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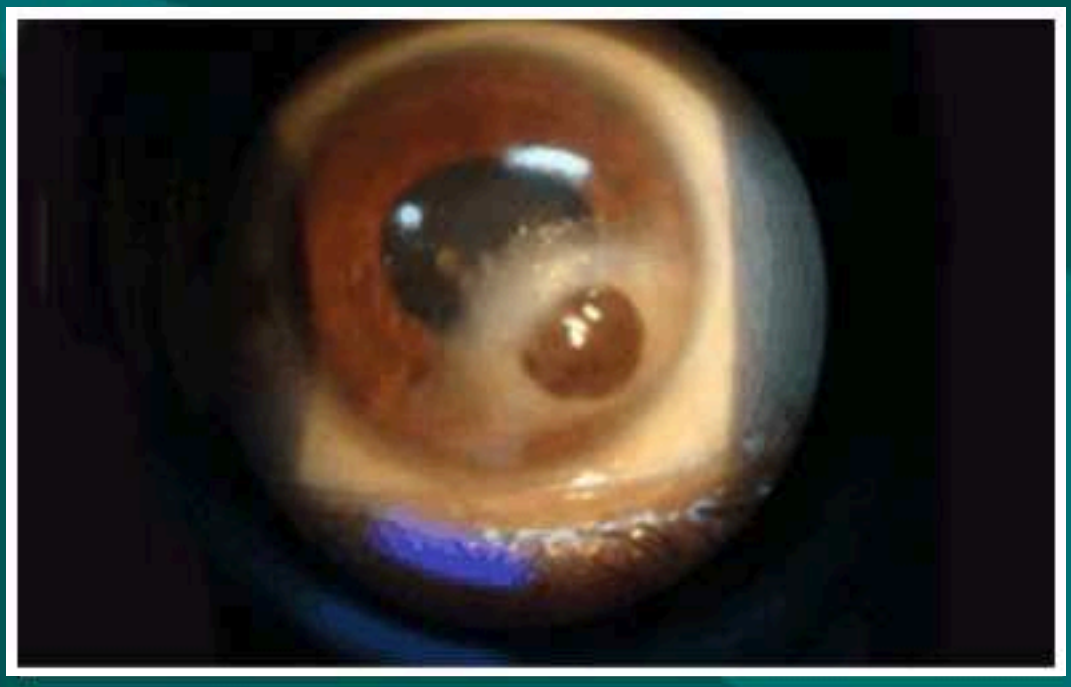

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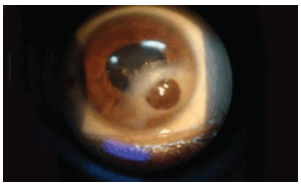

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REVIEW ARTICLE OPEN ACCESS

Photodynamic therapy: A new modality treatment in pre-cancer and cancer patients

Nagalaxmi Velpula, Kotya Naik Maloth, Srikanth Kodangal, Vani Chappidi, Stuti Goyal, Swapna Lingam

ABSTRACT

Introduction: Photodynamic therapy (PDT) is a new modality of therapy being used for the diagnosis and treatment in pre-cancer and cancer patients and various skin diseases. Photodynamic therapy is a powerful light-initiated photochemical reaction, involving the use of a photoactive dye (photosensitizer) activated by light of a specific wavelength in the presence of oxygen. This leads to the formation of oxygen free radicals which are toxic, which can damage proteins, lipids, nucleic acids and other components. Application of photodynamic therapy in dentistry is growing rapidly for the use of oral pre-cancers and cancer lesions, bacterial and fungal infections. Photodynamic antimicrobial chemotherapy (PACT) has been efficacious in the management of periodontal infections, peri-implantitis, endodontic infections and oral bio-films formation. The absence of genotoxic and mutagenic effects and no risk of developing resistance to its antimicrobial action made its use important. Photodynamic therapy is limited to superficial lesions at present. However, in future a deeper effect can be achieved by the developments in this technique. This review gives a general summary of the mechanism and clinical applications of photodynamic therapy.

Keywords: Photodynamic therapy (PDT), Photosensitizers, Photodynamic Antimicrobial chemotherapy (PACT)

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INTRODUCTION

Photodynamic therapy (PDT) is a medical treatment and it is a promising new approach for the treatment of cancers. It utilizes light to activate a photoactive dye (photosensitizer) in the presence of oxygen. This results in the formation of oxygen species, such as singlet oxygen and free radicals, causing localized photo damage and cell death. Clinically, this reaction is cytotoxic and vasculotoxic. Photodynamic therapy is also known as photoradiation therapy, phototherapy, or photochemical therapy. It also has antimicrobial properties. Photodynamic antimicrobial chemotherapy (PACT) includes an alternative antibacterial, antifungal and antiviral treatment for drug resistant organisms. Now-a-day's applications of PDT in dentistry are growing rapidly in the treatment of oral cancer, bacterial and fungal infections and the photodynamic diagnosis (PDD)

of the malignant transformation of oral lesions. The non-oncological applications of PDT include treatment of psoriasis, actinic keratosis, rheumatoid arthritis, and age-related macular degenerations [1].

HISTORY

The use of sunlight for the treatment of various skin disorders (heliotherapy) in ancient Indians and Greeks was present. The early 1900s lead to the discovery of photodynamic therapy by a German medical student, Oscar Raab observed by chance that the dye, acridine orange in the presence of light was toxic to protozoa (*Paramecium caudatum*) [2, 3]. His professor, Von Tappeneir, coined the term 'photodynamic' to describe oxygen consuming chemical reactions in vivo. In 1904, von Tappeiner and Jesionek (a dermatologist) used topical eosin and visible light to treat skin tumors, condyloma lata and lupus vulgaris [4, 5]. The first study on humans performed by German physician Friedrich Meyer–Betz with Porphyrins on his own skin in 1913 and named it photoradiation therapy (PRT) [6]. Photodynamic effects on tumors were reported until 1942 by Auler and Banzer, who injected tumor-bearing animals with hematoporphyrin and exposed them to a quartz–halogen lamp, observing necrosis and fluorescence of tumors [2, 7]. Dougherty et al. demonstrated a partial or complete response in tumors in humans when hematoporphyrin derivative (HpD) and light at 630 nm were used together [2, 8]. Hayata et al. the first to use fibroptic laser exposure to treat early bronchial cancer with PDT in 1982 [2, 9].

It was John Toth, who acknowledged the "photodynamic chemical effect" of the therapy with early clinical argon dye lasers and renamed 'photodynamic therapy'. Photodynamic therapy received even greater interest as Thomas Dougherty formed the international photodynamic association, in 1986. Its use first started in dermatology (1992), then oncology (1995), and recently in microbiology (1996) [10].

Photodynamic therapy involves three components light source (Figure 1), photosensitizing agent (photosensitizer) and tissue oxygen [1].

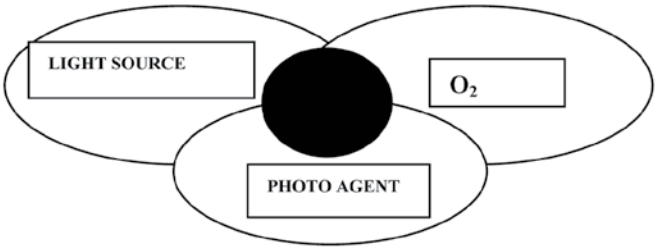

Figure 1: Photodynamic therapy involves three components—light source, photosensitizer and tissue oxygen.

LIGHT SOURCE

Photodynamic therapy requires a source of light that activates the photosensitizers (photo-active dye) by exposure to low-power visible light at a specific wave length. The therapeutic window for PDT is between 630 nm and 1200 nm as a light of wavelength, below 630 nm is absorbed by hemoglobin in the tissues and above 1200 nm is absorbed by water [11]. Human tissue transmits red light between 630 nm and 700 nm efficiently, and longer wavelength of the photosensitizers results in deeper light penetration. Most photosensitizers are activated by red light between 630 nm and 700 nm, penetration depth from 0.5 cm (at 630 nm) to 1.5 cm (at 700 nm) [1]. In the past, various variety of light sources, such as argon-pumped dye lasers, potassium titanyl phosphate (KTP) or neodymium: yttrium aluminium garnet (Nd/YAG)-pumped dye lasers, and gold vapor-pumped or copper vapor-pumped dye lasers were used. All these are complex systems and expensive. At present diode laser are used which are easy to handle, portable, and cost effective [1]. Non-coherent light sources, such as tungsten filament, quartz halogen, xenon arc, metal halide, and phosphor-coated sodium lamps are used for treatment of larger areas. Recently, non-laser light sources, are used mostly, such as light-emitting diodes (LED) which are much less expensive, small, lightweight, and highly flexible [1]. The absorption of light source by tissues is wavelength-dependent and tissue-penetration is greater at longer wavelengths [2]. The total light dose, the dose rates, and the depth of destruction vary with each tissue treated and with each photosensitizer [1].

The following are light sources specifically designed for PDT [11]:

1. Red light emission for large surface areas-metal halogen lamp (600–800 nm high power density).
2. Short arc xenon lamp (400–1200 nm).

PHOTOSENSITIZING AGENTS

A Photosensitizer is a chemical compound (usually a dye) is administered (injected or applied topically) to the patient and gets accumulated into the tissues. The tissue is then irradiated with light of a specific wavelength. Thousands of natural and synthetic photoactive compounds have photosensitizing potential. They include degradation products of chlorophyll, polyacetylenes, thiopenes, quinines, antraquinones, and 9-methoxypsoralen [1]. The majority of the photosensitizers used clinically belong to dyes, the porphyrins, chlorins, and furocoumarins.

Ideal photosensitizers should be: [1]

- Non-toxic
- Local toxicity only after activation by light source
- Accumulate maximally in tumors in short time
- High quantum yield of singlet oxygen production in vivo

- Cost effectiveness and commercial availability
- High solubility in water, injection solutions, and blood substitutes
- Short half-life period
- Rapid clearance from tissues.
- Storage and application light stability.

The various photosensitizing agents can be grouped under three generations.

First generation

The following are second generation photosensitizer:

- Photofrin dihematoporphyrin-ester (DHE)
- Hematoporphyrin derivatives (HPDs).

DHE under the commercial name of Photofrin has been most commonly used, the depth of necrosis achieved by Photofrin induced PDT is about 0.5 cm. It has no systemic toxicity except prolonged photosensitivity (approximately 6–8 weeks) [2].

Second generation

The following are second generation photosensitizer:

- 5-Aminolevulinic acid (ALA)
- Benzoporphyrin derivative (BPD)
- Temoporfin Meta-Tetra-Hydroxy Phenyl Chlorin (mTHPC)
- Talaporfin sodium (LS11)
- Foscan (mTHPC)

5-Aminolevulinic acid (ALA) is an intrinsic photosensitizer that is converted in situ to a photosensitizer, Protoporphyrin-IX. The depth of necrosis produced by ALA induced PDT not more than 1.5 mm, therefore topical ALA and its esters have been used to treat pre-cancer conditions, and basal and squamous cell carcinoma of the skin [1, 2].

The advantage of ALA over HPDs is that, it is cleared from the body more rapidly. Foscan (m-THPC), the most potent drug, induced PDT offers deeper tumor destruction (1 cm) and larger tumors (up to stage T1 tumors) can be effectively treated [2].

Third generation

The following are third generation photosensitizer:

Currently available drugs are modified by targeting with monoclonal antibodies or with non-antibody based protein carriers and protein receptors, and conjugation with a radioactive tag [1].

Currently, only four photosensitizers are commercially available namely, Photofrin, ALA, Visudyne (verteporfin) and Foscan. The first three have been approved by FDA, while all four are in use in European countries [1].

MECHANISM OF ACTION

The efficacy of PDT depends on the following mechanisms (Figure 2), direct cytotoxicity, vascular damage, inflammation and immune host defence [11].

After irradiation with a light of specific wavelength the photosensitizer under goes a transition from its ground singlet state to an excited singlet state (has high energy and short-life span). The excited singlet state molecule may follow two pathways:

(a) The molecule may decay back to its ground state emitting fluorescence light. This fluorescence property has been used diagnostically for detecting the sensitizers in tissues and for tumor localization.

(b) For the photodynamic reaction, the molecule must convert to a excited triplet state (has lower energy and longer life span) [2].

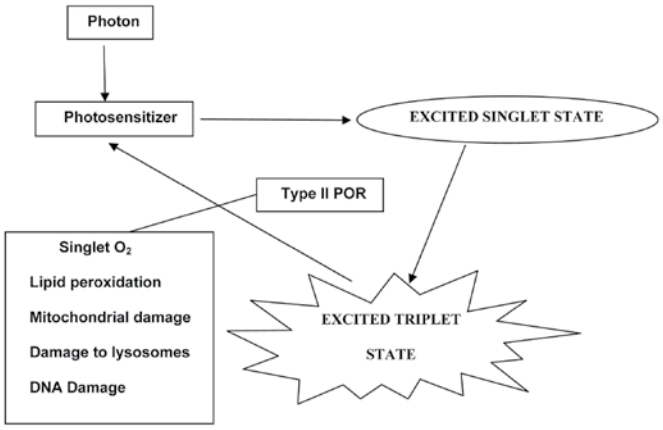

Figure 2: Mechanism of photodynamic therapy with in the cell.

The triplet state can react with endogenous oxygen present in the tissue to produce singlet oxygen (highly reactive) and other free radical species, causing a rapid and selective destruction of the target tissue. There are two mechanisms of this process:

(a) Type-I reaction involves electron transfer directly from the photosensitizer producing ions or electrons/hydrogen removal from a substrate molecule to form free radicals. These radicals react rapidly with oxygen, resulting in the production of highly reactive oxygen species (superoxide, hydroxyl radicals, and hydrogen peroxide).

(b) Type II photo-oxidation reaction (POR) produce the electronically excited and highly reactive state of oxygen (singlet oxygen).

These two reactions contribute equally in the photodynamic process of reaction [1, 11]

SIDE EFFECTS OF PHOTODYNAMIC THERAPY

The side effects of PDT are:

- The major side effect after the use of intravenous photosensitizers is photosensitivity.
- The systemic administration of the sensitizer results in residual skin photosensitivity, nausea, vomiting, metallic taste, and liver toxicity [11].
- Topically applied photosensitizer (ALA) reports burning sensation during illumination.

- Other side effects are coughing, trouble swallowing, stomach pain, painful breathing or shortness of breath. These side effects are usually temporary [1, 11].
- 5-Aminolevulinic acid may cause tachycardia and hypotension in patients with cardiovascular problems [2].

INDICATIONS OF PHOTODYNAMIC THERAPY

In 1993, Canada first approved PDT for prophylaxis of papillary bladder cancer.

Potential indications for PDT in oral medicine [11], dermatology and oncology are:

- Actinic keratosis
- Bowen disease
- Superficial squamous cell carcinoma and basal cell carcinoma
- Keratoacanthoma
- Kaposi's sarcoma
- Actinic cheilitis
- Cutaneous metastases
- Psoriasis vulgaris
- Malignant melanoma
- Early head and neck cancers
- Pre-malignant lesions and conditions in the oral cavity

ADVANTAGES OF PHOTODYNAMIC THERAPY

The advantages of PDT are [1, 10]:

- Photodynamic therapy is a localized therapy and it has only localized effects as the photosensitizer is selectively absorbed by the target tissues.
- Photodynamic therapy can be performed in out-patient or inpatient settings.
- Photodynamic therapy is more economical than radiation therapy and surgical therapy for cancer patients.
- Less invasive, no long-term side effects and can be repeated many times at the same site, if needed.
- Photodynamic therapy has excellent cosmetic results and the healing process results in little or no scarring.

LIMITATIONS OF PHOTODYNAMIC THERAPY

The limitations of PDT are [1, 10]:

- Light is needed to activate photosensitizers.
- Photosensitizers cannot penetrate more than 1.5 cm of tissue depth using with standard lasers and low powered LED technology, and hence it is less effective in treatment of large tumors.
- Photodynamic therapy cannot be used in patients, who are allergic to porphyrins.

The PDT in pre-cancer and cancer lesions is as follows.

Leukoplakia

The following are first generation photosensitizer:

Oral leukoplakia, oral erythroplakia and oral verrucous hyperplasia (OVH) are three common oral precancerous lesions. The high malignant transformation rate of oral premalignant lesions highlights the importance of early detection and treatment.

Traditional treatment for oral pre-cancers is total surgical excision that always leads to scar formation. Photodynamic therapy is an effective treatment option for human precancerous lesions because it can be used repeatedly without cumulative side effects and results in little or no scar formation [12].

The application of photodynamic therapy in oral leukoplakia significantly reduces the time of treatment in comparison with pharmacological methods involving vitamin A or active metabolites of vitamin A. Application of vitamin A requires 2 to 3 months to complete cure [13].

In 1996, Fan et al. treated oral leukoplakia cases of 12 patients using orally administrated ALA-based PDT. All 12 patients showed regression of the lesions to normal or less dysplastic [1] In 1998, Kuber et al. treated 12 patients who had been suffering from leukoplakia of the oral mucosa for several years. ALA (20% cream) was applied to the leukoplakia lesion for 2 hours. Five patients showed complete response, four patients showed a partial response and in three patients showed no response. In 2005, Chen et al. treated oral verrucous hyperplasia cases of eight patients and oral leukoplakia cases of 24 patients using topical ALA-PDT (20% gel). A complete regression of OVH was obtained and partial response of oral leukoplakia after eight treatments twice a week [1]

Oral Lichen Planus

The following are second generation photosensitizer:

Lichen planus is a relatively common chronic inflammatory mucocutaneous disease. Although the cause is not well known, T cell- mediated autoimmune phenomena are involved in the pathogenesis of lichen planus [14]. The reported frequency of malignant transformation varies greatly from 0.4% to more than 5% over a period of 0.5 to more than 20 years. Treatment options for oral lichen planus are numerous, including topical, intra lesional and systemic corticosteroids, topical cyclosporine and tacrolimus, topical and systemic retinoid, however, outcomes are often disappointing. So searching for new treatment modalities seems quite rational. The exact mechanism of action of PDT is unclear. It has been suggested that PDT may have immunomodulatory effects and may induce apoptosis in the hyper-proliferating inflammatory cells, which are present in psoriasis and lichen planus. This may reverse the hyper- proliferation and inflammation of lichen

planus [14]. Kirby et al. reported one case of hypertrophic lichen planus on the penis treated using ALA-mediated PDT twice in a week. The lesion had completely resolved after 4 weeks. At six-month follow-up there was no recurrence. Aghahosseini et al. in 2006 conducted a study in 13 patients with 26 oral lichen planus lesions with methylene blue-mediated photodynamic therapy (MB-PDT). Patients were instructed to gargle a 5% methylene blue solution in water for 5 minutes and irradiation was performed by laser light 10 minutes later. Lesions were evaluated preoperatively and postoperatively and at follow-up sessions by changes in sign and symptom (pain) scores and size of lesions. Improvement in sign scores was achieved in 16 lesions and four reticular oral lichen planus lesions disappeared completely. There was a statistically significant decrease in sign and symptom scores 1 week after treatment and at follow-up sessions up to 12 weeks. Average reduction in size of lesions was 44.3%. They concluded that MB-PDT seems to be an effective alternative treatment for control of oral lichen planus [14].

Aghahosseini et al. in 2006 conducted a study at the clinic of Iranian center for medical laser in which two patients with five oral lichen planus lesions were treated using topical PDT mediated by methylene blue (MB-PDT). Ten minutes prior to laser irradiation, patients gargled MB for 5 minutes. A diode laser (632 nm) was used as light source. The patients were followed-up on sessions 3, 7, 15 days and 1 to 9 months after PDT. Clinical improvement was achieved in 4 lesions. Two lesions showed complete remission, and another two lesions had about 50% clinically improvement 3–9 months after a single session of PDT. No response was detected in one lesion. MB-PDT seems to be an effective alternative treatment for control of oral lichen planus [15].

Oral Squamous Cell Carcinoma

The following are third generation photosensitizer:

Squamous cell carcinoma of larynx and oral cavity may be treated effectively with single-modality therapy. The preferred treatment modality is surgery for early-stage oral cancer and radiotherapy for early laryngeal cancer. However, irradiation and surgery may result in long-term morbidity. The limitation of surgical resection in the oral cavity and larynx is that it leads to the removal of vital functional tissue, such as part of the tongue in the oral cavity, which may affect speech and swallowing [16].

Radiotherapy to the oral cavity often results in long-term morbidities, such as xerostomia, dysphagia, loss of dentition, and risk of osteoradionecrosis. An optimal treatment for moderate to severe dysplasia and early carcinomas of the oral cavity and larynx would be one that is safe, effective, repeatable, minimally invasive, and devoid of permanent sequelae is the photodynamic therapy [16].

Advantage of photodynamic therapy over conventional treatment modalities in head and neck carcinoma:

The main advantage of PDT for dysplasia and early carcinoma of the larynx is the ability to preserve normal endolaryngeal tissue while effectively treating the lesion. This results in preservation of laryngeal function and voice quality. It may be performed in an outpatient setting using a single non-invasive light activation treatment, requiring a short duration for therapy. Photodynamic therapy can be repeated without the additional permanent functional laryngeal impairment that can occur with repeated conventional laser surgery or cordectomy. Photodynamic therapy spares the tissue architecture, providing a matrix for regeneration of normal tissue by leaving sub epithelial collagen and elastin intact, and spares non-cellular supporting elements. A further more important positive aspect of PDT is that it can be repeated [16].

Fan et al. in 1996 conducted a study in which 18 patients with histologically proven premalignant and malignant lesions of the mouth were sensitized with 60 mg/kg ALA by mouth and treated with laser light at 628 nm (100 or 200 J/cm^2). They concluded that PDT using ALA for dysplasia of the mouth produces consistent epithelial necrosis with excellent healing and is a simple and effective way to manage these patients. Results in invasive cancers are less satisfactory; mainly because the PDT effect is too superficial with current treatment regimens using ALA as the photosensitizing agent [17]. Colin Hopper (2000) stated that PDT is a minimally invasive treatment with great promise in malignant disease. It can be applied before, or after, chemotherapy, ionizing radiation, or surgery, without compromising these treatments or being compromised itself. Unlike radiotherapy and surgery, it can be repeated many times at the same site. Response rates and the durability of response with PDT are as good as or better than, those with standard loco regional treatments [18]. Schweitzer (2001) conducted a study to determine the efficacy of Photofrin mediated photodynamic therapy. Ten patients with early stage squamous cell carcinoma of oral cavity and oropharynx and 10 patients with squamous cell carcinoma (SqCCa) of the larynx were treated. They concluded that Photofrin-mediated PDT provides a surgical oncologic modality for potentially curative treatment of early stage oral cavity and laryngeal malignancies with minimal side effects [19].

Verrucouscarcinoma

The following are fourth generation photosensitizer:

Chen et al. (2005) conducted a study and showed that a new topical 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) protocol using a light-emitting diode (LED) light source is an effective and successful treatment modality for five cases of oral verrucous hyperplasia and one case of verrucous carcinoma. They concluded that complete regression of oral verrucous hyperplasia lesions can be achieved by less than six treatments of topical ALA-PDT once a week. Although the response of oral leukoplakia lesions to the topical ALA-PDT is not as good as the response of oral verrucous hyperplasia lesions to the same therapy, all

oral leukoplakia lesions can have at least PR after eight treatments with the topical ALA-PDT twice a week. In addition, oral leukoplakia lesions treated twice a week have a significantly better clinical outcome than oral leukoplakia lesions treated once a week [20]. Chen et al. (2005) tested the efficacy of this new treatment protocol of ALA-PDT for an extraoral verrucous carcinoma lesion at the right mouth angle and an intraoral verrucous carcinoma lesion at the right buccal mucosa of a 56-year-old male areca quid chewer and smoker. The extra oral tumor was cleared after six treatments of topical ALA-PDT and the intraoral tumor showed complete regression after 22 treatments of topical ALA-PDT. No recurrence of the verrucous carcinoma lesion was found after a follow-up period of six months. They suggested that new topical ALA-PDT protocol composed of multiple three-minute fractionated irradiations with a light emitting diode (LED) red light at 635 +5 nm for a total of 1000 s after topical application of 20% ALA for 1.5 or 2 h can be used successfully for the treatment of oral verrucous hyperplasia [21, 22].

CONCLUSIONS

Photodynamic therapy (PDT) is an alternative modality for the treatment of certain cancers. The success of PDT lies in the right combination of the parameters like photosensitizers and specific wavelength light and the application of PDT needs careful monitoring. At present, PDT is most successful for the superficial lesions of the epithelium such as basal cell cancer, microinvasive and intraepithelial dysplasias. The maximum depth of necrosis achieved by PDT is at around 1 cm hence it is not suitable for lesions greater than 1 cm diameter. Treatment of bulky tumors may be possible with interstitial PDT which involves insertion of fiber-optics in the tumor bed. In addition, PDT can be used intra-operatively just after the surgical removal of cancers which may help elimination of the residual tumor cells. During the past 30 years, PDT has been employed in the treatment of many tumor types, and its effectiveness as a curative and palliative treatment is well documented. “But why is its role in other disciplines still marginal?” In general, it is difficult to persuade clinicians to use a new technique when standard treatments yield a high response rate. Although lasers have become much less expensive, the setup of a new PDT centre remains costly. For the establishment of PDT in the routine clinical practice for the treatment of cancers, well designed preclinical studies and clinical trials are required.

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Author Contributions

Nagalaxmi Velpula – 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
Kotya Naik Maloth – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Srikanth Kodangal – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Vani Chappidi – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Stuti Goyal – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Swapna Lingam – Analysis and interpretation of data, 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.

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REVIEW ARTICLE OPEN ACCESS

Antioxidants and their implication in oral health and general health

Lingam Amara Swapna, Koppolu Pradeep, Padma Reddy, Koppolu Deepak, Stuti Goyal

ABSTRACT

Introduction: Oxygen is extremely crucial for the existence of higher organisms. As the saying goes too much of even the best is awful. High and soaring concentration of oxygen are found to be toxic, and can damage tissues. Free radicals can adversely alter lipids, proteins and DNA and have been implicated in aging and in number of human diseases. Lipids are highly prone to free radical damage resulting in lipid peroxidation that can lead to adverse alterations. Free radical damage to protein can result in loss of enzyme activity. Damage caused to DNA, can result in mutagenesis and carcinogenesis. Nature has endowed us with protective antioxidant mechanisms from many dietary components. Thus, a greater consumption of fruits and vegetables should be encouraged as they are the natural sources of these chemopreventive antioxidants with other protective factors.

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INTRODUCTION

In recent years there is an upsurge in the areas related to newer developments in prevention of disease especially the role of free radicals and antioxidants. This review compiles the pertinent possible role of 'free radicals' in disease and 'antioxidants' in its prevention, especially the current status of the antioxidants in oral diseases and future prospects and their application in dentistry. Antioxidants are compounds used by aerobic organisms for protection against oxidative stress, induced by free radicals and active oxygen species. They exert their protective action either by suppressing the formation of free radicals or by scavenging free radicals [1, 2]. A wide range of biological effects, established experimentally, may inhibit carcinogenesis. These include effects on tumor initiation, promotion and progression, cell proliferation and differentiation, as well as DNA repair, cell membrane stability and immune function [3, 4]. Dietary antioxidants such as carotenoids, vitamins C and E and selenium have received much attention as potential cancer chemopreventive agents.

Types of free radicals

Oxygen is required in many metabolic reactions, particularly for the release of energy. During these

processes, molecular oxygen is completely reduced and converted to water. However, if the reduction of oxygen is incomplete, a series of reactive radicals are formed [5–7].

Reactive oxygen species play an important role in cell signaling and metabolic processes, but also contribute to pathogenic processes in a variety of inflammatory disorders [7–11].

Healthy individuals maintain a balance between the reactive oxygen species and antioxidants.

Harmful effects of free radicals

Free radicals are highly reactive and are capable of damaging almost all types of biomolecules [2, 4]. The fact is that free radicals beget free radicals, i.e., generate free radicals from normal compounds which continue as a chain reaction.

Free radicals and diseases

Free radicals have been implicated in the causation and progression of several diseases such as

- Cardiovascular disease
- Cancer
- Inflammatory diseases
- Respiratory diseases
- Diabetes
- Cataract formation
- Male infertility
- Aging process
- Other diseases: Parkinson's disease, Alzheimer's disease, multiple sclerosis, liver cirrhosis, muscular dystrophy, toxemia of pregnancy, etc.

Antioxidants according to their location:

The following are some antioxidants according to their location [1, 5]:

(i) Plasma antioxidants: β-carotene, ascorbic acid, bilirubin, uric acid, ceruloplasmin, transferring.

(ii) Cell membrane antioxidants: α-tocopherol.

(iii) Intra-cellular antioxidants: superoxide dismutase, catalase, glutathione peroxidase.

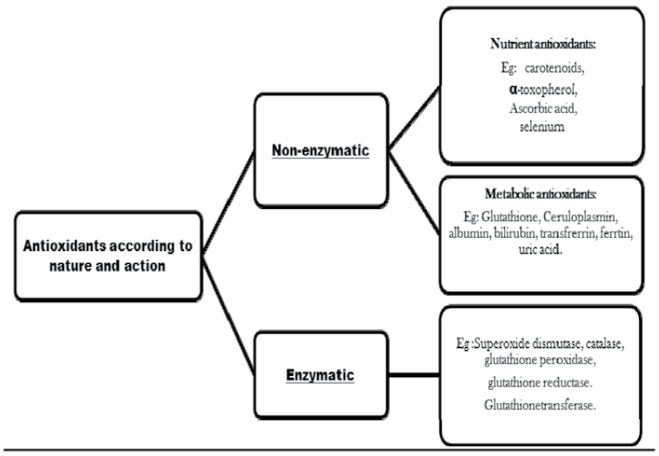

Figure 1: Type of Antioxidants.

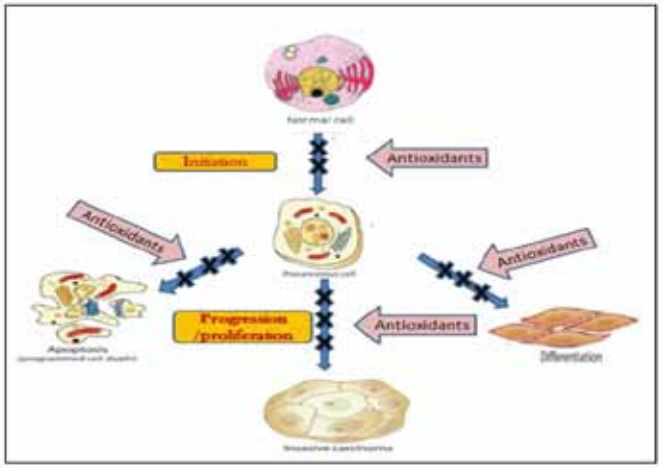

Figure 2: Proposed mechanism through which the antioxidants act. The Xs indicate the agent is hypothesized to inhibit carcinogenesis either by blocking initiation, progression/ proliferation or angiogenesis.

ANTIOXIDANTS ROLE IN THE PREVENTION OF CANCER

Antioxidants are considered as the scavengers of free radicals. DNA damage is the main culprit in the development of cancer. Greater extent of this damage is because of oxidative stress. Antioxidants are proved to cause the regression of premalignant lesions and also inhibit their development into cancer [12, 13]. In general, high intake of fruits and vegetables are associated with a protective effect against cancer (Figure 1 and 2) [14, 15].

LYCOPENE

Lycopene is an important antioxidant abundant in tomatoes. Lycopene has been hypothesized to prevent carcinogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. According to various studies, lycopene, when given in the dosage of 4.8 mg/day orally for three months, leads to the reversal of dysplastic changes in leukoplakia and when given in the dosage of 16 mg/day leads to substantial increase in the mouth opening in oral submucous fibrosis. On average, the daily permissible intake of lycopene is estimated to be 3.7 mg [16, 18].

Carotenoids: These are found in enormous quantities in green and yellow leafy vegetables. In addition, they have many other beneficial properties [19]. Furthermore, these compounds are comparatively nontoxic. Observational studies have indicated a protective effect of carotene rich vegetables, β-carotene, and carotenoids, on cancers of the oesophagus, colorectum, stomach, cervix, oropharynx,

lung, and prostate [20–23].

Beta-carotene: A precursor of vitamin A has antioxidant and free radical scavenging property. It also helps in immunomodulation, promotes increase in the numbers of T-helper and NK cells as well as cells with IL-2 receptors and inhibits mutagenesis and cancer cell growth [13, 19–23].

Vitamin C: This is a water-soluble vitamin, an important free radical scavenger in plasma and acts to reinforce active vitamin E in lipid membranes. Vegetables, citrus fruits and tubers are good sources of vitamin C [24]. The confirmation for a protecting effect of vitamin C is stronger for cancer of the stomach, and upper aerodigestive tract and weaker for other types of cancer [22–23]. It reduces vitamin E degradation, enhances chemotaxis, phagocytosis, collagen synthesis, inhibits nitrosamine formation, enhances detoxification via cytochrome P450. Blocks formation of mutagens and reduces expression of oncogenes.

Vitamin E: The most biologically active form of vitamin E is *α-tocopherol*. It is fat-soluble vitamin, major lipid-soluble antioxidant of the cell membrane. It acts as a free-radical scavenger and inhibits peroxidation [25]. It has been reported to block the in vivo development of N-nitroso compounds [26]. Vegetable oils, whole-wheat products and nuts are amongst the best sources of vitamin E. Overall, observational epidemiological studies suggest a protective effect of vitamin E against cancers of the lung, colorectum and the cervix [27, 28]. It is a free radical scavenging antioxidant, maintains membrane integrity, immune function and reduce cancer cell growth/differentiation, cell cytotoxicity, inhibits mutagenicity and nitrosamine formation, preservation of DNA and RNA including protein synthesis in cancer cells [29].

Selenium: This is a trace element and a critical co-factor for the major antioxidant enzyme glutathione peroxidase, which catalyses the oxidation of hydroperoxide [30]. Selenium is also implicated in cell signaling and immune reactions, which may furnish to its cancer chemopreventive potential [31]. Selenium and vitamin E may mutually compensate deficiency of each other and act synergistically to slow down carcinogenesis. The amount of selenium that is in our food is estimated by the selenium content of the soil in which fruits and vegetables are grown. Seafood, liver and meat are also good sources of selenium [32].

Flavonoids: These are phenolic compounds with anticarcinogenic properties. Tea polyphenols, in particular, are strong scavengers of superoxide, hydrogen peroxide, hydroxyl radicals and nitrogen oxides and may enhance the levels of antioxidant enzymes such as catalase. Flavonoids are abundantly available in fruits, vegetables and tea leaves. A number of animal studies have confirmed that catechins, the main flavonoids found in tea leaves, prevent induction of cancers of lungs, colon, esophagus, pancreas, and liver [33, 34].

Isoflavones: These are found chiefly in soy products. Isoflavones are structural isomers of flavonoids and allocate biological properties with them. They have anti-estrogenic effects, and thus could act as chemopreventive agents in hormone dependent cancers. Genistein is a prominent isoflavone in soy foodstuffs known to promote apoptosis in vivo [35]. Epidemiologic studies advocate that population in Asian countries consuming high amounts of soy products may be at lower risk for prostate cancer and breast cancer [36].

Curcumin: This is a plant phenol widely used as a spice (curry) and food-coloring agent. In vivo and in vitro studies have demonstrated that it may prevent initiation of DNA damage and is involved in anti-promotion mechanisms such as apoptosis [37]. A number of animal studies have shown that curcumin is effective in inhibiting carcinogenesis in the skin, colon, stomach mammary gland and oral cavity [38].

Other diet-derived agents

Retinoids: The best known retinoid is vitamin A or retinol, found in foods of animal origin, such as liver, milk and dairy products, egg yolk and fish liver oils, they are required for the maintenance of normal cell growth and differentiation. In contrast to carotenoids, they act primarily in the post initiation phases of promotion and progression in carcinogenesis [39, 40].

Animal studies have shown that retinoids are potent to suppress or reverse epithelial carcinogenesis at several sites. The most promising results have been reported for oral carcinogenesis [41].

Vitamin D: 1,25-dihydroxyvitamin D3 (1,25-D3) is the active form of the fat-soluble vitamin D. Major dietary sources of vitamin D include liver, fatty saltwater fish and eggs. Vitamin D inhibits proliferation and DNA synthesis, alters expression of several oncogenes, reduces lipid peroxidation and angiogenesis and induces differentiation [42]. Epidemiologic studies support an inverse association among vitamin D intake and colorectal cancer risk [43].

Folic acid: It is majorly found in fresh fruits and vegetables. Together with vitamin B12, methionine and choline, it is involved in methyl group metabolism. Much of the basic cancer research has focused on DNA methylation, and hypomethylation has been associated with DNA abnormalities [44]. A converse association involving dietary folate intake and adenomatous polyps or colorectal cancer has been stated in both case–control and cohort studies [45].

THERAPEUTIC USE OF ANTIOXIDANTS FOR ORAL LESIONS

1. Prevention of lesions in high-risk individuals.
2. The treatment of premalignant oral lesions.
3. In order to prevent recurrence of the treated

initial lesion or to prevent the development of a second or a separate primary.

Different antioxidants show significantly different levels of effectiveness in different fats, oils, and food materials due to their different molecular structures.

Limitations of antioxidants

Antioxidant therapy in human reproductive medicine is still a controversy [17]. High doses of vitamin A showed to have embryotoxic and teratogenic effects. Large doses of vitamin C (ascorbic acid) may be associated with the inhibition of ovarian steroidogenesis and increased probability of abortion [18]. Antioxidants supplements were once thought to be harmless but increasingly we are becoming aware of their interactions and potential toxicity. Also, very little is known about the long-term consequences of megadoses of antioxidants.

CONCLUSION

Dietary antioxidants protect us from the harmful affects of free radicals. Considerable evidence indicates that foods with high antioxidants nutrients play a major role in disease prevention. Efforts should be made to make these important molecules as our daily health regimen.

Finally, it can be said that

"Vegetables like carrot, tomato might someday keep the doctor away !!
Eat "fresh red fruits and vegetables" every day…
Consume them in right amounts for a healthy and long life…".

****

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Author Contributions

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Padma Reddy – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

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Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Lymphomatoid granulomatosis presenting as tinnitus in a patient with acquired immunodeficiency syndrome

Renato Quispe, J Martin Rodriguez, David McCollum

ABSTRACT

Introduction: Puzzling neurologic symptoms in an immunosuppressed patient presents the clinician with a broad and challenging differential diagnosis. Multiple neurological complications in human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)-infected individuals have been reported, the most common being cognitive dysfunction, infections, and malignancies. In patients with advanced immunosuppression any neurological symptom should be taken seriously. We report a case of Epstein–Barr virus (EBV) related lymphomatoid granulomatosis presenting in a patient with AIDS initially as tinnitus. Case Report: A 42-year-old female was presented to her physician complaining of tinnitus. Unbeknownst to her physician, she had been diagnosed with human immunodeficiency virus (HIV) 14 years prior. Her tinnitus led her to undergo a workup in outpatient clinic. However, her neurological symptoms gradually progressed to include hearing loss and diplopia. She was admitted to another hospital and underwent an extensive array of testing. Laboratory testing indicated that her HIV had progressed to AIDS. Neurological imaging revealed a brainstem lesion. She was transferred to our hospital when the brainstem lesion was deemed inaccessible by neurosurgery. Several small pulmonary nodules had been noted on computed tomography scan of her chest. Surgical biopsy with pathology and flow cytometry of a lung nodule showed EBV-related lymphomatoid granulomatosis. Soon after, a unifying diagnosis between her lung nodules and a central nervous system disease was made as flow cytometry of her cerebrospinal fluid showed an identical aberrant B cell population consistent with lymphomatoid granulomatosis with transformation to diffuse large B cell lymphoma. Unfortunately, patient's brainstem lesions progressed and patient died after a few weeks in the hospital. Conclusion: Epstein–Barr virus related lymphomatoid granulomatosis is a rare disease that can be the cause of unexplained neurological symptoms in immunocompromised individuals. We report a challenging case in which the diagnosis was only considered after lung biopsy of relatively asymptomatic pulmonary nodules.

Keywords: Lymphomatoid granulomatosis, Epstein–Barr virus (EBV), Human immunodeficiency virus, Tinnitus

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INTRODUCTION

Human immunodeficiency virus (HIV) remains one of the world's most significant public health challenges, particularly in low and middle-income countries. According to the World Health Organization (WHO), 34 million people are living with HIV worldwide, and an estimated 2.5 million people were newly infected with the virus in 2011 [1]. Patients may present with a wide range of complications with diverse and puzzling symptoms, often involving multiple organ systems. While the epidemiology of neurological complications has changed considerably since the introduction of highly active antiretroviral therapy (HAART), a wide spectrum of neurological complications in HIV-infection individuals continues to be seen. Their development occurs due to a variety of mechanisms including loss of cell-mediated immunity, aberrant activation of the immune system, and HIV infection itself [2]. The vast majority are represented by opportunistic infections, mainly cryptococcal meningitis, cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML), tuberculous meningitis and cytomegalovirus (CMV) encephalitis. Cognitive disorders are common in HIV-infected individuals, ranging from asymptomatic neurocognitive disorders to full blown HIV-dementia. Although less frequent, HIV-related malignant diseases (i.e., primary CNS lymphoma) should also be considered [3]. Peripheral neuropathies, such as HIV myelopathy and polyneuropathy, continue to be relatively common and significantly impact on quality of life [4] . When dealing with an HIV-infected patient presenting with neurological symptoms, comprehensive testing often needs to be performed with multiple etiologies sought and excluded. In this case, we present a previously untreated HIV-infected patient, who presented with progressive neurological symptoms. Eventually her symptoms were determined to be caused by Epstein–Barr virus (EBV)-related lymphomatoid granulomatosis (LYG), a rare lymphoproliferative disorder that can transform into diffuse large B cell lymphoma [5].

CASE REPORT

A 42-year-old female with untreated HIV infection presented with a progressive neurological illness. For the previous two months, she had been noticing a feeling of fullness in her right ear and tinnitus. She was seen by an ENT physician who prescribed oral antibiotics and meclizine. Her symptoms progressed to involve her left ear, followed by bilateral hearing loss and diplopia. Review of systems was positive only for a dry cough for two months. She denied fever, shortness of breath or weight loss. She was diagnosed with HIV 14 years prior but never sought medical care. Otherwise she had no medical problems and took no medications.

The patient was admitted to an outside hospital, and was found to have bilateral ophthalmoplegia, nystagmus, and right-sided facial palsy. Initial laboratory studies included an unremarkable metabolic panel and mild leukopenia. Her CD4 count was 24 cells/mm^3 and HIV viral load was 33,000 copies/mL. Magnetic resonance imaging (MRI) scan of brain showed a single enhancing process of the right pons along with ependymal enhancement of the lateral ventricles. Cerebrospinal fluid (CSF) showed normal opening pressure, 84 white blood cells/mm^3 (91% lymphocytes), glucose of 10 mg/dL, and protein of 209 mg/dL. Differential diagnosis at this time was extensive with an infectious etiology considered most likely, but malignancy also a serious consideration. Some of the most likely considerations included tuberculosis, CMV disease, Cryptococcus, toxoplasma, lymphoma, and PML. Negative CSF studies included gram stain/culture, AFB smear/culture, cryptococcal antigen, VDRL, TB PCR, JC virus PCR, cytology and flow cytometry. The CSF studies were positive for CMV DNA (9,242 copies/mL) and EBV DNA (14,900 copies/mL). Negative studies of the serum and urine included bacterial and fungal cultures, RPR, PPD, QuantiFERON®-TB Gold, urinary Histoplasma antigen, toxoplasma antibody, and Aspergillus galactomannan. A bone marrow biopsy was unremarkable. Computed tomography (CT) scan of chest revealed a 2-cm left lower lung nodule and 12 smaller nodules scattered throughout the lungs. On bronchoscopy, bronchioalveolar lavage and biopsy revealed *Pneumocystis jiroveci* organisms and chronic inflammation without dysplasia; stains and cultures were otherwise negative. She received trimethoprim/sulfamethoxazole, steroids, and empiric antituberculous therapy. Nevertheless, during the three weeks she spent at the outside hospital, her illness progressed to complete deafness, severe vertigo, unsteady gait, right-sided leg weakness and slurring of speech. She was transferred to our hospital.

At our institution the patient was continued on *Pneumocystis* and TB therapy with addition of ganciclovir given the positive CMV CSF PCR. Repeat brain MRI scan showed impressive progression after 11 days with enhancing lesions now throughout her brainstem, cerebellum, right inferolateral putamen, right thalamus, bilateral periventricular region and mild hydrocephalus (Figure 1). The CT scan of the chest again showed nodules, some with mild halo effect and cavitation (Figure 2).

The patient made no clinical improvement. At this point, the multiple negative laboratory tests for infectious etiologies, along with the lack of response to empiric tuberculosis and CMV treatment had shifted our differential diagnosis in favor of a CNS malignancy, particularly an aggressive lymphoma. Neurosurgery consult recommended against brain biopsy given the high-risk location of the lesions. Antiretroviral therapy for HIV was considered, but initially deferred due to concern for potential catastrophic Immune Reconstitution Inflammatory Syndrome (IRIS) phenomenon should the

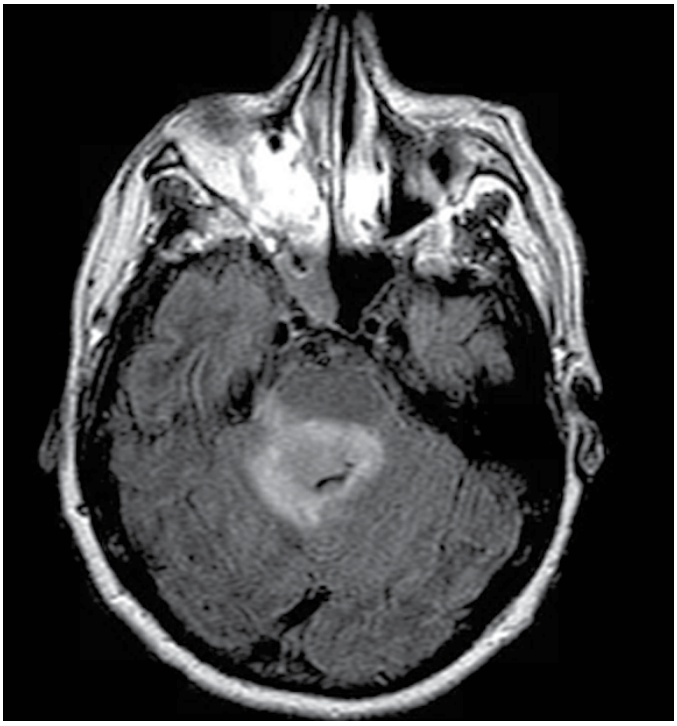

Figure 1: Magnetic resonance imaging of brain. T2/Flair imaging showing hyperintense process on in the brainstem with extension to cerebellum. Additionally, there were lesions present in the right thalamus and periventricular/ subependymal areas.

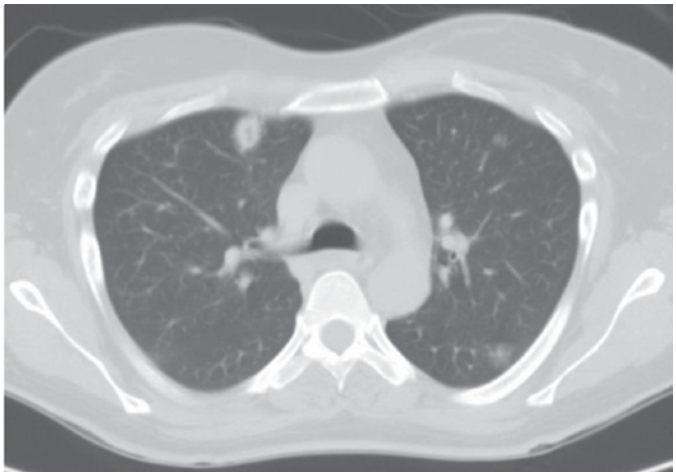

Figure 2: Computed tomography of chest showing multiple bilateral pulmonary nodules and a cavitation in the right lung.

brainstem lesions expand. On hospital day-3, a biopsy of the pulmonary lesions via video-assisted thoracoscopy (VATS) was obtained. Pathology of the pulmonary nodule revealed an angiocentric infiltrate of lymphocytes with large areas of necrosis. Within the infiltrate, certain areas showed a confluent sheet of atypical CD20-positive B cells (Figure 3). The B cells stained positive for EBV by chromogenic in situ hybridization (CISH) (Figure 4). These findings were consistent with lymphomatoid granulomatosis with areas of transformation to diffuse

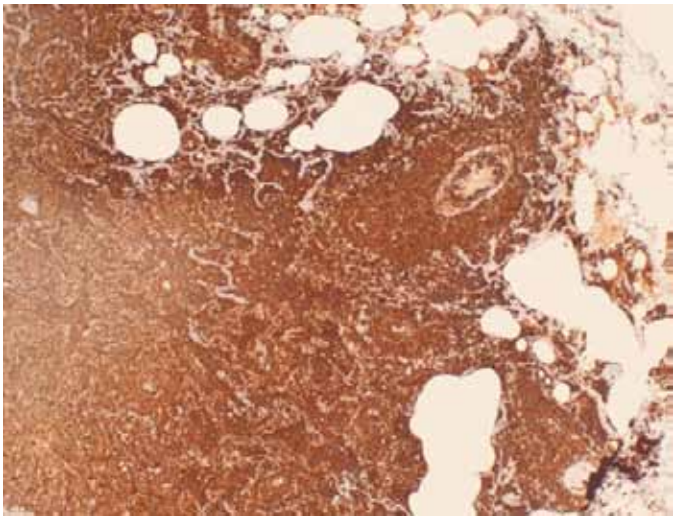

Figure 3: Area showing confluent sheet of large CD20-positive B cells within the infiltrate (Immunohistochemistry, CD20, x130).

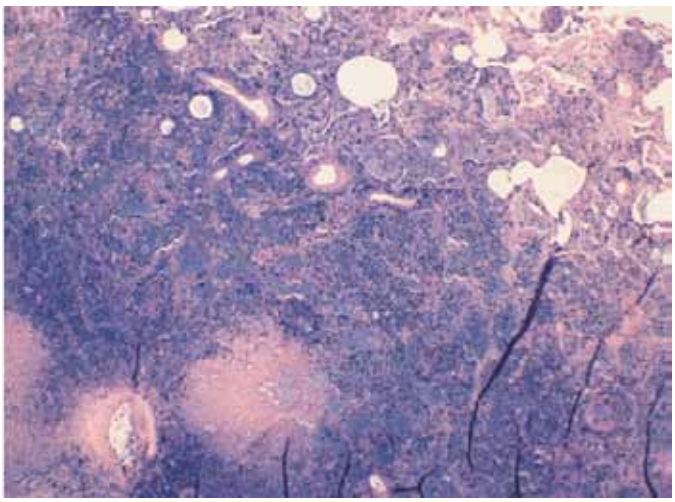

Figure 4: EBV-encoded RNA (EBER). B cells stained positive for EBV using chromogenic in situ hybridization (CISH, 130x).

large B cell lymphoma (DLBCL). Flow cytometry of the lung nodule revealed 31% aberrant B cells, consistent with non-Hodgkin lymphoma. Repeated lumbar puncture on hospital day-9 revealed that CSF EBV DNA had now increased to 146,000 copies/mL and CSF flow cytometry found an aberrant population of B-lymphocytes (CD20+, CD19+, CD10-, and lack surface immunoglobulin light chain expression) identical to those found in the lung nodule consistent with the diagnosis LYG with transformation to DLBCL. Hence a unifying diagnosis of both the pulmonary and CNS processes was made by the identical flow cytometry of the lung nodule and CSF.

DISCUSSION

Lymphomatoid granulomatosis is a rare EBV-associated extra nodal angiocentric and angiodestructive

lymphoproliferative disorder with a high mortality rate. It was first described in 1972 by Liebow et al. as a condition that predominantly affects the lungs, with overlapping features of granulomatosis with polyangiitis (formerly Wegener's granulomatosis) and lymphoma, not fitting with other forms of lymphoma [6, 7]. LYG is classified by the 2008 WHO classification as among the diffuse large B cell lymphomas [8].

The largest case series reported that most patients with LYG are middle-aged adults with a mean age of 48 years, and the male-to-female ratio is 2:1 [5]. LYG is more common in immunodeficiency states, especially AIDS but can be seen in immunocompetent individuals as well [5]. While most HIV-infected patients who present with LYG are not on HIV therapy, it can also present as an IRIS phenomenon shortly after initiation of antiretroviral therapy [9].

Symptoms are usually present for a few months prior to diagnosis [10]. Pulmonary involvement is almost always present [11]. Chronic cough, fever and dyspnea are the most common presenting complaints. A crucial factor contributing to the frequent delay in diagnosis of LYG is its ability to mimic various infectious diseases, vasculitides, and malignancies [5, 10]. Bilateral pulmonary infiltrates or nodules are usually seen. The nodules often have irregular margins and may cavitate, or wax and wane. Despite its lymphoproliferative nature, lymphatic tissue sites are not involved [10]. Following skin (39%), CNS (30%) is the most commonly affected extra-pulmonary site [11]. CNS presentations are nonspecific and varied. A retrospective review of LYG cases at the NIH found that 52% had abnormalities on brain MRI scan [12]. The variable spectrum of findings included multiple focal intraparenchymal lesions (most common) and involvement of leptomeninges and cranial nerves (next most common). These results are compatible with our patient who presented with cranial nerve findings (auditory symptoms) consistent with her initial pontine lesion, but whose final MRI scan had progressed to show multiple intraparenchymal lesions. There are several reports of LYG confined exclusively to the CNS [13].

Since the clinical findings are nonspecific, diagnosis is based on histology. The pathological hallmark of LYG is classically described as a nodular replacement of lung parenchyma by a mixed mononuclear cell infiltrate containing CD20-positive large B lymphocytes and CD3-positive small lymphocytes showing prominent vascular invasion. Supportive findings include necrosis and positive in situ hybridization for Epstein–Barr encoded RNA [5]. EBV infection can be observed in biopsies from some sites while absent from others, so that its absence does not rule out the diagnosis in a proper scenario [14]. Furthermore, the same biopsy specimen may simultaneously contain EBV positive and negative areas, encouraging surgical instead of core needle biopsies [5]. The presence of EBV and the angiocentricity help differentiate from other non-Hodgkin's lymphomas [5]. In our case the repeated CSF analysis was also helpful in the diagnosis, finding that the EBV DNA level had greatly increased and malignant cells were now present on flow cytometry.

The overall prognosis of LYG is poor, with 60% of mortality and a median survival of 4 years [10] although spontaneous remissions have been reported [11]. Treatment is not standardized. In most of the published series first-line treatment consists of corticosteroid therapy, with or without cyclophosphamide [15]. Other therapies that have been attempted and reported on with mixed results include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (cyclophosphamide, vincristine, prednisolone), rituximab (anti-CD20 monoclonal antibody), interferon α-2b and autologous stem cell transplantation.

The patient continued to deteriorate, CNS lesions progressed, and the patient developed respiratory failure on hospital day-8. Tuberculosis therapy was discontinued. HIV therapy was started on hospital day-9 with raltegravir, tenofovir and emtricitabine without improvement. The oncology consultant recommended against chemotherapy due to the patients poor performance status. The patient was unable to be weaned from the ventilator. Due to the patient's extensive disease and lack of therapeutic options, the patient was finally extubated in a palliative manner, which was according to her wishes. The patient expired immediately upon extubation, which was hospital day-24 at our institution.

CONCLUSION

This patient was found to have lymphomatoid granulomatosis, a very rare Epstein–Barr virus related malignancy. Lymphomatoid granulomatosis is a predominantly pulmonary disease, but neurological symptoms can predominate. We should be aware that HIV patients, especially those who are more immunosuppressed, could have two or more disorders explaining involvement of multiple organs, or a single entity affecting multiple anatomical locations like in this case.

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Author Contributions
Renato Quispe – 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

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David McCollum – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

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Authors declare no conflict of interest.

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LIST OF ABBREVIATIONS

LYG: LymphomatoidGranulomatosis; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; CNS: Central Nervous System; CSF: Cerebrospinal fluid; AFB: Acid-fast bacilli; PCR: Polymerase chain reaction; DLBCL: Diffuse large B cell lymphoma; HAART: Highly active antiretroviral therapy; JC: John Cunningham virus; MRI: Magnetic Resonance Imaging.

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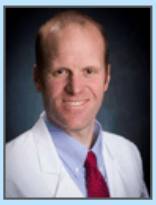

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CASE REPORT OPEN ACCESS

Short-lived delirium caused by single-shot corticosteroids

Johannes Prottengeier, Stefan Leucht, Torsten Birkholz

ABSTRACT

Introduction: Corticosteroids have many indications in medicine. Side effects are not uncommon, but psychiatric disorders in response to a single dose treatment are very rare. Case Report: We report of a previously mentally healthy 43-year-old female who received a single dose of 4 mg intramuscular dexamethasone and subsequently developed a short-lived delirium within hours of administration. Conclusion: Steroid delirium and psychosis are well known in literature, but reports on such an immediate adverse reaction are rare. The underlying biochemical mechanisms are unknown, but prognosis upon discontinuation of steroid intake is generally favorable.

Keywords: Steroids, Delirium, Single-shot corticosteroids, Adverse drug reaction

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INTRODUCTION

Since the discovery of cortisone (Edward Kendall being awarded the Nobel Prize for Medicine for this achievement in 1950) steroids have found multiple indications in modern drug therapy. Besides their use in immunologic and allergic disorders and many more, they have also proven themselves beneficiary as co-analgesics in chronic pain disorders [1]. Adverse drug reactions to corticosteroids are plentiful and psychiatric side effects are well-known with long-term administration of high doses [2–4]. We report a rare case of short-lived delirium caused by a single and low-dose application of dexamethasone intended as a co-analgetic in a previously mentally healthy patient. Secondly, we will illustrate the clinical characteristics, risk factors, treatment options and proposed mechanisms of disease of steroid induced delirium and psychosis.

CASE REPORT

A female in her mid-forties consulted her orthopedist for the aggravation of chronic severe back pain first diagnosed years before. The physical examination showed again muscle tension and pain in both cervical and lumbar region. No neurological deficits were detected. No other complaints were stated and the patient made a mentally unimpaired impression. The orthopedist injected 4 mg of dexamethasone intramuscular and sent the patient home in a stable condition. A few hours later, she called her general practitioner complaining of general discomfort, unrest, anxiety and tightness in her throat. He paid a home visit and suspected anaphylaxis, immediately injected clemastine and ranitidine, and alerted our emergency medical service.

At our initial assessment patient history revealed no pre-existing allergies. Her medication consisted of transdermal fentanyl (50 µg/hr) and metamizole (on

demand, up to 500 mg q.i.d.). There were no detours from her daily routine other than the visit to the orthopedist, no extra medication, no illicit or recreational drugs. Physical examination showed no signs of allergy: oral mucosa appeared normal, there was no bronchoconstriction, flush or pruritus. A basic neurological examination found no abnormalities. Except a noticeable agitation, all movements were precise and thinking appeared to be coherent, as she could explain the situation rationally to her children just coming home from school.

There was no sound explanation for the symptoms and anaphylaxis seemed unlikely: the patient was admitted to the emergency room. Within few minutes of the transfer to the hospital, she developed severe anxiety and confusion. She experienced visual and acoustical hallucinations of her children and husband, tried to climb off the stretcher while the ambulance was still driving and had to be restrained physically. All efforts of talking her down were futile, and there was practically no clinical response to 5 mg of midazolam intravenously.

Just after arrival in the emergency room, the patient had developed a deliriant state. She experienced further hallucinations of her family, tried to undress herself and was totally unresponsive to questions and instructions.

The attending physician in the emergency room thought of akathisia because of a noticeable motoric unrest as a potential diagnosis, but there was no pathognomonic pattern of movement and probatory injection of 5 mg biperiden intravenous had no clinical effect. Intravenously administered, repeated doses of diazepam made the patient markedly calmer and responsive to orders, but with persisting formal symptoms of the delirium. The diagnosis of this probably steroid-induced delirium was confirmed by the consulting neurologist. In the meantime, the symptoms had resolved partially, and he advised against any further intervention. It took another eight to twelve hours before the symptoms finally resolved. The patient then had an uneventful clinical course and was discharged home the next morning with no residual symptoms.

Further history of the patient showed that she never had experienced psychotic symptoms before. Several follow-ups with neurologist and psychiatrist, the latest 6 months after the initial incident, revealed no further abnormalities or formal diagnoses besides the known chronic pain disorder. Interestingly, she could recollect the events quite in detail, but had no explanation for her behavior.

DISCUSSION

In this case, the most likely explanation for such a extremely short-term but serious mental alteration of the patient is the single low dose of steroids (4 mg dexamethason).

Adverse psychiatric reactions to steroids have been known since Harvey Cushing first formulated ‘Dyspituitarism’ in 1932 and this case again reminds of the great variety in their clinical manifestations [2]. Most commonly are mood disorders such as mania or depression [3]. Furthermore, there have been reports of insomnia, agitation, aggressive behavior or cognitive disorders up to full dementia [4]. And with relevance to our case there have been many reports of delirium and psychosis, whereas literature does not clearly differentiate between the two entities in connection with steroids [5]. The development of steroid-induced delirium and psychosis is generally assumed to be dose-dependent and to be a function of time. Some studies found prevalence of up to 18·4% in patients receiving more than 80 mg/die of prednisone [6]. It usually takes 7–14 days of treatment before the onset of symptoms [7]. A rapid onset of disease as experienced with our patient has not been reported before. In this case, there are no obvious confounding factors. Ranitidine has been reported to cause confusion, even delirium [8]. But the timeline of events indicates otherwise: The onset of symptoms was well before ranitidine was given.

The immediate treatment of steroid induced delirium and psychosis could consist of antipsychotics and additional sedatives [9]. Prognosis of steroid induced mental disorders is generally favorable. The abstinence from the drug itself usually results into full clinical recovery [9]. When steroids are an essential part of a therapeutic regime and cannot be stopped or reduced, there have been reports that steroid psychosis can be prevented by prophylactic lithium, gabapentin or neuroleptics such as chlorpromazine [10].

Neither co-morbidities nor even previous steroid induced delirium or psychosis themselves are predictors for their occurrence [11]. The underlying biochemical mechanisms are unclear. Steroids interfere with glutamate levels and can cause hippocampal dysfunction [12]. How altered hippocampal glutamate levels could result in distinct psychiatric disorders has not been explained yet. After all, the vast majority of steroid treatments do not cause any mental alteration.

CONCLUSION

Psychiatric disorders following treatment with corticosteroids are well known, but such an immediate adverse reaction to a single dose of 4 mg of dexamethasone has not been reported before. Bridging with mild sedatives allowed for a spontaneous remission of symptoms. The underlying biochemical mechanisms of this adverse drug reaction however are still unclear.

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Author Contributions

Johannes Prottengeier – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Stefan Leucht – Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
TorstenBirkholz – Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
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CASE REPORT OPEN ACCESS

Sympathetic ophthalmitis following adherent leucoma: A rare association

Perwez Khan, Priyanka Shivhare, Lubna Khan, Ramesh Chand Gupta, Zia Siddiqui

ABSTRACT

Introduction: Sympathetic ophthalmitis is a rare condition. It occurs due to bilateral granulomatous pan uveitis following penetrating trauma or surgery in one eye. Penetrating injury to eye causes exposure of uveoretinal antigens to regional lymph nodes via conjunctival lymphatics thereby inciting delayed T cell hypersensitivity. Case Report: A 35-year-old male patient presented with headache and sudden painless dimunition of vision in both eyes preceded by development of adherent leucoma in left eye due to a perforated bacterial corneal ulcer five months before. Best corrected visual acuity was finger counting close to face in both eyes. Anterior segment examination revealed few keratic precipitates (KPs), 1+ cells and retrolenticular flare in both eyes. Fundus examination revealed exudative retinal detachment in right eye but left eye could not be assessed due to adherent leucoma. B-scan ultrasonography (B-scan) revealed exudative retinal detachment in both eyes. Patient was managed medically with intravenous methyl prednisolone 1 g for 3 days followed by oral steroids which led to complete resolution of disease process in both eyes. After treatment the best corrected visual acuity was 20/30 in right and 20/80 in left eye. Conclusion: Patients with adherent leucoma subsequent to a perforated corneal ulcer may remain at an increased risk of developing sympathetic ophthalmitis during their lifetime. However, timely medical intervention can lead to good visual prognosis for both exciting as well as the sympathizing eye. Long-term follow-up is necessary as recurrences following cessation of treatment are known to occur.

Keywords: Sympathetic ophthalmitis, Adherent leucoma, Perforated corneal ulcer, Exudative retinal detachment, Methyl prednisolone

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INTRODUCTION

Sympathetic ophthalmitis is defined as bilateral granulomatous pan uveitis that follows penetrating trauma or surgery in one eye [1]. An incidence of 0.19% following penetrating injury and 0.007% following intraocular surgery has been reported [2]. It is believed to be an autoimmune reaction to uveal antigen that involves a cell mediated immune response [3]. The common denominating factor in majority of cases is presence of a

penetrating injury in which wound healing is complicated by incarceration of iris, ciliary body and choroid [3, 4]. It affects both eyes and usually occurs between two weeks to three months after trauma but it can extend up to many years, 80% cases occur within three months and 90% within a year [5]. It has an insidious onset with progressive course and exacerbations. The classical description of signs include granulomatous mutton fat keratic precipitates (KPs), anterior chamber and vitreous inflammations with or without yellow white lesions in the retinal periphery. Other fundal lesions like retinal detachment, papillitis, optic atrophy and vasculitis are reported uncommonly with anterior segment inflammation [6]. Cases who present early with only fundus lesions are usually associated with minimal or no anterior segment inflammation, this atypical form of sympathetic ophthalmitis is termed posterior sympathetic ophthalmitis. The posterior form of disease is encountered in 5% of all cases of sympathetic ophthalmitis, is invariably accompanied by late development of anterior uveitis. It is neither clinically nor pathologically different from classical form [7].

CASE REPORT

A 35-year-old male patient presented to our institution with complaints of blurring of vision in both eyes and headache for 15 days. The patient had a history of perforated bacterial corneal ulcer five months before in his left eye leading to adherent leucoma. Best corrected visual acuity in both eyes was finger counting close to face. Anterior segment examination of both eyes showed few KPs, +1 cells and mild retrolental flare while left eye had adherent leucoma in addition to above findings (Figure 1). On fundus examination of right eye exudative retinal detachment and few choroidal lesions over fundus were detected (Figure 2), while left eye fundus could not be accessed due to adherent leucoma. The intraocular pressure was 12 mmHg in both eyes. The systemic evaluation did not reveal any evidence of a focus of infection, vitiligo, alopecia, dysacousia or meningeal signs. The erythrocyte sedimentation rate (ESR), chest X-ray, enzyme-linked immunosorbent assay (ELISA) for toxoplasma, venereal disease research laboratory test (VDRL) test and audiometry were within normal limits.

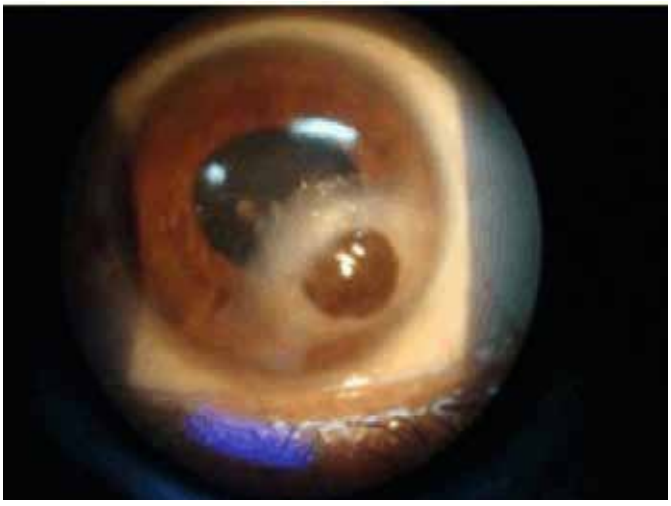

Figure 1: Slit Lamp photograph of left eye (exciting eye) of patient showing adherent leucoma.

Ultrasonography for the posterior segment revealed retinal detachment in both eyes (Figures 3 and 4). The fluorescein angiogram of the right eye showed multiple hyperfluorescent spots at the level of the retinal pigment epithelium in the venous phase which persisted in the late phase. In addition, there was coalescence of the dye in the area of the exudative detachment. Based on the typical history and clinical signs, a diagnosis of sympathetic ophthalmitis was made and the patient was initiated on high dose intravenous steroids with 1 gram methyl prednisolone for three days followed by oral steroids 50 grams in single dose for one week which was then slowly tapered over the next three months. Resolution of the exudative detachment with recovery of best corrected visual acuity to 20/200 in both eyes occurred after 72 hours following the initiation of intravenous steroids (Figure 5).

At one week patient became asymptomatic with a visual acuity of 20/60 in right eye and 20/80 in left eye with no evidence of disease activity. Visual acuity improved to 20/30 in right eye and 20/80 in left eye at one month follow-up and remained the same with no sign of relapse.

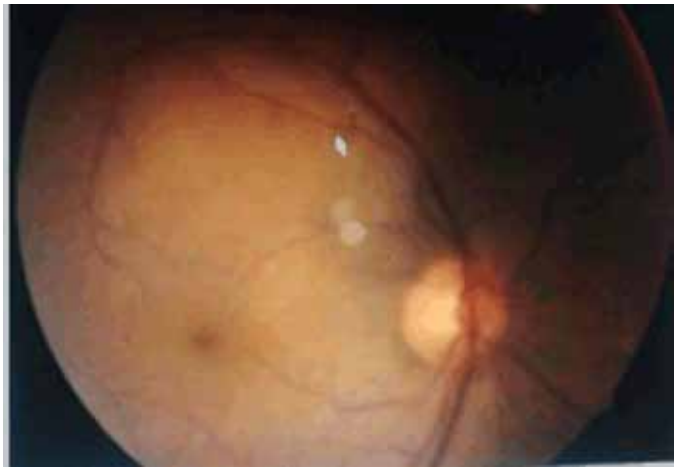

Figure 2: Fundus photograph of right eye (sympathising eye) showing exudative retinal detachment.

DISCUSSION

Sympathetic ophthalmitis may occur with varying degree of severity, from a mild anterior uveitis or peripapillary choroiditis to a severe panuveitis with mutton fat keratic precipitates or posterior uveitis.

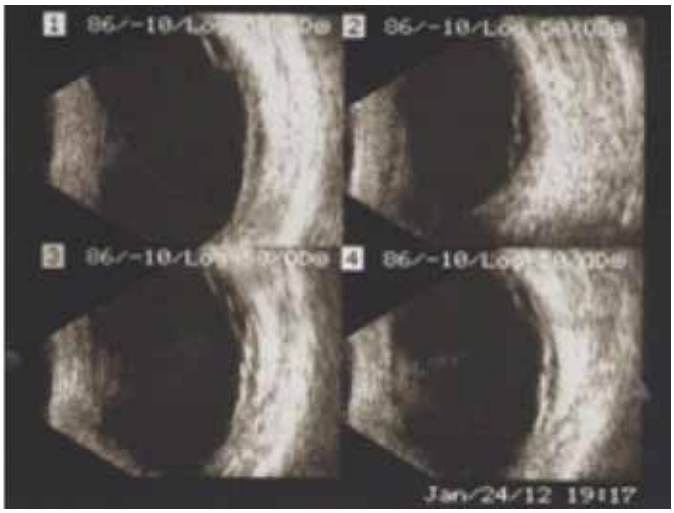

Figure 3: Ultrasonography B-scan of right eye showing exudative retinal detachment.

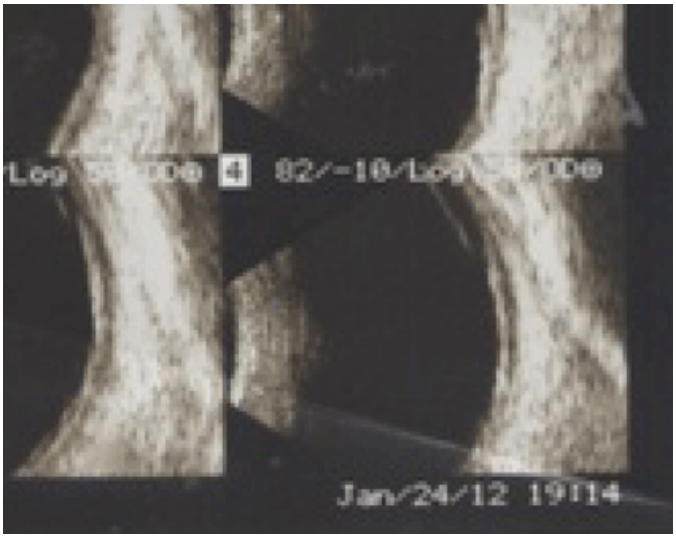

Figure 4: Ultrasonography B-scan of left eye showing exudative retinal detachment.

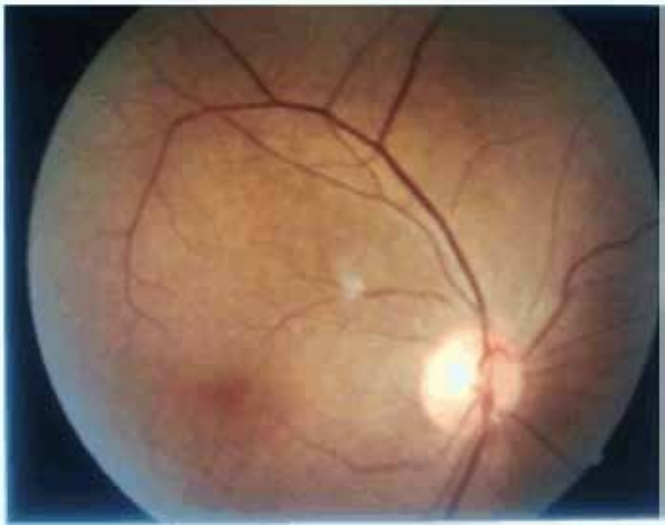

Figure 5: Fundus photograph right eye of same patient after 10 days of treatment with steroids showing complete resolution of retinal detachment.

Some cases with sympathetic ophthalmitis may present with only fundal lesions with no or minimal anterior segment inflammation. Sympathetic ophthalmitis may be accompanied by headache, pleocytosis of spinal fluid, dysacousis, tinnitus, alopecia, poliosis and vitiligo [8]. The systemic association is similar to those seen in Vogt–Koyanagi–Harada (VKH) syndrome [8]. Diagnosis of posterior sympathetic ophthalmitis was rendered in the present case as patient had signs and symptoms of posterior segment involvement with minimal anterior segment inflammation along with history of perforated corneal ulcer five months back leading to adherent leucoma. Sympathetic ophthalmitis is not easily diagnosed. Only 20% of clinically suspected cases are confirmed by histopathologic evaluation [4]. The history of a penetrating injury or surgery and bilateral ophthalmitis serve as basis for diagnosis, along with typical ocular and associated findings, fundus fluorescein angiography and B-scan may assist in diagnosis.

The role of a perforated corneal ulcer in the pathophysiology of sympathetic ophthalmitis is to provide intraocular uveoretinal antigens an access to the regional lymph nodes via conjunctival lymphatics [3]. This may cause a sensitizing reaction to these antigens and set up a delayed T cell hypersensitivity, which may be responsible for the disease process [3]. Exciting eye with hopeless visual prognosis should be enucleated within two weeks after injury to prevent autoimmune reaction [8]. Once the disease has developed, enucleation of the exciting eye may not prevent the inflammation in the sympathizing eye [9]. An attempt to preserve the eye should be made if good visual prognosis is expected because sometimes in patients with sympathetic ophthalmitis, the exciting eye can have better visual prognosis than the sympathizing eye [10]. Topical corticosteroids eye drops and cycloplegics decrease inflammation, formation of medications can be used. It requires long term treatment and follow-up because recurrent episodes after cessation of treatment can occur [11].

CONCLUSION

Patients with adherent leucoma subsequent to a perforated corneal ulcer may remain at an increased risk of developing sympathetic ophthalmitis during their lifetime. However, timely medical intervention can lead to good visual prognosis for both exciting as well as the sympathizing eye. Long-term follow-up is necessary as recurrences following cessation of treatment are known to occur.

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Author Contributions

Perwez Khan – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Priyanka Shivhare – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Lubna Khan – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Ramesh Chand Gupta – Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Zia Siddique – Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

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CASE REPORT OPEN ACCESS

A case of basal cell carcinoma secondary to nevus sebaceous

Nursel Dilek, Recep Bedir, Derya Yüksel, Arzu Ataseven

ABSTRACT

Introduction: Nevus sebaceous is a congenital hamartomatous lesion that usually appears on the scalp and neck. With the advance of age, benign and malignant tumor changes on nevus sebaceous lesions may occur, these tumors are usually benign. Malignant transformation is very rare on the sebaceous nevus and the basal cell carcinoma is the most common. Case Report: A 50-year-old female patient was admitted to our clinic with a 5×3 cm sized a verrucous erythematous plaque on the left parietal region of head. Total surgical excision was performed and histopathological examination of the sample revealed a basal cell carcinoma developed on ground of nevus sebaceous. Conclusion: To highlight importance of this rare malign development, a case of basal cell carcinoma on the ground of nevus sebaceous is presented.

Keywords: Nevus sebaceous, Tumor, Basal cell carcinoma

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INTRODUCTION

Nevus sebaceous is a benign congenital hamartomatous lesion most commonly shows sebaceous malformation but different proportions of epithelial, follicular and apocrine malformation can be seen [1]. The lesions appear at birth as small swelling almost insensible and they can progressively begin to appear thickened and irregular borders at late childhood and adulthood. It usually appears on hairy skin and face but it also appears on the neck and less frequently on the body. The scalp lesions show alopecic features [2].

Nevus sebaceous presents 0.05–1% of outpatients applying to the dermatology clinic. Nevus sebaceous occurs with equal frequency in males and females. Nevus sebaceous are generally sporadic, lesions are thought to develop as a result of para dominant inheritance in cases of inherited nevus sebaceous [1, 3]. About 14% of nevus sebaceous cases develop to malignancies in late childhood and adulthood period, most of the malignancies are benign [2, 4]. Benign tumors include syringocystadenoma papilliferum (5%), trichoblastoma (4.5%), trichilemmoma (2.5%) and sebaceoma (2.1%). Malign conversions, which are less than 1%, includes basal cell carcinoma (BCC) and squamous cell carcinomas [4]. Malignant changes occurs in about 10–30% of the patients 40–70 years of age [5, 6].

Several theories have been proposed for the proliferative changes in nevus sebaceous. Deletions in the patched gene has been determined in nevus sebaceous and it has been reported that this deletion causes the development of BCC and other tumoral structures by

activation of patched-hedgehog signaling pathway, although this idea has not been supported by further studies [1].

Herein, a case of BCC on the ground of nevus sebaceous is presented with review of available literature.

CASE REPORT

A 50-year-old female patient was admitted to our clinic with alopecic lesion which present from birth in hairy skin, which was enlarged in the recent year and became a reddish stalked mass. She had no complaint apart from bleeding of the lesion while combing hair.

The patient had no self and family genetic background for cancer and routine laboratory findings were within normal limits (hemogram, biochemistry, whole blood). Dermatological examination revealed a 5×3 cm sized a verrucous erythematous plaque on the left parietal region of head, on which there was 1×1 cm erythema on the right upper corner. She had no similar lesions on other parts of the body. Total surgical excision was performed with preliminary diagnosis of syringocystadenoma papilliferum, trichoblastoma and BCC. We made an incision through the full three layers of the skin around the obvious area of the skin cancer. The specimen was removed and the edges of the wound were pulled together using plastic surgery techniques. Histopathological examination of the sample revealed a BCC (ulceration of epidermal surface, infiltrating basolateral cell islands to dermis, positive staining in basaloid cells with CD10) developed on ground of nevus sebaceous (Figures 1 and 2) and no tumor was detected within the surgical limits. The patient was referred to the plastic surgery department with suggestion of total excision of nevus sebaceous due to potential of new malignity progression. Another medical management was not given. The patient did not receive any radiotherapy.

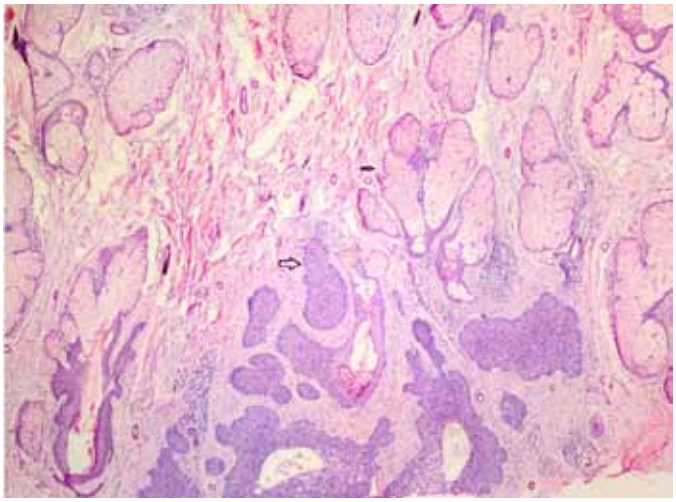

Figure 1: Basal cell carcinoma in the background of sebaceous nevus. Sebaceous glands (thin arrow), basal cell nests (thick arrow), (H&E stain, x400).

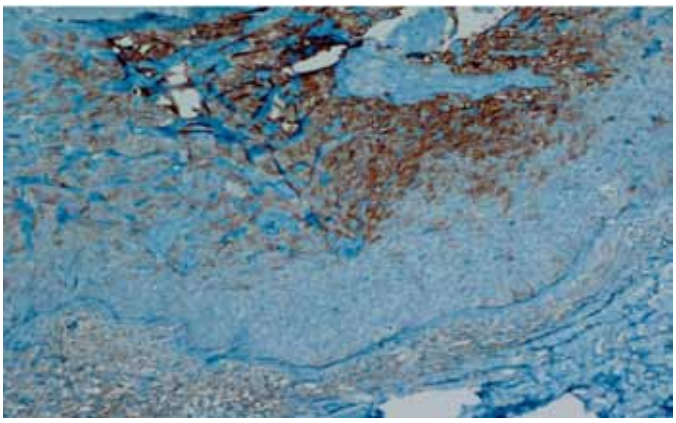

Figure 2: Strong positive staining in basaloid cells with CD10

DISCUSSION

*N*evus sebaceous is a congenital hamartomatous malformation, also known as organoid nevus, first described in 1895 by Jadassohn, describes alterations of glands involving epithelial, pilar, sebaceous, eccrine and apocrine structures with various levels of follicular, sebaceous and apocrine differentiation [1, 7].

Nevus sebaceous presents as a solitary lesion, usually present at birth and it may develop in early childhood. Clinically, it appears as mild swelling, shiny velour plaque at birth and infancy. At puberty, by the effects of the androgen hormones the sebaceous glands maturates and became functioning resulting in the development of yellow, papillomatous-verrucous lesions [8, 9].

Arising of tumor from nevus sebaceous usually occurs at puberty or later stages. Most common benign tumors are syringocystadenoma papilliferum and trichoepithelioma and trichoblastoma. Less frequently occurring tumors includes leiomyoma, syringoma, spiradenoma, hidradenoma and keratoacanthoma [5, 10, 11].

Malignant transformations on the ground of nevus sebaceous are very rare whereas BCC is the most common among these. Recent studies indicate that the rate of BCC development on the ground of nevus sebaceous is not 10% as suggested by previous studies but, in fact, it is less than 1% [2, 4, 5]. Two retrospective studies involving 596 and 757 patients, those diagnosed as BCC were confused and they actually had trichoblastoma and therefore despite suppositional rate transformation of BCC on the ground of nevus sebaceous is much rarer [5, 10, 12].

Basal Cell carcinoma cases especially the nodular type should be histopathologically differentiated from eccrine spiradenoma, nodular hidradenoma and trichoepithelioma or trichoblastoma like benign adnexal proliferations. Typical nodular BCCs with telangiectasia

may be present as pearl appearance elevated nodules of ulceration or cysts. Histopathologically, large lobule basaloid cells with peripheral *palisading nuclei* may appear. The lobules may involve mucinous degenerations [11, 13].

Eccrine spiradenoma is well bordered intradermal nodule with no connection with epidermis. The tumor contains small cells with dark-colored nuclei and larger cells with light color nuclei. Mitosis and dyskeratosis is not common. Nodular hidradenoma has no connection with the epidermis and the rate of mitosis is low. It may differentiate towards the eccrine channel. This tumor may invade deeper than nodular BCC. Necrosis is not common, peripheral cell palisades and mucin deposits do not appear. Differentiating BCC from trichoepithelioma or trichoblastoma can be difficult. These tumors may contain focal calcifications. Small keratin cysts may be present. But basaloid cell proliferation is not typical and mucin formation is rare. Mitotic activity and apoptosis is decreased. Typically, these tumors presents with mild or moderate fibrosis formation around dermis. Stromal changes are more prominent compared to the normal dermis. The decomposition of stroma may be present. CD34 is positive or stroma of trichoblastoma while being negative for BCC. Focal positive staining of BCC with cytokeratin 7, 8, and even more staining with CD10 is important for differentiation of trichoblastoma or trichoepithelioma [5, 11, 13]. Additionally, the presence of ulceration in BCC is another important parameter in differentiation from trichoblastoma [5, 13].

Ulceration in surface epidermis and connection between the epidermis bazaliod islands were evident in our case. Immunohistochemical examination revealed CD10 and positive staining in the basaloid cells while no positive staining in the stromal cells.

Among to other malignant tumors arising from nevus sebaceous are apocrine carcinoma, squamous cell carcinoma and malignant eccrine poroma [10]. Patients with nevus sebaceous should closely be clinically followed and any changes suspicious of evoking tumor should be sampled for pathology. At early stage, total surgical excision remains a matter of debate. Some suggests early period prophylactic excision for prevention of malignant development while others find this unnecessary [5, 8].

CONCLUSION

In this article, a case of basal cell carcinoma on the ground of nevus sebaceous is presented with aim of highlighting the significance of this rare entity.

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Author Contributions

Nursel Dilek – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published
Recep Bedir – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Derya Yüksel – Analysis and interpretation of data, Drafting the article, Final approval of the version to be published
Arzu Ataseven – 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.

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CASE REPORT OPEN ACCESS

Supraclavicular course of the cephalic vein

Juan David Ramírez, Luis Carlos Sáenz, Diego Rodríguez, Alejandro Jiménez Restrepo, Francisco Villegas

ABSTRACT

Introduction: Vascular access for transvenous pacemaker and cardioverter defibrillator implants is frequently obtained by using the cephalic cutdown technique. Sometimes anatomical variations may limit insertion of one or several leads. We describe a case of a patient with an anomalous supraclavicular course of the left cephalic vein. Case Report: A 61-year-old male with background of ischemic heart disease, hypertension, diabetes mellitus, obstructive sleep apnea and dyslipidemia, was referred to our institution after four months of recurrent syncopal episodes. A bradycardia–tachycardia syndrome was diagnosed and decided to proceed with permanent pacemaker implantation. Through a cutaneous incision in the left deltopectoral groove, we dissected the tissue planes until the left cephalic vein became visible. Fluoroscopy in anterior-posterior projection showed clear supraclavicular course of the cephalic vein. This access was abandoned by removing both wires and ligating the proximal end of the cephalic vein. Through a fluoroscopy/venogram guided axillary puncture using the modified Seldinger technique and the retained wire technique, double central vein access was secured, allowing the passage of right atrial and ventricular leads. A dual chamber pacemaker was implanted. Conclusion: Although the supraclavicular course of the cephalic vein is a rare anatomical variant, it is important to recognize its presence as it may lead to potential complications related to lead dysfunction, erosion or collateral vascular damage if used as an access for permanent lead placement. Alternative central vein access is strongly recommended in such cases.

Keywords: Pacemaker, Implantable cardioverter-defibrillator, Cephalic vein, Implanted electrode

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INTRODUCTION

Vascular access for transvenous pacemaker and cardioverter defibrillator implants is frequently obtained using the cephalic cutdown technique. This method excludes the risk of pneumothorax and subclavian crush syndrome. Despite its benefits, this technique requires surgical dissection skills and there are potential anatomical variations in its course and diameter which may limit or complicate insertion of one or several leads. We describe the case of a patient with an

anomalous supraclavicular course of the left cephalic vein complicating the implantation of a pacemaker system. We present a review of the available medical literature on this issue.

CASE REPORT

A 61-year-old male with background of ischemic heart disease with moderate left ventricular impairment, hypertension, diabetes mellitus, obstructive sleep apnea and dyslipidemia, was referred to our institution after four months of recurrent syncopal episodes. A 24-hour Holter monitor documented persistent atrial fibrillation with rapid ventricular response (up to 167 BPM) alternating with symptomatic bradycardia episodes (29 BPM) and up to six seconds diurnal pauses during atrial fibrillation. As a consequence of the bradycardia–tachycardia syndrome and the requirement for up-titration of beta-blocker therapy permanent pacemaker implantation was needed.

Through a cutaneous incision in the left deltopectoral groove, we dissected the tissue planes until the left cephalic vein became visible. Direct vein punctures allowed for venous access and passage of two hydrophilic wires without difficulty. Fluoroscopy in anterior-posterior projection showed clear supraclavicular course of the cephalic vein (Figure 1). A venogram confirmed anomalous drainage of the left cephalic vein into the ipsilateral external jugular vein. Subsequently, both wires were removed and the terminal portion of the cephalic vein was ligated to achieve hemostasis. Through a fluoroscopy/venogram guided axillary puncture using the modified Seldinger technique and the retained wire technique, double central vein access was secured, allowing the passage of right atrial and ventricular leads, which were subsequently connected to a dual chamber pacemaker and implanted without complications in a usual pre-pectoral position. The patient was discharged from the hospital the next day after chest X-ray confirmed proper lead placement and device interrogation documented adequate sensing and pacing parameters for both leads (Figure 2). After one week of follow-up, the device was functioning properly and the incision showed normal healing without evidence of infection.

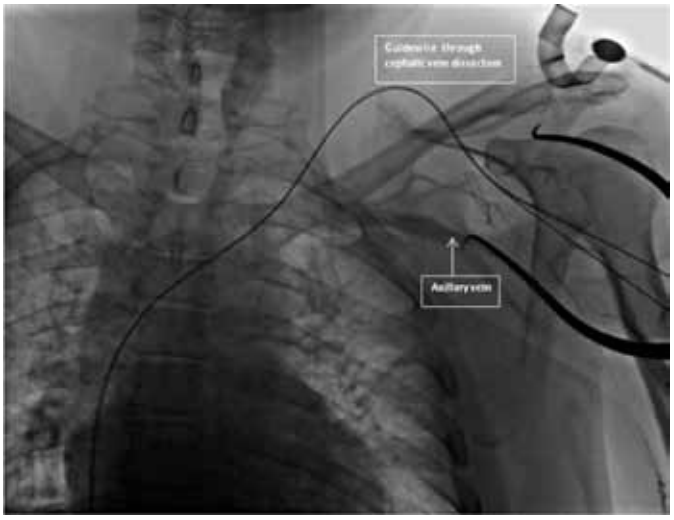

Figure 1: Venography showing the unusual course of the guidewires inserted via the cephalic cutdown technique. Note the supraclavicular trajectory of the guidewires and its spatial relationship with the axillary and subclavian veins, filled with contrast.

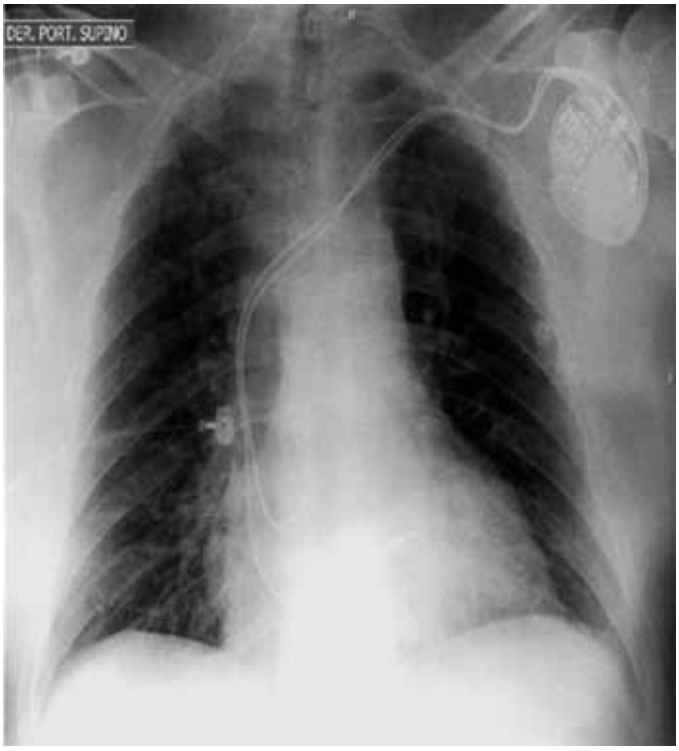

Figure 2: Chest X-ray after pacemaker implantation.

DISCUSSION

There are two common approaches for cardiac rhythm device leads implantation, epicardial and transvenous. Most leads are placed via the transvenous approach due to the long-term reliability and performance when compared to epicardial leads. The two favored techniques for gaining central venous access are the cutdown technique (commonly employed for the cephalic vein) or the Seldinger venipuncture technique (for axillary or subclavian vein access). Knowledge of the normal venous anatomy of the clavicular and axillary regions, including its potential anatomical variants, is paramount to avoid complications. The preferred access for a cutdown technique approach is the cephalic vein, which is a part of the superficial venous system of the upper extremities [1].

The normal course of the cephalic vein runs along the radial aspect of the forearm, draining blood from the dorsum of the hand. It communicates with the deep venous system of the forearm at the basilic vein. Once

it crosses the elbow at the antecubital fossa, it moves towards the lateral aspect of the biceps and at the proximal third of the arm dives in between the pectoralis major and deltoid muscles, joining the axillary vein just inferior to the clavicle [1, 2]. Anatomical studies have documented variations in the course of the cephalic vein, but the clinical cases reported in medical literature are rare, and include cases with absence or small diameter of the cephalic vein, accessory veins running parallel to the cephalic vein or even pre-clavicular or supraclavicular anomalous courses (<1% of all dissection series, accounting for less than five reported cases in the medical literature) [3–6]. Only in the case described by Trigano et al. an attempt placing the electrodes was undertaken. However, this case had an anomalous cephalic course draining into the proximal subclavian vein, contrary to our case where a supraclavicular course of the cephalic vein drained into the external jugular vein; the recommendation in such cases is to leave the access and find an alternative approach to avoid lead erosion [5, 6]. The cephalic vein cutdown is a safe technique to gain central venous access, preventing the well-known complication of subclavian crush syndrome. Its main limitation is the difficulty to separate tissue planes in patients with anatomical deformities or morbid obesity as well as a longer total procedural implant time and the potential need for abandoning access if the vein caliber is small or, less frequently, due to anomalous course (as in this case).

CONCLUSION

Although the supraclavicular course of the cephalic vein is a rare anatomical variant, it is important to recognize its presence as it may lead to potential complications related to lead dysfunction, erosion or collateral vascular damage if used as an access for permanent lead placement. Alternative central vein access is strongly recommended in such cases.

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Author Contributions

Juan David Ramirez – 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
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CASE REPORT OPEN ACCESS

Insulinoma located in the head of the pancreas: Is there an alternative to surgery?

Marcin Balawejder, Katarzyna Skórkowska-Telichowska, Tomasz Kuniej, Renata Tuchendler

ABSTRACT

Introduction: Insulinoma is a gastrointestinal tumor, usually benign, which derived from pancreatic beta cells and typically induced by endogenous hyperinsulinism with an incidence rate of 1–4 cases per million inhabitants each year. This case report describes the diagnostic challenges and dilemmas associated with finding optimal treatment for an insulinoma located in the head of the pancreas. Case Report: A 41-year-old female was presented with recurrent, nagging headaches, loss of attention and episodes of anxiety accompanied by a feeling of 'heart palpitation'. Based on the test results, reactive hypoglycemia was diagnosed and further symptomatic treatment was recommended. The patient was admitted again nine years after her initial hospitalization for symptoms of hypoglycemia. Abnormally, high insulin and peptide C secretion was found. Computed tomography (CT) scan revealed a tumor with a size of 1.8x1.3x2.2 cm located within the uncinate process of the pancreas. Pancreatoduodenectomy was recommended. However, the patient refused surgery. She was given somatostatin analogues leading to a satisfactory clinical effect. Computed angiotomography was done which confirmed the presence of an abundantly vascularized tumor within the head of the pancreas. Embolization with histoacryl glue was performed. Due to the ineffectiveness of embolization, treatment with short-acting and then long-acting synthetic somatostatin analogues was reintroduced. A follow-up CT scan conducted six months after the procedure revealed regression of tumor size. Conclusion: Treatment of choice for insulinoma is surgery, but conservative treatment is recommended when surgery is impossible or contraindicated. Afferent vessel embolization is a safe treatment option. Chemotherapy may be an option for inoperable, malignant tumors.

Keywords: Insulinoma, Hypoglycemia, Somatostatin analogues, Afferent vessel embolization

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INTRODUCTION

Insulinoma, a tumor which is derived from pancreatic beta cells, is the most common cause of hypoglycemia induced by endogenous hyperinsulinism [1]. Its incidence rate is 1–4 case(s) per million inhabitants each year. It is usually a benign tumor that may occur as a part of a

syndrome known as MEN 1 (multiple endocrine neoplasia 1) [2].

Clinical manifestations include the Whipple's triad. These include hypoglycemic symptoms such as sweating, shivering, heart palpitation, but mainly consists of the symptoms of neuroglycopenia such as headaches, visual disturbances, confusion, drowsiness, speech disturbance, behavioral abnormalities and tremors. Insulinoma is confirmed by reduction in fasting glucose levels <40 mg/dL (2.2 mmol/L), which typically resolves after carbohydrate administration [3]. Laboratory examinations show inappropriately high concentrations of insulin (>36 pmol/L or 6 IU/L) relative to glucose levels, C peptide >200 pmol/L and proinsulin >5 pmol/L during the fasting test of up to 72 hours [1, 3].

CASE REPORT

In 2001, a 41-year-old female was admitted to the Department of Endocrinology of the 4th Military Clinical Hospital in Wrocław for non-specific complaints. These included recurrent, nagging headaches, loss of attention, episodes of anxiety accompanied by a feeling of 'heart palpitation' as well as trembling of her hands and increased sweating. These symptoms typically appeared within three hours of a meal and resolved up to 30 minutes after taking simple carbohydrates. The patient's previous laboratory examination showed a reproducible decrease in blood glucose levels to a minimum of 20 mg/dL, which correlated with her symptoms. The patient had no significant clinical history and had not been medically treated in the past.

During her hospitalization, a combined evaluation of her blood glucose, insulin, and C peptide levels was carried out (Table 1). Thyroid and adrenal gland function were also assessed. Based on the test results, reactive hypoglycemia was diagnosed and further symptomatic treatment was recommended.

The patient was admitted again to the Department of Endocrinology nine years after her initial hospitalization. This time her medical history included more pronounced symptoms of hypoglycemia— they were more frequent, more severe and more difficult to reverse, accompanied by symptoms of neuroglycopenia occurring several times a week. The patient also reported an episode of syncope with a short-term loss of consciousness. In between her hospitalizations, she had been treated for stage II arterial hypertension (according to WHO classification) for several years. The treatment included therapy with perindopril, indapamide and metoprolol succinate.

Physical examination at admission revealed obesity (BMI 34.5 kg/m^2). The combined evaluation of blood glucose, insulin, and C peptide levels were repeated. The patient was subjected to a 5-hour oral glucose tolerance test with 75 grams of glucose, a fasting test and an assessment of adrenal and thyroid gland function (Table 1).

The results showed abnormally high insulin and peptide C secretion compared to glucose levels and normal functioning of the thyroid and adrenal glands.

Supplementary diagnostic imagining of the abdominal cavity using an ultrasound scan revealed no abnormalities, apart from signs of hepatic steatosis. Computed tomography (CT) scan revealed a tumor with a size of 1.8x1.3x2.2 cm located within the uncinate process of the pancreas (Figure 1). The lesion displayed intensive contrast enhancement in the arterial phase of the examination, which was characteristic of insulinomas and associated with their abundant vascularization.

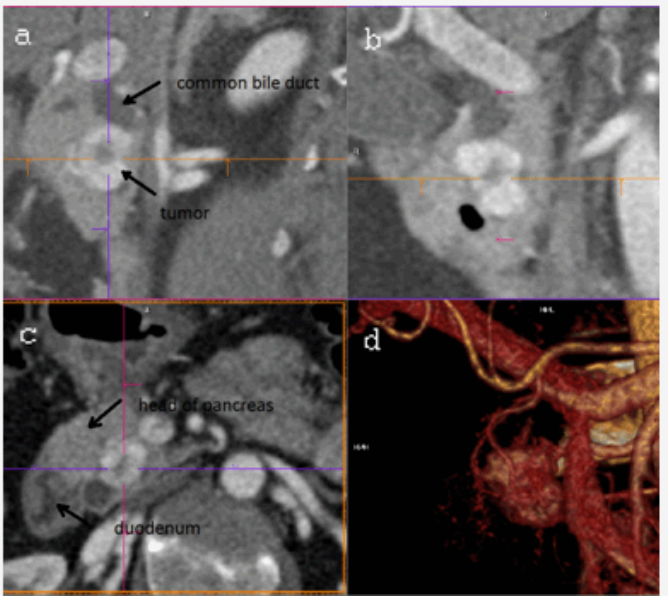

Figure 1: The initial computed tomography scan with cross sections in three basic dimensions and a volume rendering (bottom left corner) revealed a tumor within the head of the pancreas, which was adjacent to the common bile duct and showing intensive contrast enhancement.

The patient was pre-approved for surgery. Pancreatoduodenectomy was recommended because the lesion was localized within the head of the pancreas, in the proximity of the common bile duct and the inferior vena cava, as well as the abundant vascularization of the tumor. However, the patient did not give her formal consent to the procedure. Therefore, treatment with short-acting, and later long-acting synthetic somatostatin analogs were started, leading to a satisfactory clinical effect - no hypoglycemia incidents were observed (Table 2).

Pharmacological therapy was discontinued approximately half a year later. Symptoms of hypoglycemia reoccurred within three months following treatment discontinuation. As continuation of pharmacological treatment was impossible and the patient still refused to give her consent to surgery, investigation of the tumor blood supply and obliteration of the supplying vessels was suggested as an alternative treatment.

Table 1: Clinical evaluation of patient before treatment.

THYROID HORMONES														
Hospitalization							1st day				2nd day			
TSH (µIU/mL, reference values 0.27–4.20)							0.6				0.994			
fT4 (ng%, reference values 0.93– 1.7)							1.3				1.42			
DAILY GLUCOSE, INSULIN AND C-PEPTIDE PROFILES														
Time	3 a.m.		7 a.m.		10 a.m.		3 p.m.		4 p.m.		8 p.m.		12 p.m.	
Hospitalization	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st	2nd day	1st day	2nd day
Glucose (ng %, fasting reference values 74–100)	-	-	57	34	-	81	-	26	104	-	30	44	39	-
Insulin (µIU/mL, fasting reference values 3.21–16.32)	7.1	-	5.9	35.4	-	139.9	-	181.9	15.5	-	17.1	171.4	10.2	-
C-peptide (ng/mL, fasting reference values 0.8–4.2)	3.6	-	2.7	5.4	-	11.1	-	11.6	6.3	-	6.4	12.5	4.5	-
STATIC ASSESSMENT OF GLUCOCORTICOID LEVELS														
Time							7 a.m.				8 p.m.			
Hospitalization							1st day		2nd day		1st day		2nd day	
Cortisol (nmol/L, reference values for 7 a.m. 171–536, for 8 p.m. 64–340)							633.8		773.4		81.5		71.1	
ACTH (pg/mL, reference values 0.0– 46.0)							49.6		75.7		-		7.7	
Hospitalization							1st day				2nd day			

Table 1: *(Continued)*

24-hour urine cortisol level (nmol/24 h, reference values 100–379)	-					1724.8						
GLYCATED HEMOGLOBIN												
Hospitalization		1st day				2nd day						
HbA1c (%, reference values 4.0–6.0)		8.9				4.7						
PROLONGED ORAL GLUCOSE TOLERANCE TEST WITH 75 grams OF GLUCOSE												
Time	0 hour		1 hour		2 hours		3 hours					
Hospitalization	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st day	2nd day				
glucose (ng %, fasting reference values 74–100)	-	39	-	206	-	240	-	115				
Insulin (μIU/ml, fasting reference values 3.21–16.32)	-	24.3	-	81.3	-	101.0	-	114.2				
INSULIN-INDUCED HYPOGLYCEMIA TEST												
Time	0 Test started at the blood glucose level of 40 mg/dL		30 minutes		60 minutes		90 minutes		4 hours		5 hours	
Hospitalization	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st day	2nd
Cortisol (nmol/l, reference values for 7 a.m. 171–536, for 8 p.m. 64–340)	-	592.5	-	330.5	-	220.8	-	162.4	-	28	-	30
ACTH (pg/ml, reference values 0.0–46.0)	-	20.1	-	7.2	-	7.7	-	7.2	-	83.6	-	39.6
FASTING TEST												
Time	7 a.m.		10 a.m.		2 p.m.		4 p.m.					
Hospitalization	1st day	2nd day	1st day	2nd day	1st day	2nd day	1st day	2nd day				

Table 1: *(Continued)*

Glucose (ng %, fasting reference values 74–100)	-	64	-	142	-	47	-	33				
Insulin (μIU/mL, fasting reference values 3.21–16.32)	-	24.0	-	179.0	-	42.9	-	-				
Hospitalization					1st day				2nd		413.9	-
Cortisol (nmol/L, reference values for 7 a.m. 171–536, for 8 p.m. 64–340)	-				655.0							
CHROMOGRANIN A												
Hospitalization					1st day				2nd			
Chromogranin A (mg/mL, reference values 0.0–100.0)	-				24.9							

Table 2: Clinical evaluation of patient after treatment.

DAILY GLUCOSE, INSULIN AND C-PEPTIDE PROFILES								
Time	7 a.m.		10 a.m.		3 p.m.		8 p.m.	
After treatment	synthetic somatostatin analogues	embolization	synthetic somatostatin analogues	embolization	synthetic somatostatin analogues	embolization	synthetic somatostatin analogues	embolization
Glucose (ng %, fasting reference values 74–100)	114	44	123	48	128	37	146	32
Insulin (μIU/mL, fasting reference values 3.21–16.32)	4.9	20.4	27.7	107.9	22.2	44.9	35.2	89.1
C-peptide (ng/mL, fasting reference values 0.8–4.2)	1.99	5.49	10.70	10.50	6.03	7.81	6.83	11.30

PROLONGED ORAL GLUCOSE TOLERANCE TEST WITH 75 grams OF GLUCOSE during treatment with synthetic somatostatin analogues						
Time	0	1 hour	2 hours	3 hours	4 hours	5 hours
Glucose (ng %, fasting reference values 74–100)	86	184	90	66	70	91
Insulin (μIU/mL, fasting reference values 3.21–16.32)	7.70	97.3	3.4	36.1	4.3	4.3

FASTING TEST during treatment with synthetic somatostatin analogues								
Time	7 a.m.	10 a.m.	12 a.m.	2 p.m.	4 p.m.	6 p.m.	9 p.m.	12 p.m.
Glucose (ng %, fasting reference values 74–100)	100	96	96	95	95	99	98	103

Table 2: *(Continued)*

Insulin (μIU/mL, fasting reference values 3.21–16.32)	8.7	3.8	4.8	1.6	3.6	<0.2	2.0	2.0
GLYCATED HEMOGLOBIN								
After treatment	synthetic somatostatin analogues					embolization		
HbA1c (%, reference values 4.0–6.0)	6.1					5.2		

Computed angiotomography was performed at the Clinical Department of Proctological and Minimally Invasive Surgery, Medical University of Wrocław in order to assess therapeutic possibilities for tumor embolization. This examination confirmed the presence of an abundantly vascularized tumor within the head of the pancreas (size 1.5x1.2x2.1 cm) which was adjacent posteriorly and laterally on the right with the common bile duct, posteriorly with the inferior vena cava and supplied by the small branches of the superior mesenteric artery and a very small branch of the gastroduodenal artery. The diameter of the examined vessels made it impossible to precisely investigate their location. Therefore, it was decided to carry out a selective contrast-enhanced computed angiotomography following afferent artery catheterization. This examination revealed the tumor's supplying vessels, which originated from the first branch of the superior mesenteric artery. Embolization with histoacryl glue was performed. A control arteriography revealed the obliteration of the supplying vessels and the tumor, which did not show any contrast enhancement.

Neither clinical nor laboratory indicators of hypoglycemia were observed directly after the procedure.

Within five months following the procedure, the patient had a reoccurrence of hypoglycemia symptoms. Her blood glucose level had decreased to approximately 40 mg/dL. Further examinations revealed increased insulin levels, which showed a correlation with observed hypoglycemia (Table 2).

Due to the ineffectiveness of embolization, treatment with short-acting and then long-acting synthetic somatostatin analogs were reintroduced, accompanied by a low glycemic index diet. The achieved therapeutic effect was satisfactory (glucose level: 51–67 mg/dL at 7 a.m., 115–143 mg/dL at 10 a.m., 79–89 mg/dL at 3 p.m., and 95–119 mg/dL at 8 p.m.).

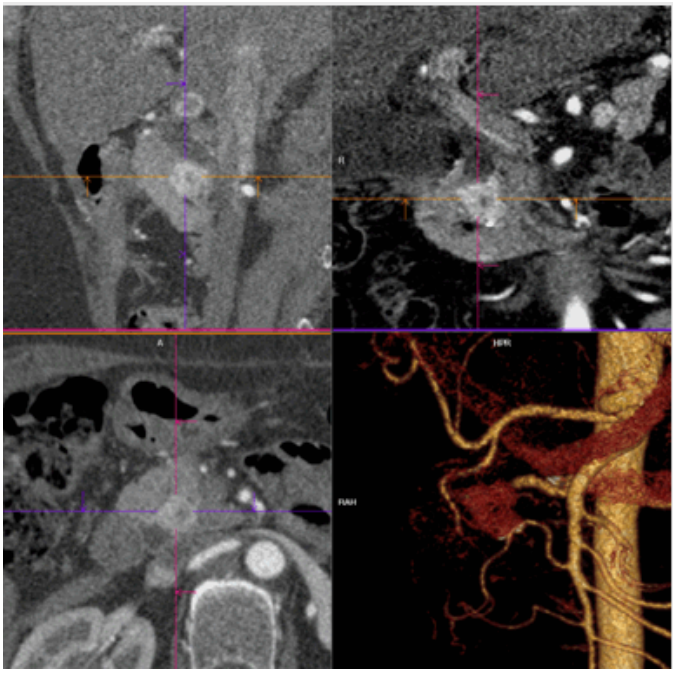

Figure 2: A follow-up computed tomography scan revealed tumor volume reduction; a small, hyperdense focus within the lower pole of the tumor, visible in the sagittal section, apparently corresponded to the embolic material.

A follow-up CT scan conducted six months after the procedure revealed the presence of embolic material in the inferomedial portion of the tumor and the regression of its size (Figure 2). Tumor volume reduction from 5 mL to 2.5 mL was confirmed using tumor-monitoring software; this reduction correlates with the suboptimal effect of the earlier embolization procedure.

At present, the patient is continuing her treatment with the long-acting synthetic somatostatin analog with satisfactory clinical consequences. She is also being monitored for the long-term effects of limiting arterial blood supply to the tumor. If the desired effects are not achieved, pharmacotherapy may be continued or the Kausch–Whipple procedure may be performed. Additionally, a second embolization may also be considered.

DISCUSSION

Diagnostic imaging in insulinoma can often be difficult due to the small size of the tumor which is <2 cm diameter in 80% of cases. This is why multiple imaging techniques are used [2].

Surgery is the treatment of choice for insulinoma, while the choice of surgical procedure depends on tumor size, location and histopathological characteristics. Laparoscopic tumor resection is recommended in tumors located in the body or tail of the pancreas. Classic surgery is performed, if exact tumor location is impossible to determine, or when multiple lesions are suspected [4]. It is then possible to use the intraoperative ultrasound scan and to perform gradual pancreatectomy with the intraoperative insulin level measurement in order to assess the extent of the surgery. When the lesion is located within the head of the pancreas, it is usually necessary to carry out a pancreatoduodenectomy, an extensive surgical procedure associated with a high risk of intraoperative and postoperative complications, significantly decreasing the quality of life, particularly in patients with neuroendocrine tumors [5]. If the tumor is malignant, total pancreatomy and lymphadenectomy can be performed [1].

Conservative treatment is recommended when surgical intervention is impossible due to the lack of consent or patient's health status, or when radical treatment is contraindicated due to advanced disease. Somatostatin is a natural inhibitor of pancreatic, intestinal and pituitary hormones and somatostatin analogues are used to prevent hypoglycemia. While observational studies have confirmed the efficacy of glycemia control using long-acting somatostatin analogues, this treatment is only effective in patients whose tumors contain somatostatin receptors [6], i.e., approximately 50% of all insulinomas.

Short-acting somatostatin analogues are used solely to stabilize a patient's condition and assess their therapeutic response to a drug. Diazoxide (not available in Poland) can be used as an alternative treatment but it causes edema, renal damage and hirsutism [3]. Interferon alpha can also be used as a part of conservative treatment. In case of inoperable, malignant tumors, chemotherapy using 5-fluorouracil and streptozotocin are viable options [1].

Single case reports describe afferent vessel embolization, a method of neuroendocrine tumor treatment which reduces tumor mass and relieves or leads to a complete resolution of hypoglycemic symptoms in an insulinoma [7]. It is sometimes used also as the preoperative strategy for tumor mass reduction before an extensive and aggressive surgery [8]. In the latter case it is a safe treatment method, especially when embolization involves a selectively chosen vessel. It shortens the duration of the consecutive surgery and reduces blood loss during the procedure [9, 10].

CONCLUSION

While the treatment of choice for insulinoma is surgery, conservative treatment is recommended when surgery is impossible or contraindicated. Afferent vessel embolization is a safe treatment option, while chemotherapy may be a treatment option for inoperable, malignant tumors.

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Author Contributions

Marcin Balawejder – 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

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

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

Renata Tuchendler – 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.

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CASE REPORT OPEN ACCESS

Lateral medullary syndrome post-chiropractic manipulation in a 25-year old female with headache

Matthew Kynan Burrage, Clare Therese Costello

ABSTRACT

Introduction: Cervical chiropractic manipulation for the treatment of back and neck pain is becoming increasingly commonplace, especially amongst younger adults. It may also give rise to serious complications, such as dissection of cervical arteries with resultant stroke syndromes. This case report reviews the literature surrounding this issue and highlights the importance of correctly diagnosing cerebrovascular pathology in young adults. Case Report: We describe a case of a 25-year-old female with delayed onset of focal neurology and lateral medullary syndrome post-chiropractic cervical manipulation. Magnetic resonance angiogram and computed tomography angiogram confirm lateral medullary infarction and bilateral vertebral artery dissection. Conclusion: Currently, chiropractic manipulation and complications are a relatively topical issue and some of the potential serious complications are discussed in this case. Certain posterior circulation stroke symptoms belong to distinct clinical syndromes and it is important to be aware of these when assessing patients with possible posterior circulation ischemia. This is especially important in younger populations, where misdiagnosis as migraine may be a common pitfall. Headache and focal neurology following chiropractic cervical manipulation should be managed and investigated with a high index of suspicion for vertebral artery dissection.

Keywords: Lateral medullary syndrome, Chiropractor, Vertebral dissection

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INTRODUCTION

Lateral medullary syndrome, a posterior circulation stroke syndrome with a distinct set of clinical findings, is a recognized consequence of vertebral artery dissection. Cervical artery dissection (including vertebral artery dissection) is a documented complication of chiropractic cervical spinal manipulation. This report presents a case of a young female who presented with bilateral vertebral artery dissection post-chiropractic manipulation. The incidence and clinical outcomes of vertebral artery dissection, and the pathophysiology and clinical findings present in lateral medullary syndrome, will be discussed.

CASE REPORT

A 25-year-old female presented to the emergency department in October 2011 with occipital headache of four-week duration and new onset dizziness, paresthesia, dysphagia, and 'pulling to the left', which developed whilst jogging that morning. History revealed visits to a chiropractor with posterior headache and neck pain, four weeks and one week prior to this presentation.

Cervical manipulation was performed on both occasions. Worsening left occipital and cervical pain developed following the second visit, with associated nausea and vomiting.

Neurological examination revealed an ataxic gait with falling to the left. Facial inspection revealed a left ptosis and miosis, consistent with partial left-sided Horner's syndrome. Nystagmus was present with rapid horizontal phase towards the right. Left-sided facial weakness and bulbar involvement was evident with a flattened left nasolabial fold, decreased left palatal movement, and uvula deviation to the right. Decreased pin-prick sensation and loss of temperature discrimination was detected over the left maxilla and throughout the right upper and lower limbs. Posterior columns were intact.

Left-sided cranial nerve signs, ipsilateral Horner's syndrome, and contralateral spinothalamic involvement suggested lateral medullary syndrome. A provisional diagnosis of a left medullary lesion secondary to vertebral artery dissection was made given the lack of typical stroke risk factors and the history of recent spinal manipulation. Differentials included embolic phenomena and tumor given the patient's age.

Magnetic resonance imaging (MRI) scan revealed a DWI-enhancing lesion in the left lateral medulla (Figure 1). Subsequent magnetic resonance angiography (MRA) was suspicious for left vertebral artery dissection. A follow-up MRI scan at 4th-week post-incident revealed a new, asymptomatic, lesion in the right cerebellum. Repeat MRA (Figure 2A) and CTA (Figure 2B) of the vertebral arteries revealed bilateral vertebral artery dissection with bilateral posterior inferior cerebellar artery (PICA) territory infarcts. The patient was managed conservatively with aspirin and atorvastatin, progressing well with rehabilitation.

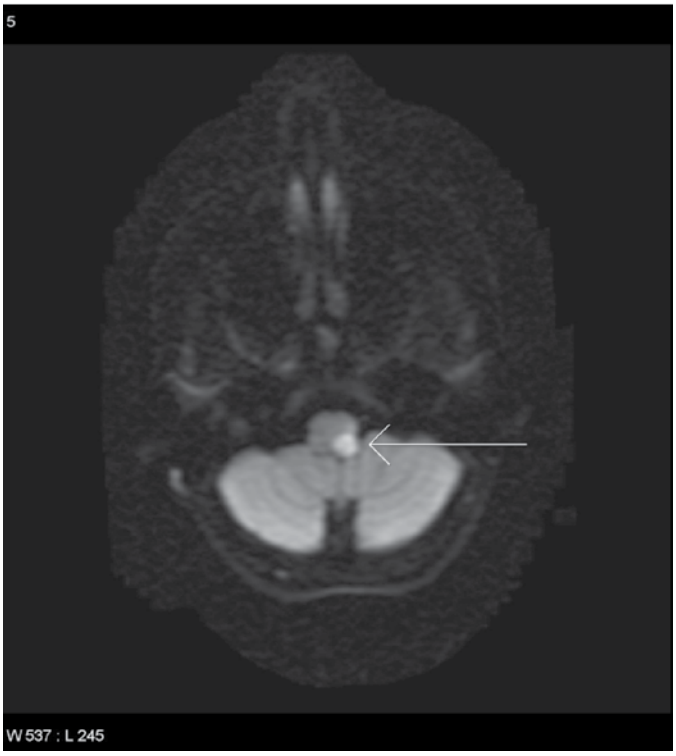

Figure 1: Left lateral medullary infarct caused by bilateral vertebral artery dissection. Diffusion weighted image on mangetic resonance imaging demonstrates a rounded focus of restricted diffusion consistent with a left lateral medullary infarct (arrow).

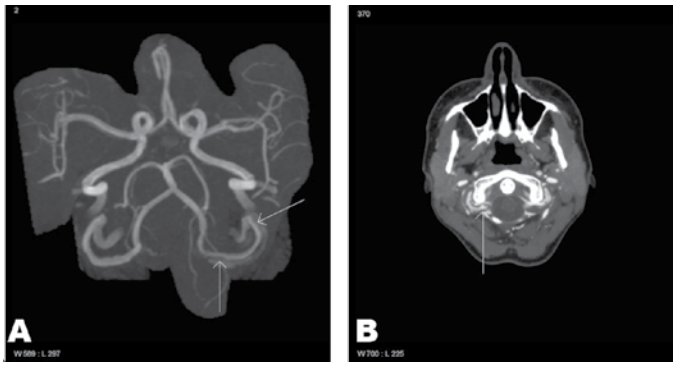

Figure 2: (A) Magnetic resonance imaging demonstrates bilateral vertebral artery irregular luminal narrowing consistent with bilateral vertebral artery dissection. This is more easily appreciated on the left (arrows). (B) Computed tomography angiogram of neck demonstrating irregular luminal narrowing and a focal dilatation of the right vertebral artery consistent with vertebral artery dissection and a dissecting aneurysm (arrow). Left vertebral artery dissection also present.

DISCUSSION

Lateral medullary syndrome (or Wallenberg syndrome) is a recognised complication of posterior circulation infarction, usually the result of ipsilateral vertebral artery or PICA occlusion [1]. Clinical features are related to vestibulocerebellar, sensory, bulbar and autonomic nuclei involvement (Table 1). Spinothalamic tract involvement leads to impaired pain and temperature sensation over the contralateral side of the body (due to fiber decussation in the spinal cord), while Horner's

Table 1: Features of lateral medullary syndrome [2].

General Symptoms	Ipsilateral Signs	Contralateral Signs
Dizziness * Vertigo Falling / veering to one side (ipsilateral) * Difficulty sitting upright without support Dysphagia * Diplopia *	Loss of pain and temperature sensation in face * Horner's syndrome (ptosis, miosis, anhydrosis) * Paralysis of palate * Laryngeal and pharyngeal paralysis Nystagmus (rotational component)	Loss of pain and temperature sensation in trunk and limbs * Uvula deviation * Nystagmus (rapid horizontal phase) *

syndrome (ipsilateral ptosis and miosis) is related to descending sympathetic tract impairment [1].

Cervical artery dissection (internal carotid or vertebral artery dissection (VAD) has an annual incidence of 2·6-3·0 per 100,000 people [2]. It is the primary cause of 2% of ischemic strokes but accounts for 10–25% in young adults [2].

There have been case reports associating chiropractic manipulation with unilateral and bilateral VAD and epidemiological links have been established [3, 4]. Spinal manipulation therapy is an independent risk factor for VAD and accelerates embolization in existing lesions [4]. The vertebral artery is particularly susceptible to cervical manipulation due to its mobility within the vertebral foramina, its proximity to the vertebral bodies, and its sharp directional change [3].

The aim of early diagnosis and treatment of VAD is to prevent progression to ischemic stroke and other thrombotic complications. Currently, there are no published multi-cohort trials evaluating anti-coagulation versus anti-platelet agents for treatment of VAD. A recent meta-analysis for internal carotid artery dissection revealed no significant difference in outcome between anticoagulants and anti-platelets [5]. Prognosis is usually favorable for VAD, with low recurrence rates, good functional recovery and high rates of recanalization [3].

CONCLUSION

Chiropractic spinal manipulation is a recognised cause of vertebral artery dissection (VAD) presenting symptoms may vary from ipsilateral occipital headache to signs of cerebral ischemia such as lateral medullary syndrome. Patients presenting with headache and focal neurology following spinal manipulation should be managed with a high index of suspicion.

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Author Contributions
Matthew Kynan Burrage – 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
Clare Therese Costello – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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CASE REPORT OPEN ACCESS

Torsion of the vermiform appendix: A rare intraoperative finding

Muhammad Yaman Adi, Mohammad Bader, Ingo Jester

ABSTRACT

Introduction: Torsion of the vermiform appendix is a rare intraoperative diagnosis. The clinical presentation is identical to that of acute appendicitis, with preoperative investigations playing a minimal role. The aetiology of the torsion is unclear, though it has been associated with fecoliths, lipomas and mucoceles of the appendix. Case Report: This case report describes a rare presentation of a four-year-old boy with a history and examination classical of acute appendicitis. Intraoperatively, a torsion of the vermiform appendix was found. The clinical presentation and operative intervention are reviewed. Conclusion: Torsion of the vermiform appendix is a rare cause of acute abdominal pain, mimicking acute appendicitis in presentation. Clinicians need to be aware of this intraoperative diagnosis and be able to manage it in the theatre.

Keywords: Torsion, Vermiform appendix, Appendicitis, Pediatric

****

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INTRODUCTION

Torsion of the vermiform appendix is a rare intraoperative diagnosis. It was first reported in 1918, which was clinically identical in presentation to acute appendicitis [1]. It has been reported 30 times in the last century, half of which were in pediatric patients [2]. The aetiology of the torsion is unclear. Herein, we present a four-year-old boy with acute appendicitis and diagnosed as appendicular torsion.

CASE REPORT

A four-year-old boy was presented with a three-day history of central abdominal pain and vomiting. Pain was localized to the right iliac fossa. On examination, he was pyrexial. He had a tender abdomen with rebound tenderness in the right iliac fossa. He had a past medical history of adenotonsillectomy and grommet insertions.

No hematological or radiological investigations were required. Clinical examination was suggestive of acute appendicitis. Therefore, he was taken to operation theatre for a laparoscopic appendicectomy on the same day.

At the time of operation, he was discovered to have 720 degrees torsion of the vermiform appendix (Figure 1) with ischemic changes in the distal half. A thrombosed vessel was visualized. A perforation was not present. The appendix had adhered to the inner inguinal opening, however a patent orifice was not seen. The appendix

was then peeled off this area and three endoloops were applied and appendicectomy was performed. He made an uneventful recovery and was discharged the following day. His histopathology was consistent with hemorrhagic infarction of the appendix.

Histopathology

Macroscopic: The appendix measured 7x1x1 cm with a congested surface and hemorrhagic attached fat 3x2 cm. On the cut surface the appendix wall was brown and had hemorrhagic luminal contents.

Microscopic: This confirmed severe acute congestion of the appendiceal wall associated with extensive mucosal, subserosal as well as mesoappendiceal hemorrhage. The mucosa was completely necrotic and focally the necrosis extended into the muscularis propria. Acute serosal inflammation was also present.

Diagnostic summary: Hemorrhagic infarction of the appendix.

DISCUSSION

Even though acute appendicitis is one of the most common surgical emergencies, torsion of the vermiform appendix, which mimics acute appendicitis, is a rare phenomenon. It is unclear how the torsion develops though several aetiologies have been reported. Some have described it as a primary event due to the appendix being of a longer length, having poor fixation and narrow mesentery. Others have reported cases as a secondary event due to irregular peristaltic movements of the appendix [1], inflammation of the distal appendix [3], or presence of fecoliths, lipomas and mucoceles of the appendix [4–6]. Mostly, the appendix torsion is in a counterclockwise direction (as in this case) [6].

It is difficult to describe the exact cause of the torsion in this case. We theorized two questions: Was the torsion a primary event that caused tip inflammation, which then led it to adhere to the anterior abdominal wall? Or did the inflammation of the appendix cause the tip to adhere to the abdominal wall, which then led to the torsion by secondary means such as poor fixation or bowel peristalsis? Other secondary factors, such as fecoliths, lipomas or mucoceles, were not present in this case.

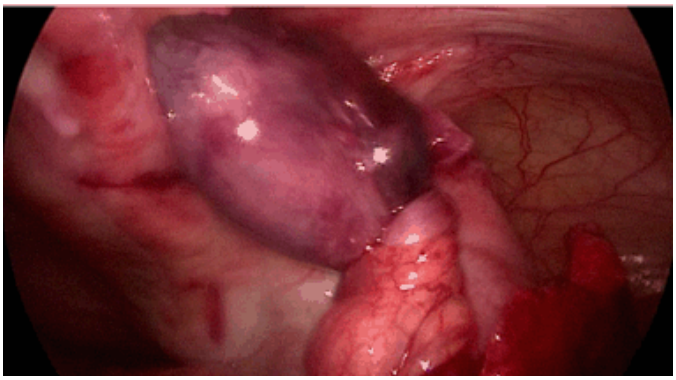

Figure 1: Intraoperative laparoscopic photograph: Torsion of the vermiform appendix (720 degrees).

The position of the appendix in these cases is commonly described as lying free or pelvic [7]. However, the case reported revealed an appendix that had adhered to the anterior abdominal wall.

Imaging does not play major role in these cases. One report described how an ultrasound scan performed twice showed a distended bowel loop on both the occasions [8], but still underwent an operation for diagnostic and therapeutic measures. This patient had the same outcome as the case reported above, though investigations were not performed in our case.

CONCLUSION

Torsion of the vermiform appendix is a rare finding in patients presenting as an acute appendicitis. The diagnosis remains an intraoperative one, with preoperative investigations playing a minimal role. The torsion can be caused by a primary or secondary event. Nonetheless, they will have an appendectomy performed, and therefore the operating surgeon needs to be aware of this intraoperative finding and how to manage it.

****

Author Contributions

Muhammad Yaman Adi – Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Mohammad Bader – Conception and design, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Ingo Jester – Conception and design, Analysis and interpretation of data, Critical revision of 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

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CASE REPORT OPEN ACCESS

The role of intravascular ultrasound scan and thin-sliced coronary computed tomography angiography in diagnosing aortic dissection causing acute myocardial infarction

Daisuke Nagatomo, Daizaburo Yanagi, Takeshi Serikawa, Masanori Okabe, Yusuke Yamamoto

ABSTRACT

Introduction: Acute aortic dissection is a disease of high mortality. The symptoms may mimic other conditions and misdiagnosed, such as acute coronary syndrome, coronary involvement complicates the clinical scenario and increases mortality. Case Report: We herein report a case of an acute myocardial infarction caused by acute aortic dissection. Without noticing the aortic dissection, we performed emergent coronary angiography, which showed severe stenosis of the proximal right coronary artery. Intravascular ultrasound scan led us to suspect aortic dissection. However, we performed balloon angioplasty because the patient's hemodynamic status was unstable. ECG-gated coronary computed tomography angiography provided a definitive diagnosis, and the patient underwent successful surgical repair of the aortic dissection. Conclusion: Acute coronary syndrome associated with acute aortic dissection is not rare. However, the management of these conditions depends on the details of each case. This case demonstrates the difficulty of treating such cases in the real world. Herein, we describe educational imaging findings and briefly discuss the management of cases involving acute coronary syndrome associated with acute aortic dissection.

Keywords: Coronary computed tomography angiography, Acute aortic dissection, Acute myocardial infarction

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INTRODUCTION

Patients with acute aortic dissection (AAD) may initially present with only signs of acute coronary syndrome (ACS), such as ST elevation on electrocardiograms (ECGs). In such situations, the correct diagnosis may be missed. A diagnosis of acute coronary syndrome may lead to the inappropriate administration of thrombolytic agents, resulting in catastrophic consequences. Transthoracic echocardiography is useful as a simple imaging test. However, its diagnostic capability is sometimes insufficient in the emergency room. Although the exact diagnosis can be reached, the management of these conditions remains controversial, with only a few reports in literature.

CASE REPORT

A 62-year-old male with the sudden onset severe chest pain was transferred to our emergency room by ambulance. He had a history of aortic valve replacement (AVR) due to aortic regurgitation of the tricuspid valve four years earlier. The AVR had thus been performed using a mechanical valve and the prothrombin time-international normalized level at admission was 1.76. He did not suffer from back pain and no laterality of the blood pressure was observed. An ECG showed ST-segment elevation in leads II, III and aVF (Figure 1), suggesting inferior acute myocardial infarction (AMI). A chest X-ray showed no abnormalities. On the trans thoracic echocardiography neither mechanical valve failure or cardiac tamponade was observed. We performed emergent coronary angiography, which revealed a long tight lesion in the proximal segment of the right coronary artery (RCA) (Figure 2) and normal left coronary artery. We planned to perform emergent percutaneous coronary intervention (PCI), however, intravascular ultrasound (IVUS) scan performed before PCI revealed a hypoechoic mass around the stenoticlesion. The narrowing lumen appeared not to be occupied by thrombi, but rather was oppressed by the surrounding mass (Figure 3). These findings suggested that ascending aortic dissection had caused AMI. Although we considered emergent surgical repair, we decided to perform PCI first because the ST level was still elevated and the patient's hemodynamic status was unstable. Balloon angioplasty improved the flow of the RCA, and the hemodynamics was stabilized. We did

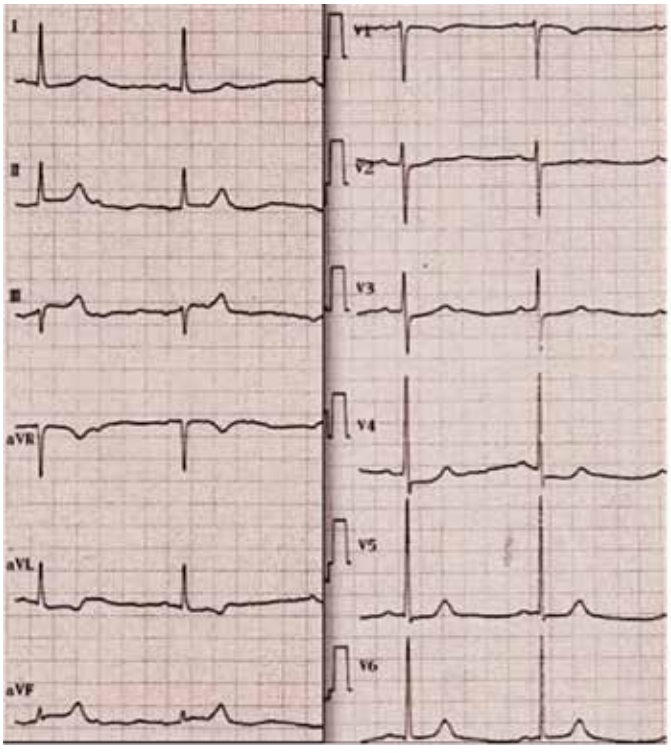

Figure 1: An electrocardiograms showing ST-segment elevation in leads II, III and aVF, suggesting acute myocardial infarction.

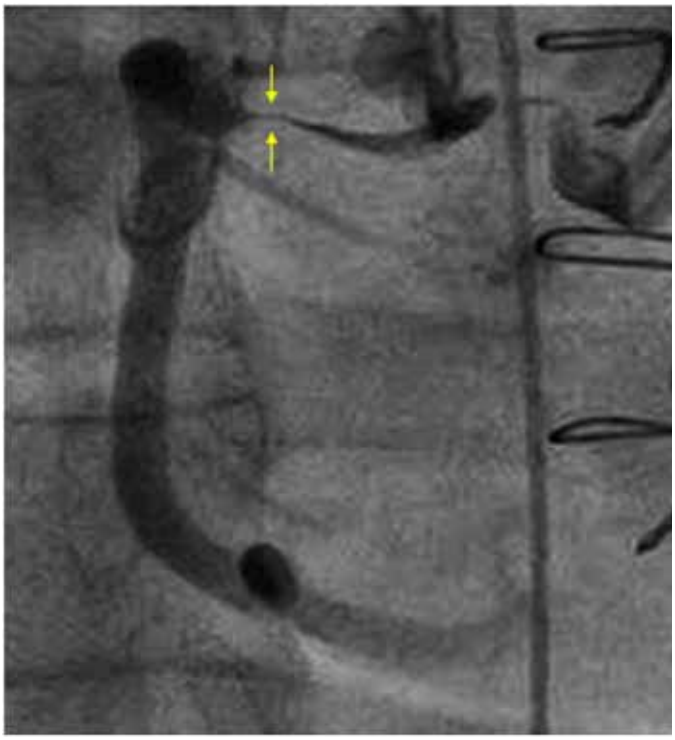

Figure 2: Coronary angiography showing a long, tight lesion in the proximal right coronary artery (arrow).

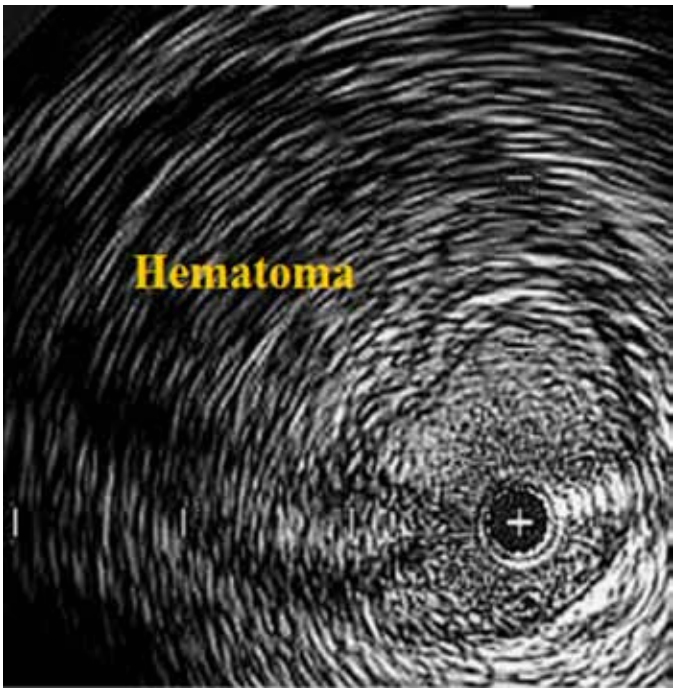

Figure 3: On intravascular ultrasound scan, a hematoma (arrow) was observed around the coronary artery. The narrowing lumen of the right coronary artery did not appear to be occupied by atheromatous plaque or thrombi but rather oppressed by the surrounding mass. The mass continued to the aorta on manual pull-back of the intravascular ultrasound catheter.

not implant any stents because we wished to avoid the use of antiplatelet agents and did not recognize the acute recoil after balloon angioplasty. Acute aortic dissection was definitely diagnosed following contrast-enhanced computed tomography (CT) angiography (Figures 4 and 5), which clearly showed that the proximal RCA was embedded and oppressed by the intramural hematoma (Figure 5A). The left main trunk was mildly oppressed by the communicating false lumen of the dissection (Figure 5B–C). The patient underwent successful surgical repair of the aortic dissection.

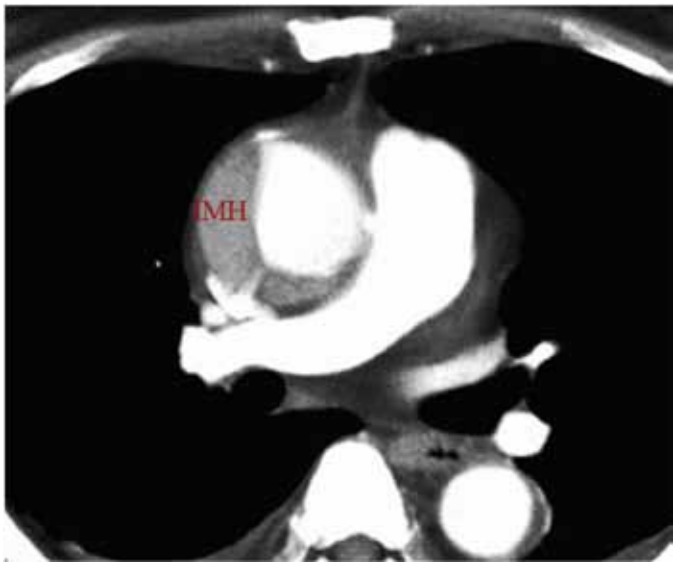

Figure 4: Computed tomography scan showing an intramural hematoma in the ascending aorta.

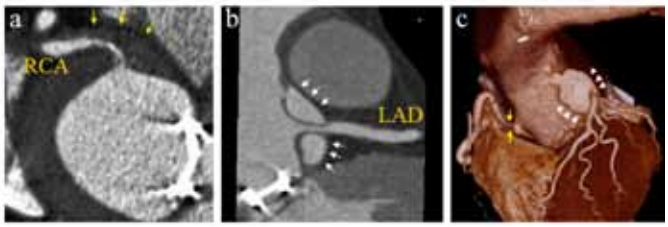

Figure 5: (A) Coronary computed tomography angiography showing the right coronary artery was embedded and oppressed by the intramural hematoma (yellow arrow), (B) On multi-planar reconstruction imaging, the left main trunk appeared to be mildly oppressed by the communicating false lumen (white arrow), (C) Volume rendering imaging showed that the proximal segment of the right coronary artery was oppressed (yellow arrow) and the left main trunk was embedded in the communicating false lumen (white arrowhead).

DISCUSSION

Acute aortic dissection can occur as one of the most serious complication late complications after AVR. Predictors of AAD after AVR include fragility and thinning of the ascending aorta, aortic dilatation, AR at initial AVR (especially, bicuspid aortic valve) and hypertension [1]. In addition, coronary involvement is a fatal complication of AAD, with a reported incidence of from one to two percent [2]. However, AAD itself sometimes fails to demonstrate any of the classical physical findings, such as a widened mediastinum, aortic regurgitation or the laterality of blood pressure, and up to 30% of patients suffering from AAD are therefore initially suspected to have other conditions [3, 4].

In this case, we could not diagnose AAD based on either the physical findings, chest X-ray or transthoracic echocardiography in the emergency room even though the patient had a history of AVR. Therefore, if when treating AMI patients in the emergency room, especially those with inferior AMI, clinicians should suspect the existence of aortic dissection at the back of the AMI [4]. However, if aortic dissection cannot be diagnosed in the emergency room in such cases, emergent CAG should be performed. Once AAD is identified as the cause of AMI, the question arised as to how the patient should be managed in the catheterization laboratory? It is controversial to first perform emergent surgical repair of the aorta, or primary PCI before surgery. Furthermore, whether to implant a stentis a difficult choice. The use of strong antiplatelet therapy can result in surgical difficulties, while the strong radial force of the implanted stent would assure a more stable coronary flow. Therefore, this decision should be made based on whether the patient is stable hemodynamically [5]. The findings of IVUS scan and coronary CT angiography in the present case are very educational, as they clearly showed AAD involving the coronary artery. In addition, this case highlights the difficulty of treating similar cases in the real world.

CONCLUSION

Acute coronary syndrome associated with acute aortic dissection is not rare. However, the management of these conditions depends on the details of each case, and there are many cases that the guidelines cannot be applied. This case demonstrates the difficulty in treating similar cases in the real world. We performed balloon angioplasty, refraining from using stenting before surgery, and subsequently obtained a good result. We believe that this therapeutic regimen is a potential treatment choice in cases involving a poorly disturbed coronary flow.

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Author Contributions

Daisuke Nagatomo – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

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Takeshi Serikawa – Conception and design, Acquisition of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Masanori Okabe – Conception and design, Critical revision of the article, Final approval of the version to be published
Yusuke Yamamoto – Conception and design, Drafting the article, Critical revision of the article, Final approval of the version to be published

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Yamamoto (MD and PhD) is now heading Cardiovascular and Aortic Center of Saiseikai Fukuoka General Hospital, Fukuoka, Japan. He is also clinical professor of Kyushu University (Cardiology), Fukuoka, Japan. He researched the pathophysiology of coronary artery spasm at Kyushu University and published several papers in Circulation 1986;74:826, Circulation Research 1987;60:113, 1987;61:772 and JACC 1989;63:33. Then, he studied Cardiac PET in Hammersmith Hospital of London University and wrote some papers in J Nucl Med 1991;32:2169, J Physiol 1992;446:219, Circulation 1992;86:167, 1992;86:1738, 1996;94:792 and 1996;94:808. His present interest is the relationship between ischemic heart disease and environmental issues, especially air pollution.

CASE REPORT OPEN ACCESS

A case of brucella endocarditis of the native aortic valve

Aydin Rodi Tosu, Şerafettin Demir, Murat Selçuk, Mustafa Kemal Avşar

ABSTRACT

Introduction: Brucella endocarditis is a rare but severe complication of brucellosis. Although it is observed in less than 2% of the brucellosis cases, it is the main cause responsible for up to 80% of infection-related deaths in brucellosis. Case Report: Herein, we present a case of Brucella endocarditis that developed on a native aortic valve. The diagnosis was proven by positive blood cultures and isolation of *Brucella melitensis* from the excised valve. Conclusion: Although endocarditis associated with brucella infection is rare, it may be more frequently observed in the regions where brucellosis is endemic. Therefore, especially in these regions, Brucella endocarditis must be considered during the diagnosis of infective endocarditis.

Keywords: Brucella endocarditis, Aortic valve, *Brucella melitensis*

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INTRODUCTION

Brucellosis is a zoonotic disease caused by bacteria from the genus *Brucella* and widely observed around the world [1]. Since it can involve every organ or tissue, no specific clinical diagnosis is possible and it can lead to various complications that can affect multiple systems. Although endocarditis is rarely observed, it is also the complication that leads to the highest mortality rates by brucellosis. In literature, the frequency of endocarditis related to brucellosis has been reported to be under 2% [1, 2]. Therefore, this agent must be considered in cases of infective endocarditis in regions where brucellosis is endemic.

CASE REPORT

A 43-year-old male was presented to our clinic with the complaints of fever, had recent history of trichiniasis, malaise, and pain in the knee and waist regions for the last three weeks. According to the patient history, he was diagnosed with brucellosis four months ago and was under medical treatment. The patient was a farmer and stock-breeder from a village. During his physical examination, his blood pressure 90/55 mmHg, peak pulse 102 bpm, and body temperature was 38.5°C. His respiratory sounds were normal and he had a 2/6 cardiac systolic ejection murmur at right 2.intercostal

space. There was no sign of organomegaly and other systemic examinations were normal. The laboratory tests revealed the following results: hemoglobin 10.9 mg/dL, hematocrit 33.2%, leukocytes 14.400, thrombocytes 225.000, sedimentation rate 76 mm/hour, and CRP 178 mg/L. The transthoracic echocardiography indicated and an ejection fraction of 62% and a mobile vegetation (mean/max gradient 32/54 mmHg) on the right coronary cusp of the aortic valve. The aortic valve had a diameter of 23x17 mm, which pointed out an aortic stenosis (Figure 1). The patient was admitted to the cardiology clinic with the pre-diagnosis of infective endocarditis and started on a regimen of gentamicin (160 mg/day) and vancomycin (2 g/day). When the standard brucellosis agglutination test indicated a 1/1280 (+) result, gentamicin and vancomycin were replaced with rifampicin (600 mg/day), doxycycline (200 mg/day) and trimethoprim/sulfamethoxazole (TMP-SMX) (320/1600 mg/day) based on the diagnosis of brucellosis endocarditis. Also, *Brucella melitensis* growth was observed in the three blood cultures. The transesophageal echocardiography performed on the fifth day of the treatment indicated minimal decrease in the dimensions of the vegetation with continued aortic stenosis. Based on the cardiovascular surgery consultation, the patient was taken to surgery. During the surgery, after a median sternotomy was performed, the cardiopulmonary by-pass was initiated and blood cardioplegia was administered under a medium-deep hypothermia. The aortotomy revealed 1 cm vegetation in the right coronary cusp. Severe stenosis was observed in the valvular area and all three cusps showed thickening and loss of mobility, which were especially apparent in the right coronary cusp. The valve was excised together with the vegetation and replaced with a Nr. 23 St. Jude prosthetic valve. During the postoperative period, the patient showed a normal recovery. *Brucella melitensis* growth was observed in the culture of the excised valve. No complications occurred in the wake of the successful surgery. The pathological examination of the excised valve also indicated *Brucella melintesis* growth. During the postoperative follow-up of the patient, his fever was reduced and his laboratory findings were improved. After the second postoperative month, the treatment was continued with rifampicin and TMP-SMX until the sixth month. During the control visit at the first postoperative month, the infection was observed to subside and the transesophageal echocardiography indicated no vegetation. The patient, who was implanted a normal functional prosthetic aortic valve, is currently under monitoring and remains asymptomatic.

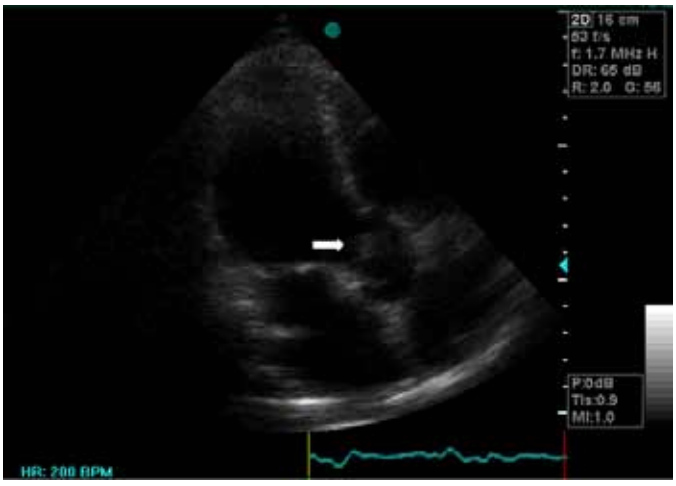

Figure 1: The vegetation on the aortic valve from the apical five-chamber view in the transthoracic echocardiography.

DISCUSSION

Although brucellosis is widespread throughout the world, it is a zoonotic disease endemic to the Mediterranean countries and the Middle East [3]. It is transmitted through direct contact with animals or environments infected through the excrements of infectious animals [3, 4]. Among the bacteria of the genus *Brucella*, *B. melitensis* has the highest rate of virulence and causes the most severe disease [1, 4]. The patient history had revealed that the patient was involved in stock breeding and was already diagnosed with brucellosis four months ago. In patients with *B. melitensis* infection, osteoarticular (sacroiliitis), genitourinary (epididymo-orchitis in men) and neural (meningitis) involvement is frequently observed [1]. In brucella endocarditis, aortic valve involvement is frequently observed and endocarditis is the most common cause of death [5, 6]. Endocarditis is a complication which may be overlooked during the course of brucellosis unless it is specifically considered. The diagnosis of infective endocarditis due to brucellosis is based on the epidemiological factors, clinical findings, serologic tests, blood culture and echocardiography [1–8]. Echocardiographic examination is a noninvasive method which may be helpful both in the diagnosis of infective endocarditis and in the decision for surgery. Echocardiography is a method that also reveals the valvular structure and the presence of any masses such as abscesses or vegetation [9–11]. Various antibiotics including tetracyclines, doxycycline, trimethoprim/sulfamethoxazole, rifampin and streptomycin can be effectively used for the treatment of brucellosis endocarditis. The antibiotic regimen should include multiple types of antibiotics over a few weeks [3, 12]. Although the related literature recommends only medical treatment in brucella endocarditis, the general treatment approach also involves surgery subsequent to the medical treatment [3, 8, 9, 13]. The suggested duration of the postoperative antibiotic treatment is between 1 month and 1 year [14].

In our patient, the diagnosis was based on the clinical observation, positive serology tests, observation of the vegetation on the aortic valve through echocardiography and the detection of *Brucella melitensis* growth in more than one blood culture as well as the excised valve. In spite of the antibiotherapy, only minimal reduction was

observed in the vegetation during the transesophageal echocardiography performed on the fifth day. Since the patient's symptoms did not show any improvement, he was referred to surgery. The two blood cultures obtained with one week interval at the end of the first surgical month and incubated for four weeks showed no bacterial growth. The postoperative antibiotherapy was continued until the sixth postoperative month. No relapses occurred during the six month follow-up period of the patient.

CONCLUSION

Although endocarditis associated with brucella infection is rare, it may be more frequently observed in the regions where brucellosis is endemic. Therefore, especially in these regions, brucellosis endocarditis must be considered during the diagnosis of infective endocarditis.

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Author Contributions

Aydın Rodi Tosu – Substantial contributions to the conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Şerafettin Demir – Substantial contributions to the conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Murat Selçuk – Substantial contributions to the conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Mustafa Kemal Avşar – Substantial contributions to the conception and design, Acquisition of data, 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.

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CASE REPORT OPEN ACCESS

Mechanical ileus following a ruptured abdominal aneurysm

Margaretha M Tjeenk Willink, Robert Haverlag, Robert C Minnee

ABSTRACT

Introduction: Many different factors are known to be able to cause an ileus. Case Report: A 72-year-old male underwent an endovascular procedure to treat his ruptured abdominal aneurysm. He developed a mechanical ileus five days after surgery. During re-operation an enormous retroperitoneal hematoma was revealed, causing the obstruction. Conclusion: Radiological re-evaluation can be useful and operative exploration must be considered in case of imminent perforation and/or after unsuccessful (conservative) therapy of an ileus. One should be aware that a retroperitoneal hematoma following a ruptured abdominal aneurysm can, in rare cases, cause a large bowel obstruction and therefore may need surgical intervention.

Keywords: Ileus, Abdominal aneurysm, Bowel obstruction, Retroperitoneal hematoma

How to cite this article

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INTRODUCTION

Many different factors have been identified to be able to cause an ileus. Both a paralytic ileus and a mechanical ileus (i.e., bowel obstruction) are known complications after surgery [1]. Causes of a postoperative ileus include medication, metabolic, neurogenic, infectious or obstructive issues such as adhesions.

A large bowel obstruction due to a retroperitoneal hematoma following a ruptured abdominal aneurysm however is rare. To our knowledge no publication has ever described a similar case.

CASE REPORT

A 72-year-old male presented with pain in his lower back. The patient reported an acute onset with abdominal discomfort. His medical history consisted of total hip replacement on the left side, total knee replacement on the right side, transient ischemic attack and spinal disc herniation. He had no history of abdominal surgery or other medical problems. Furthermore, he was not taking any medication, and both social- and family history were of no additional value. The vital signs were normal. Physical examination revealed a painful pulsating mass in the abdomen. Laboratory findings, including C-reactive protein, leukocyte and hemoglobin levels were normal. A contrast-enhanced computed tomography (CT) scan showed a descending thoracic aortic dissection and a ruptured abdominal aorta aneurysm infrarenally. The patient was admitted to the hospital and underwent an emergency endovascular procedure to treat both the dissection and the ruptured aneurysm. Five days after the operation, he developed an ileus. He reported abdominal discomfort with nausea and vomiting. Bowel sounds were high pitched. His abdomen was distended with a painful right lower quadrant during palpation. Laboratory studies included (normal adult range): hemoglobin 6.3

g/dL (8.5 – 11.0 g/dL), leucocytes 17.0 x 10^9/L (4 to 10), thrombocytes 359x10^9/L (150 to 400), and C-reactive protein (CRP) 223 mg/L (<10). Plain abdominal X-ray showed a dilated cecum suspected of a volvulus (Figure 1). A colonoscopy was performed showing only fecal contamination of the colon, which was treated with enema's. A computed tomography scan of the abdomen was performed which confirmed distension of the cecem without showing a possible cause. Due to insufficient effect after conservative treatment a laparotomy was performed 12 days after the initial operation, during which a large retroperitoneal hematoma causing a mechanical obstruction by compressing the large bowel, was revealed. The cecum was distended to a diameter of +/-15 cm. No gangrene was seen and the ileocecal valve was competent. However, due to an imminent perforation of the cecum based on a large serosal tear, an ileocecal resection had to be done, leaving the patient with an ileostomy (Figure 2).

Patient was discharged without any additional complications.

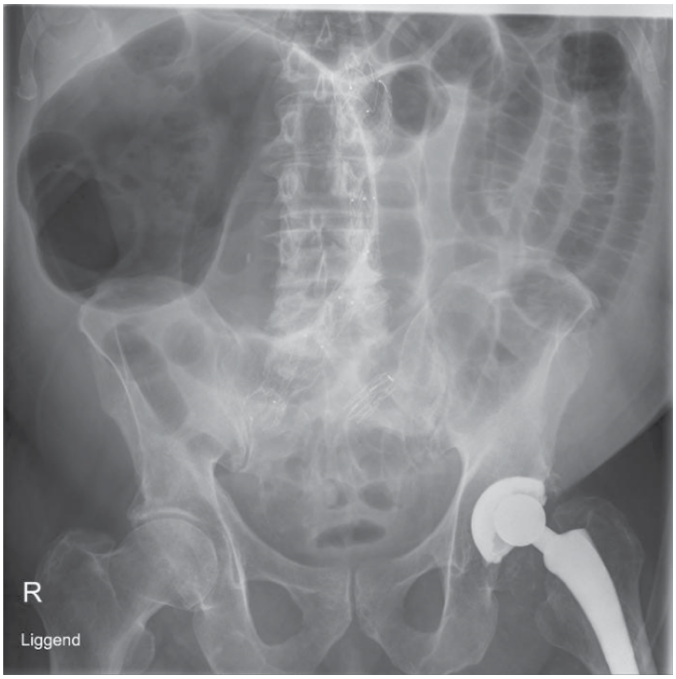

Figure 1: X-ray showing distended bowel.

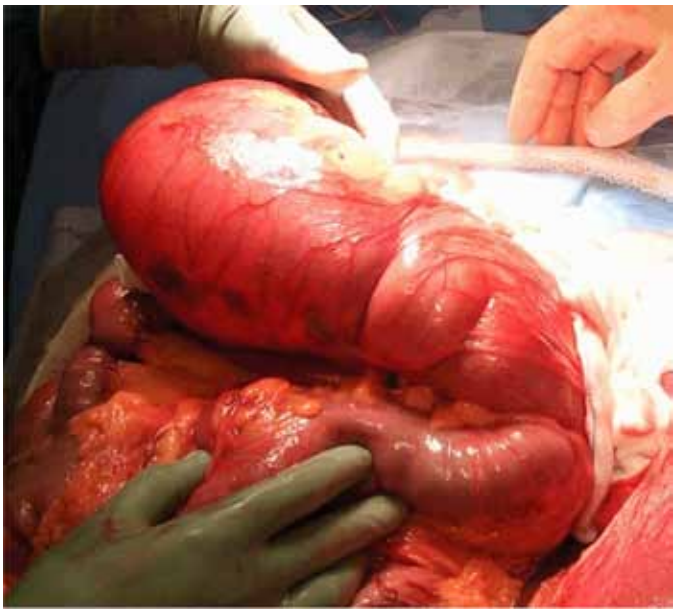

Figure 2: Distended bowel during laparotomy.

DISCUSSION

This is the first publication reporting a large bowel obstruction due to a retroperitoneal hematoma, following endovascular repair of a ruptured abdominal aneurysm.

Politoske described a case of a ruptured abdominal aneurysm presenting as an obstruction of the left colon [2]. Duodenal and small bowel obstructions have been seen more frequently after infrarenal aortic aneurysm repair [3]. The reported incidence of duodenal obstruction ranges from less than 1–2.5% and is always located in the third or fourth part of the duodenum [4, 5]. Lord suggest that the obstruction is usually caused by perigraft collagenous adhesions and is probably less likely to occur if the mobilized duodenum is not replaced directly over the aorta during the resuturing of the retroperitoneum [6].

Both an ileus and mechanical bowel obstructions are known complications after surgery [1]. Malinzak et al. found that these gastrointestinal complications are seen with a similar frequency after endovascular aneurysm repair as after open aortic repair [7]. Especially, after large vascular procedures such as abdominal aortic aneurysm repair one must also consider ischemic colitis as a cause of postoperative abdominal discomfort [8].

A retroperitoneal hematoma, sometimes present after abdominal aneurysm repair, hardly ever requires surgery. In case it causes an ileus, usually due to peritoneal irritation [9], continuous nasogastric suction should be employed and total parenteral nutrition initiated. Radiological re-evaluation can be useful and operative exploration must be considered in case of possible obstruction, imminent perforation and/or after unsuccessful conservative therapy.

CONCLUSION

One should be aware that a retroperitoneal hematoma following a ruptured abdominal aneurysm can, in rare cases, cause a large bowel obstruction and therefore may need surgical intervention.

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Author Contributions

Margaretha M Tjeenk Willink – 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
Robert Haverlag – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Robert C Minnee – Substantial contributions to conception and design, acquisition of data, 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

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CASE IN IMAGES OPEN ACCESS

Arrhythmogenic right ventricular dysplasia masquerading as right ventricular outflow tract tachycardia

Daniel Pop-Mandru, Gabriel Cismaru, Dana Pop, Dumitru Zdrenghea

ABSTRACT

Introduction: Ventricular tachycardia is a frequent complication in patients affected by arrhythmogenic right ventricular dysplasia. The disease is characterized by malignant ventricular arrhythmias with poor outcome, right ventricular dilation and replacement of the myocardium with fatty and fibrous tissue. On the other hand, right ventricular outflow tract tachycardia does not appear to have any significant effect on cardiac mortality as it arises in the absence of any structural heart disease. Case Report: Herein, we discussed a 62-year-old female patient with ventricular tachycardia that suggested right ventricular outflow tract tachycardia. Based on echocardiography, electrophysiological study and magnetic resonance imaging the final diagnosis was arrhythmogenic right ventricular dysplasia. During electrophysiological study two ventricular tachycardias were induced, one hemodynamically stable and one with hemodynamic deterioration. The patient received an implantable cardioverter-defibrillator for prevention of sudden cardiac death. Conclusion: Electrophysiological study in combination with other diagnostic tools such as magnetic resonance imaging, echocardiography and 12-lead electrocardiography is useful for the differential diagnosis between arrhythmogenic right ventricular dysplasia and right ventricular outflow tract tachycardia and contributes to decision of implantable cardioverter defibrillators implantation.

Keywords: Ventricular tachycardia, Electrophysiological study, Arrhythmogenic right ventricular dysplasia, Implantable cardiac defibrillator (ICD)

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INTRODUCTION

When the ventricular tachycardia (VT) exhibits a left bundle branch block (LBBB) pattern with an inferior axis, differential diagnosis must be made between arrhythmogenic right ventricular dysplasia (ARVD) and right ventricular outflow tract tachycardia (RVOT).

An ARVD is a disease that affects predominantly the right ventricle and is characterized by life-threatening malignant ventricular arrhythmias. It involves replacement of myocardium with fatty and fibrous tissue.

This myocardial damage is associated with ventricular tachycardia and increased risk of sudden cardiac death [1]. Recommendations concerning the diagnosis and management of patients with ARVD were developed. The diagnosis is difficult and is currently based on electrocardiography (ECG), echocardiography, magnetic resonance imaging (MRI) scan, and right ventricular biopsy [2].

Idiopathic VT from RVOT is monomorphic and generally not familial. It shows specific morphologic features: LBBB morphology and QRS axis directed inferiorly. Echocardiography and MRI scan show normal RV and RVOT although small anatomical changes have been demonstrated during MRI examination [3, 4].

The difference between ARVD and RVOT is important when discussing prognosis and management options. An RVOT is considered to be curative with radiofrequency catheter ablation. This is the first line treatment for symptomatic patients [3]. The role of ablation in ARVD is more limited with lower acute success rates and with high later recurrences. The progressive nature of the disease and the risk of sudden cardiac death by severe ventricular arrhythmias make the implantable cardioverter defibrillators (ICD) implantation the principal recommendation in this group of patients.

CASE REPORT

A 62-year-old female was presented with palpitations in a district hospital and 12-lead ECG revealed wide QRS complex tachycardia suggesting RVOT. She was referred to our department for electrophysiological study and ablation. During the last month, she presented similar episodes with palpitations and dizziness. An LBBB morphology with inferior axis suggested RVOT (Figure 1). On admission, the patient had no sign of cardiac failure. No previous similar medical history was found in her family. On physical examination, her blood pressure was 130/70 mmHg. Neither moist nor dry rale could be auscultated in her lungs. Heart rate was 70 bpm. The systolic cardiac murmurs auscultated at the tricuspid valve was 2/6 ~ 3/6. She had no signs of pitting Oedema at lower extremities. The transaminase level was normal including the renal function and the ionogram. Her chest X-ray showed mild increase of transverse cardiac diameter with uplifted apex and rounded left heart border (Figure 2). Electrocardiography demonstrated normal sinus rhythm with a heart rate of 77 bpm, incomplete right bundle branch block (RBBB), right-axis deviation, low voltage in the leads of the extremities, ventricular extrasystoles (with RBBB morphology), and T-wave inversion in leads V1 through V_3 (Figure 3). Epsilon wave was apparent in leads V1 and V2. (Figure 4). Two-dimensional echocardiography showed enlargement of right ventricle (40 mm from parasternal great axis), with reduced right ventricular function: (low TAPSE value and S-wave in TDI at the free lateral wall of the right ventricle), associated with right atrium enlargement and severe tricuspid valve insufficiency. Further echocardiographic findings were a grade II mitral valve insufficiency and left ventricular ejection fraction of 50% (Figure 5).

After signing a consent form, the patient underwent an electrophysiological study under cover of antiarrhythmic drugs which revealed two types of VT induced by ventricular programmed stimulation. The first VT associated pre-syncope and was stopped by ventricular overdrive (Figures 6–8). The second VT was rapid with a cycle length of 300 ms, evoluated with syncope and

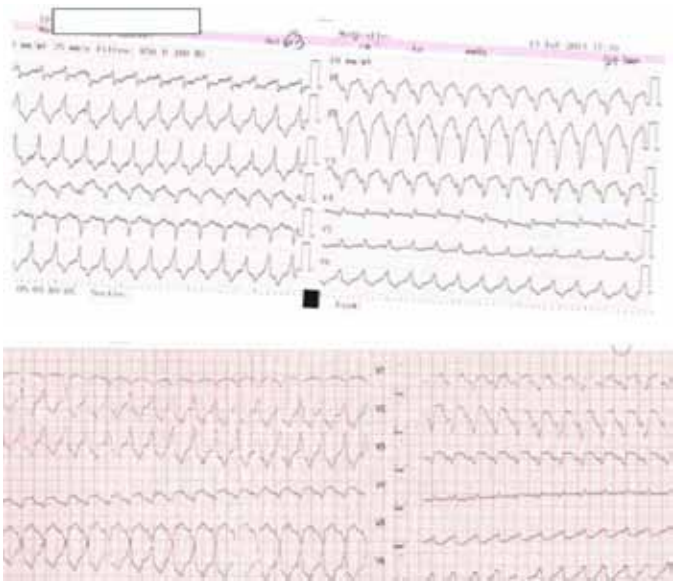

Figure 1: Recording of 12-lead electrocardiogram during four hours lasting tachycardia, showing: large QRS complex tachycardia with a left bundle branch block morphology and inferior axis; heart rate of 165 bpm. Positivity in leads II, II and avF suggests upper part of the right ventricle (right ventricular outflow tract) as origin of the ventricular tachycardia.

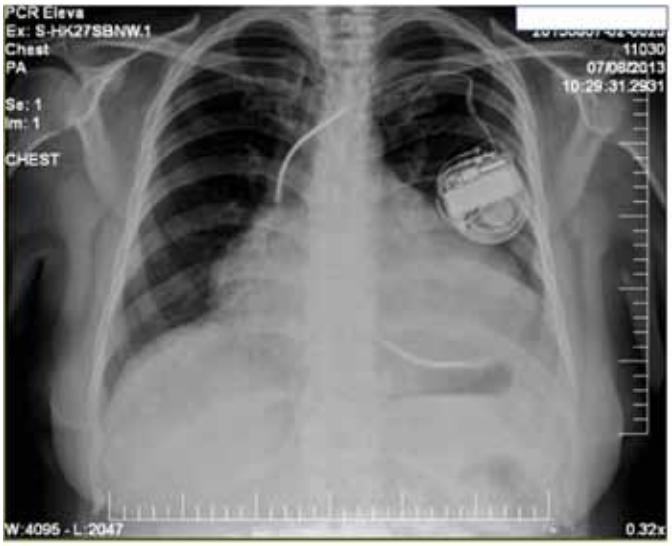

Figure 2: Chest X-ray in posterior-anterior view showing enlargement of the cardiac silhouette with a prominent right and left ventricular contour and with an automatic implantable cardioverter-defibrillator in the left pectoral area.

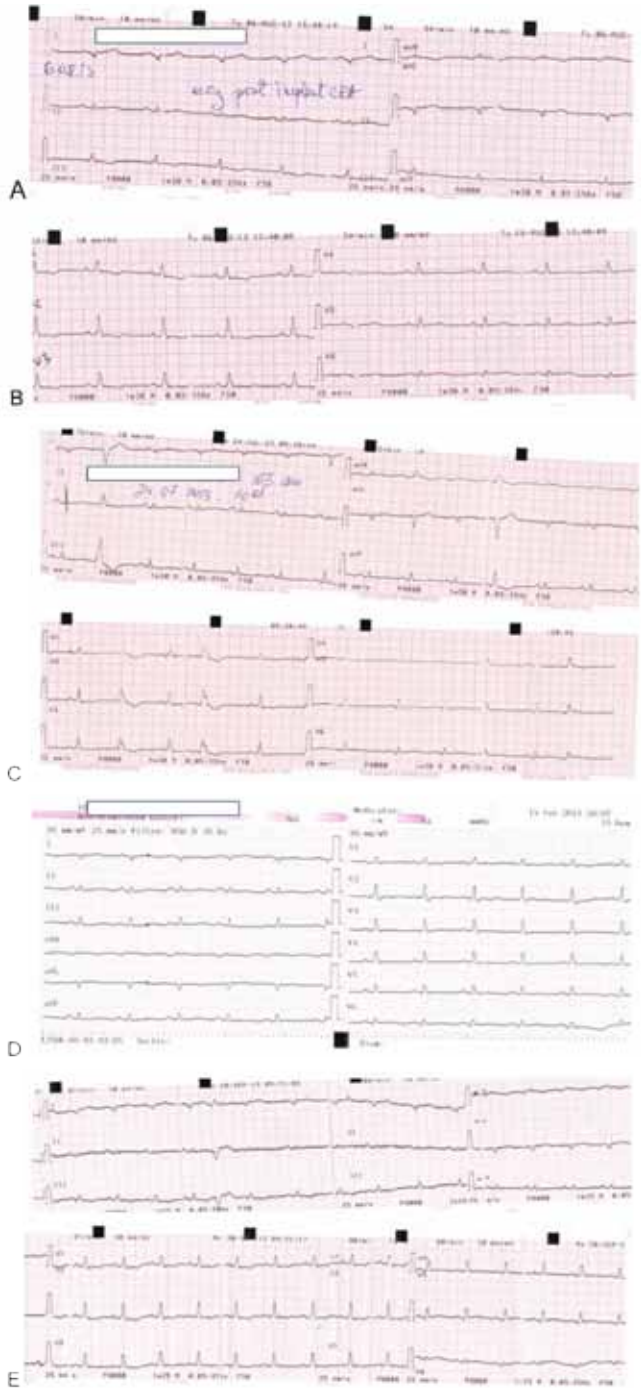

Figure 3: (A) Electrocardiography during admission to our hospital showing sinus rhythm, right-axis deviation, low voltage of the extremities, (B) incomplete right bundle branch block, T-wave inversion in leads V1 to V3, (C) ventricular extrasystoles with a right bundle branch block appearance, (D) Limb lead misplacement can be suspected based on negative QRS complex on the Figure 3A in leads D1 and avL. But actually the P wave is positive confirming good position of the leads. In fact extreme dilation of the right ventricle changed the QRS electrical axis to the right, and (E) One month after defibrillator implantation the outpatient control shows the same aspect in the limb leads and precordial leads. Concerning the positivity of the QRS complex from V1 to V5, this is also due to extreme dilation of the right ventricle and displacement of the interventricular septum to the left. This is why depolarization wavefront circulates towards V1 and positivates this lead.

necessitated electrical shock for restoration of sinus rhythm (Figure 9 and Figure 10). No isoproterenol was administrated because VTs were induced during basal state.

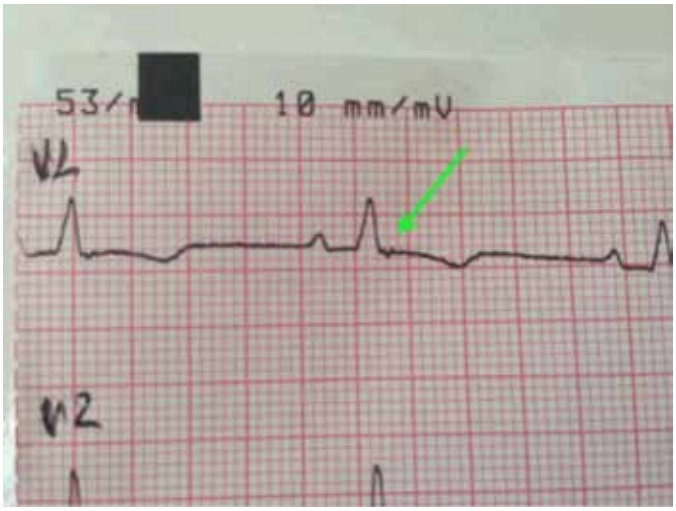

Figure 4: Presence of the epsilon wave at the end of the QRS complex in V1 lead.

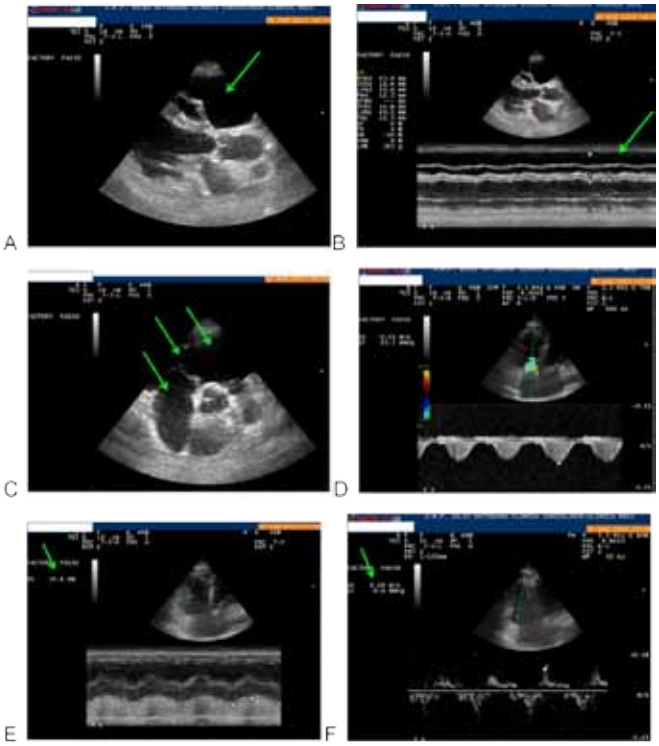

Figure 5: (A) Echocardiographic image in the parasternal long axis view showing dilation of the right ventricle in two-dimensional mode, (B)in M-mode, (C) parasternal short axis at the level of great arteries showing, right atrial, right ventricular and right ventricular outflow tract dilation, (D) apical four chambers: tricuspid regurgitation in the doppler view, (E) apical 4 chambers showing reduced right ventricular function with low TAPSE at the lateral free wall tricuspid anulus, and (F) reduced right ventricular function demonstrated by reduced amplitude of the S wave in tissue Doppler imaging.

Figure 6: Ventricular tachycardia (VT1) induced during electrophysiological study. 12-lead electrocardiography shows a left bundle branch block QRS shape, negative in inferior leads (II, III and avF) and predominantly negative QRS complex in V2 to V6 suggesting origin of the tachycardia at the apex of the right ventricle.

Figure 7: External and intracardiac electrograms during VT1 with: leads V1, V5 and V6 and electrograms from: high right atrium (HRA), His bundle proximal (His p), medium (His m) and distal (His d), coronary sinus - only the distal pole (CS d) being shown- and right ventricular apex (RVap). The ventricular electrogram (RVap) is concomitant with the QRS complex, but atrial electrograms (HRA) are dissociated from the ventricle confirming ventricular tachycardia.

Cardiac MRI scan presented the typical manifestation of ARVD which showed enlargement of right ventricle with aneurysmatic protrusion of the right ventricular free wall as well as dyskinetic areas of the outflow tract, without enlargement of left cavities. The wall of right ventricular outflow tract, the free wall of right ventricle and apex had fatty tissue infiltration.

Despite medical therapy with amiodarone and beta-blockers we could induce VTs during electrophysiological study, so finally she underwent ICD implantation. At one month outclinic control no spontaneous arrhythmia was detected by the ICD under 400 mg amiodarone and 100 mg metoprolol.

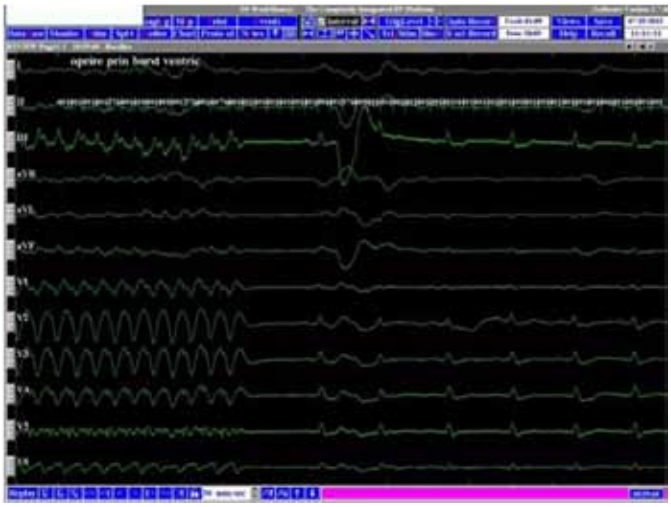

Figure 8: Ventricular tachycardia being stopped during electrophysiological study by ventricular overdrive.

Figure 9: Induction of VT2 by ventricular extra stimuli. VT2 has a right bundle branch block appearance, with positive QRS complex in inferior leads: II, II avF, negative in lateral leads: D1 and avL; and positive from V1 to V4 in precordial leads- suggesting origin in the upper part of the right ventricle (e.g., peri-tricuspid area).

Figure 10: VT2 being stopped by an electrical shock.

DISCUSSION

Most of the right ventricular tachycardias show a LBBB morphology with an inferior axis. The differential diagnosis is either idiopathic RVOT or ARVD. The diagnosis of ARVD is based on task force criteria, regarding: 12-lead ECG signs, combined with structural abnormalities that can be revealed by echocardiography, ventriculography, MRI scan and endomyocardial biopsy [1, 2]. An RVOT is a tachycardia not combined with other cardiac diseases or obvious structural cardiac abnormalities [3]. The presence of epsilon wave (on 12-lead ECG), spontaneous and induced episodes of VT, dilation of right ventricle (in echocardiography) and fibrosis with fatty tissue infiltration in MRI scan had an important role in the diagnosis of ARVD in our patient.

A first criterion for differentiation in the electrophysiological laboratory between two types of VT is the mode of induction: with 82% of the ARVD patients being inducible with ventricular extrastimuli in the study of O'Donnel et al. versus only 3% in the RVOT group, indicating the reentrant mechanism of the VTs in the majority of patients with ARVD [4]. In our case the two VTs were induced by ventricular extrastimuli.

Secondly, O'Donnell et al. reported that electrophysiological study revealed more than one morphology of inducible VTs (a range of one to six VTs), with 71% of the patients having more than one morphology [4]. In contrast, the patients with RVOT all had only one morphology. The different morphologies in the ARVD group is best explained by the presence of an extensive arrhythmogenic substrate allowing the perpetuation of multiple circuits [5, 6]. We found three VT morphologies in the same patient: one spontaneous, and two induced during electrophysiological study originating from a right ventricle that showed extended damage at the MRI (apex, right ventricle free wall and right ventricular outflow tract).

The three VTs had different morphologies: two with LBBB pattern and one with RBBB pattern. As previously reported, RBBB can be observed during VT and does not exclude a right ventricular origin [6]. All RBBB morphology VTs in the paper of Miljoen et al. exhibited a peri-tricuspid circuit [6].

Several approaches have been proposed for treating VT in ARVD. Ablation rarely abolishes all arrhythmias in ARVD. The progressive nature of the disease and the acute success rate (reported to be lower than 40%) makes ICD implantation a valuable alternative, shown to reduce mortality in ARVD [7]. Implantable cardioverter defibrillator therapy provides life-saving protection by effective termination of the tachycardia [8]. Our patient manifested one spontaneous VT that was well tolerated hemodynamically, and two induced in the electrophysiological lab: one pre-syncopal that was stopped by ventricular overdrive and one with hemodynamic intolerance that necessitated electrical shock for termination. The contribution of electrophysiological study in our patient allowed the decision to implant a cardioverter defibrillator for the prevention of sudden cardiac death.

CONCLUSION

According to this case and to other similar reports in medical literature, electrophysiological study in combination with other diagnostic tools such as magnetic resonance imaging, echocardiography and 12-lead electrocardiography becomes useful for the differential diagnosis between arrhythmogenic right ventricular dysplasia and right ventricular outflow tract tachycardia and contributes to decision of implantable cardioverter defibrillators implantation.

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CLINICAL IMAGE OPEN ACCESS

Moyamoya by magnetic resonance imaging scan

Caroline Edward Ayad, Ahmed Alamin Alnoor, Aymen El-Mesallamy

CASE REPORT

A 15-year-old Sudanese male was referred to the Magnetic Resonance Imaging (MRI) department with severe headache. Brain MRI axial T_1, T_2, diffusion, post contrast series, fluid attenuation inversion recovery (FLAIR) and time-of-flight Magnetic Resonance Angiography (TOF-MRA) techniques were obtained. Images showed tiny punctuate signal void in all pulse sequence in both basal ganglia. Also there are a number of collaterals seen surroundings the mid brain and within the supra sellar cistern.

In post-contrast enhancement images there are obvious enhanced collaterals within the sulci of both cerebral hemispheres, the posterior fosse structures including the brain stem appeared intact. The obtained diffusion weighted images showed no evidence of recent ischemic insult. There was no obvious intra axial mass lesion, signal of blood degradation or extra axial fluid collection.

Magnetic resonance angiography (MRA) described both internal carotid arteries; they showed obvious occlusion of their supraclinoid portions without well formed circle of Willis, besides tortuous collaterals seen surrounding cistern forming A net-like appearance, the vertebral arteries as well as the basilar artery were intact.

An MRA revealed bilateral supraclinoid internal carotid arteries occlusion without well formed circle of Willis and collateralization as moyamoya disease (Figure 1).

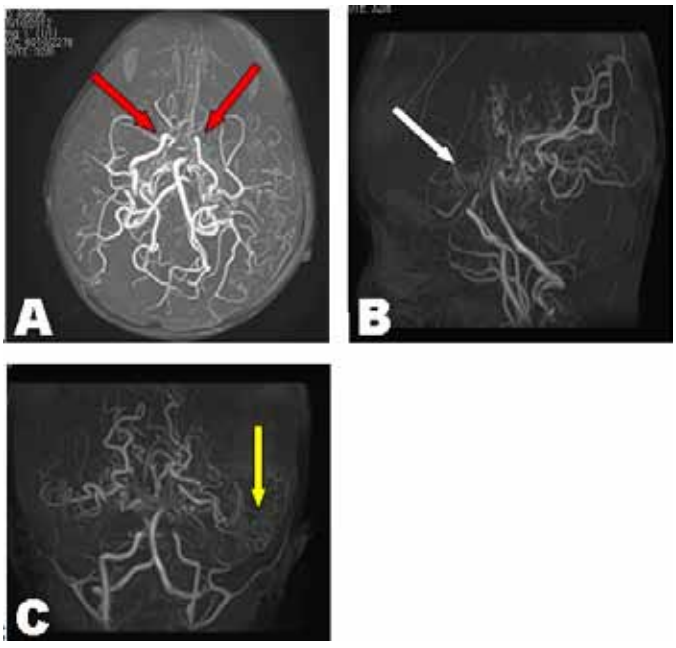

Figure 1: Magnetic resonance angiography axial, sagittal, coronal brain images of a 15-year-old Sudanese child showing Moyamoya Disease (A) Both internal carotid arteries explain obvious occlusion (red arrows) of their supra clinoid portion, (B) Circle of Willis (white arrow) is not well formed, (C) Tortuous collaterals are seen surrounding cistern forming net like appearance (yellow arrow).

DISCUSSION

Moyamoya is a rare cerebrovascular disease among Japanese [1]. Ethnicity-incidence ratios for Whites as compared to Asian-Americans were 1:4.6, and as compared to African-Americans was 1:2.2. To the best

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of our knowledge, no similar cases have been reported in Sudanese population in existing literature [2]. The pathogenesis of moyamoya is idiopathic progressive arteriopathy of childhood; where occlusion of the circle of Willis, narrowing of distal internal carotid artery (ICA) and proximal circle of Willis vessels with secondary collateralization are detected the disease is poorly understood and may be due to genetic and environmental factors [3, 4]. The diagnosis of moyamoya disease can be diagnosed by different imaging modalities and radiographic evaluation and it primarily depends on angiographic results, including occlusion of the supraclinoid ICA and formation of extensive collateral vessels [1, 3]. Several previous studies have revealed that Moyamoya disease can be identified on contrast-enhanced computed tomography (CT) or MRI scans, owing to their sensitivity to ischemic changes [5–7].

Three-dimensional CT angiography have limitations in diagnosis of moyamoya disease because of the limited spatial resolution, difficulty in covering the whole intracranial vasculature network of leptomeningeal anastomotic channels [1]. The assessment of cerebral ischemia associated with moyamoya by diffusion-weighted MRI scan has value in disease evolution [8]. Infarctions are better delineated with T_1- and T_2- imaging [9, 10]. The MRI findings in T_1 are multiple dot-like flow voids in basal ganglia, T_2-weighted images are of high signal small vessel cortical and white matter infarcts, collateral vessels appear as “net-like” cisternal filling defects , FLAIR shows Bright sulci at leptomeningeal “ivy sign”[3]. Another MR protocols are useful in moyamoya; T_2star gradient recall echo is useful prior hemorrhage ,T_1 with contrast shows lenticulostriate collaterals with enhancing “dots” in basal gangila and “net-like” thin vessels in cisterns, Leptomeningeal enhancement gives “ivy sign”, MR spectroscope shows Lactate in acutely infarcted tissues and NAA/Cr and Cho/Cr ratios frontal white matter increase after revascularization, perfusion-weighted imaging (PWI) shows low perfusion deep hemispheric white matter, is relatively high perfusion posterior circulation, PWI may be abnormal even if MRI scan is normal [3].

Moyamoya on MRI is Characterized by diminishing of flow voids in the internal carotid and middle and anterior cerebral arteries together with collateral flow voids in the basal ganglia and thalamus [11–13].

Magnetic resonance angiography has been used to demonstrate the intracranial vessels, where it is non invasive, no contrast media, and ionizing radiation is used. MRA is useful in the diagnosis of moyamoya disease as mentioned by Yamada et al. [14]. MRI scan has been proposed to be used instead of conventional cerebral angiography [12].

CONCLUSION

Regardless of the excellent diagnostic value, broad imaging protocols and noninvasive nature, it has been proposed that magnetic resonance angiography should be used as a diagnostic imaging modality for moyamoya disease.

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Caroline Edward Ayad – 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

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

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

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