A, Mondin V. Screening tests to evaluate distant metastases in head and neck cancer. ORL J Otorhinolaryngol Relat Spec 2001 Jul-Aug;63(4):208–11.
4. de Bree R, Haigentz M Jr, Silver CE, et al. Distant metastases from head and neck squamous cell carcinoma. Part II. Diagnosis. Oral Oncol 2012 Sep;48(9):780–6.
5. Chen YW, Chen IL, Lin IC, Kao SY. Prognostic value of hypercalcaemia and leucocytosis in resected oral squamous cell carcinoma. Br J Oral Maxillofac Surg 2014 May;52(5):425–31.