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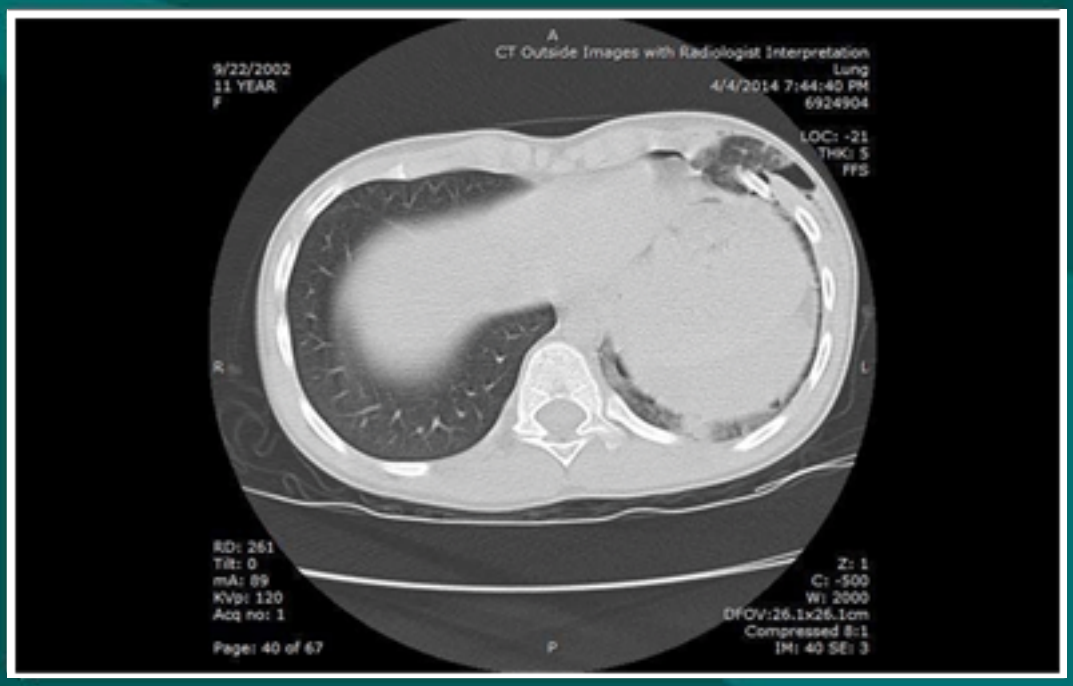

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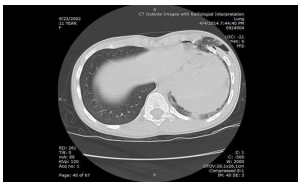

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CASE SERIES PEER REVIEWED | OPEN ACCESS

Single step root coverage with modified bridge flap technique: A pilot study

Sandeep J. N., Jaspreet Kaur, Sushama R. Galgali

ABSTRACT

Introduction: Marginal tissue recession is a condition commonly encountered in clinical practice and is characterized by displacement of gingival margin. To overcome the limitations of original bridge flap technique which demands adequate attached gingiva apical to recession, a modification of this technique is imposed to cover the denuded root with insufficient attached gingiva. Case Series: Three patients with either Millers class I or class II recession were treated with this technique and followed six months postoperatively. An average of 76% of root coverage was obtained with this modified technique. Conclusion: The present technique reported an excellent postoperative outcome showing great coverage of exposed root surface with vestibular deepening in single step and can be performed in areas with inadequate attached gingiva apical to recession defect.

Keywords: Attached gingiva, Bridge flap, Gingival recession, Modified bridge flap

How to cite this article

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INTRODUCTION

Mucogingival problems form a definitive diagnosis that includes an array of clinical findings, namely gingival recession (GR), shallow vestibule, inadequate width of attached gingiva (AG) and aberrant frenum [1]. Surgical endeavor by Goldman [2] for the correction of three specific problems, namely periodontal pockets that extend beyond mucogingival junction reaching the alveolar mucosa, an abnormal traction of the frenum that can transmit tension for the gingival margins causing recession, and the functional condition of a shallow vestibule that promotes a decrease of the attached gingiva levels, initiated the era of mucogingival surgery that has motivated other clinicians to develop numerous refinements.

Multiple techniques have been developed to obtain predictable root coverage. “Margaff” in 1985 proposed bridge flap technique to cover gingival recession [3]. However, this technique requires adequate attached gingiva apical to recession. So to overcome this limitation, the present technique modified the original bridge flap technique to cover the denuded root in patients with inadequate attached gingiva apical to recession.

CASE HISTORY

Three patients either with Millers class I and II recession, otherwise systemically healthy in an age group of 20–30 years were selected after phase I therapy. The study was conducted in accordance with local ethical committee and written informed consent was obtained

from those who agree to participate. The following parameters were recorded using UNC-15 probe at the baseline and six months after procedure (Figures 1 and 3).

- Recession width (RW)
- Recession height (RH - distance between fixed reference point on acrylic stent to gingival margin)
- Width of keratinized gingiva (GW)

Surgical technique

This technique presents a combination of coronally repositioned flap and a modification of original bridge flap. After administering local anesthesia (2% lignocaine hydrochloride with 1:80000 epinephrine), the following incisions were made (Figure 2):

- First oblique incision made slightly coronal to the CEJ at distal and mesial papilla of recession.
- Secondly, two vertical incisions were made from the line angles of adjacent teeth to recession and extends beyond mucogingival junction till the labial mucosa.

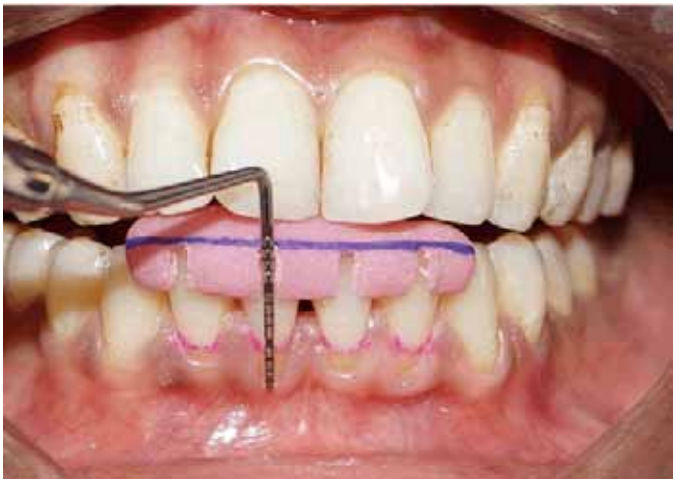

Figure 1: Preoperative photograph showing recession on teeth 31, 32, 41 and 42 along with insufficient attached gingiva.

Figure 2 :Intraoperative photograph showing multiple (with a combination of vertical, horizontal and sulcular) incisions to raise modified bridge flap.

- After giving sulcular incision partial thickness falp was elevated
- Then the horizontal incision given in the labial mucosa to connect two vertical incisions and the flap was mobilized coronally till it covers the denuded root. After de-epethelialising the papilla, the flap was secured using individual sling sutures. Periodontal dressing was given followed by postoperative instructions.

Patients were prescribed antibiotics (novamox 500 mg thrice daily for 5 days) and analgesic (dicloron-P twice daily for 3 days). Chlorhexidine mouthwash (0.2%) was prescribed for four weeks after surgery. Sutures were removed after 10 days. All procedures were performed by same clinician and both preoperative and postoperative measurements were recorded by same individual.

RESULTS

The present technique reported an excellent postoperative outcome showing average of 76% coverage of exposed root surface (Table 1).

DISCUSSION

A wide variety of periodontal plastic surgical procedures have been described to correct mucogingival problems and to cover the denuded root surface [4]. An evaluation of adequate width of attached gingiva in patients with multiple recessions is an important factor before deciding on any procedure for root coverage [4] an unresolved controversy still exists in literature regarding the adequate attached gingiva for periodontal Health maintenance [5] the contemporary opinion suggests that the regions with less than 2 mm attached gingiva and thin gingival tissue are at increased risk of gingival recession and facilitate subgingival plaque formation because of incomplete pocket closure [1]. Hence, mucogingival

Figure 3: Postoperative photograph (six months) with marked increase in width of the attached gingiva.

Table 1: Preoperative and Postoperative clinical measurements with average % of root coverage

Case no.	Millers classification	Tooth no	Preoperative			Postoperative (6 months)			% of root coverage
			RW	RH	GW	RW	RH	GW	
1	Class1	31	3	12	14	0	10	14	71.3
	Class1	32	3	12	14	0	10	14	71.3
	Class1	41	3	14	15	2	11	14	64.6
	Class2	42	4	12	14	2	10	14	71.3
II	Class1	31	3	11	14	2	10	14	79.9
	Class2	41	3	12	15	0	11	15	79.7
III	Class2	34	4	13	17	0	11	19	71.6
	Class1	35	5	12	14	0	10	16	71.3

Abbreviations: RW=Recession width, RH=Recession height, GW= Width of keratinized gingiva

therapy should be advocated for gingival augmentation and to create adequate vestibular depth in areas with insufficient attached gingival [6, 7].

Contrary to the reports of Margaff et al. 1985, Romanos et al. 1993 and vijayalakshmi et al. 2008, who all stressed very little on the gain of width of attached gingiva by bridge flap technique [3, 8, 9] study we have modified original bridge flap technique by giving two vertical incision extending beyond mucogingival junction till labial mucosa. The purpose of this technique is to eliminate donor site surgery, to increase predictability, better patient compliance, to satisfy patient's esthetic demands and to match the tissue color of grafted area. This technique is indicated when a single surgical procedure is desired to predictably cover the denuded root surfaces, in cases where inadequate keratinized gingiva apical to recession is available, and also to increase the width of attached gingiva with vestibular deepening at one step. We kept our study cases limited to the mandibular arch to get unbiased results as well as to be able to treat multiple mucogingival problems at the same time. The present technique presents a cost-effective single-step entity to correct mucogingival problems at a time with less morbidity to donor tissue.

CONCLUSION

The present technique reported an excellent postoperative outcome showing great coverage of exposed root surface with vestibular deepening in single step and can be performed in areas with inadequate attached gingiva apical to recession defect. It also offers additional advantages like less surgical trauma, less postoperative complications and better patient's satisfaction.

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Author Contributions

Sandeep J. N. – 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

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

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

Guarantor

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Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Neuroleptic malignant syndrome in severe vascular dementia: Diagnostic challenge due to baseline impaired mental status

Thein Swe, Akari Thein Naing

ABSTRACT

Introduction: Neuroleptic malignant syndrome (NMS) is a life-threatening disease more often considered than truly diagnosed. The NMS is a life-threatening neurologic emergency associated with the use of antipsychotic drugs and characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia. Case Report: A 69-year-old wheel chair bound male with past medical history of severe vascular dementia with behavioral problems, schizoaffective disorder referred from nursing home due to fever for 1 day. According to his room-mate, his baseline mental status use to be drowsy and disoriented. Vitals showed temperature 102°F (38.8°C), tachycardia, high blood pressure 140/90 mmHg, tachypnea and low oxygen saturation of 87% on room air. Arterial blood gases showed hypoxia and respiratory alkalosis with high A-a gradient. Also suspected infection due to leukocytosis with neutrophilia. However, we kept neuroleptic malignant syndrome (NMS) in mind since patient was taking haloperidol for episodic agitation although haloperidol dose was unchanged and no new drugs were added. When total creatine kinase came back as 3142 IU/L, he was managed successfully with dantrolene and amantadine. Conclusion: Neuroleptic malignant syndrome can be difficult to diagnose in the presence of baseline altered mental status. It is important to have early diagnosis of NMS in patients who presented with altered mental status and muscle rigidity with underlying dementia and psychiatric illness.

Keywords: Altered mental status, Dantrolene, Amantadine, Dementia, Neuroleptic malignant syndrome

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a life-threatening disease more often considered than truly diagnosed. Initial diagnosis of NMS would be difficult if a patient has severe dementia. Muscle rigidity and elevated total creatine kinase play an important role in considering diagnosis. Many of NMS cases are due to change in class or dose of antipsychotic medications, however, it can also occur in patients on long-term stable dose and sometimes it is unrelated to dose.

CASE REPORT

A 69-year-old wheel-chair bound male with past medical history of severe vascular dementia with behavioral problems, schizoaffective disorder, seizure disorder, hypertension was referred from nursing home to emergency room (ER) for fever for one day.

He had a history of hospitalization in a psychiatric ward one month before because of agitation. After that he was discharged with oral haloperidol 2 mg twice daily and this dose remained the same for the next six months. He was also taking carbamazepine 200 mg per os ibid and divalproex sodium 750 mg per os ibid for seizure, and amlodipine 5 mg per oral once daily for hypertension.

At the admission, the patient was drowsy and less responsive than usual. He did not open his eyes in response to verbal stimuli, he was not communicative at all, was minimally responsive to painful stimuli but presented involuntary movements of his upper extremities. He was more awake, alert and oriented to time and place before coming to ER. Physical examination was also conducted in ER and patient was also drowsy and less responsive. Vital signs upon admission were: temperature 102°F (38.8°C), heart rate 110 beats/min, blood pressure 150/90 mmHg, respiratory rate 20 breaths/min, oxygen saturation 87% on room air. Neck was supple. Pupils were normal, equal and reactive to light. Respiratory, cardiovascular and abdominal examinations were normal apart from tachypnea and tachycardia. Neurological examination revealed muscular rigidity of upper limbs even if they were moving spontaneously sometimes. Reflexes were normal and Babinski sign was downgoing. Lower limbs motor exam and sensory exam in 4 limbs could not be assessed well because patient was drowsy and not co-operative. However, they were moving spontaneously against gravity and motor of both upper and lower limbs were at least 3/5.

Blood tests showed white blood cells 11.6x10^9/L, neutrophil percentage (auto) 71.3 % (normal = 40–70%), normal potassium, blood urea nitrogen 34 mg/dL, creatinine 1.9 mg/dL, glomerular filtration rate 28.1 mL/min, glucose 135 mg/dL, calcium 9.4 mg/dL, aspartate aminotransferase 95 IU/L, bilirubin 0.6 mg/dl, alanine aminotransferase 55 IU/L, alkaline phosphatase 49 IU/L. Lactic acid was 13.5 mg/dL and total creatine kinase 3142 IU/L. Urinalysis showed normal except large blood with red blood cell 5–15 cell/high power field. Coagulation studies were normal. Arterial blood gas revealed pH 7.52 units, pCO2 36 mmHg, pO2 65.3 mmHg, HCO3 28.3 mmol/L, oxygen saturation 95 %, A-a gradient 117.3 mmHg on nasal cannula 3 liters of oxygen. Anion gap was normal. Valproic acid and carbamazepine drug levels were normal. Two days later, blood and urine cultures were negative.

Patient was admitted to intensive care unit (ICU) directly from the ER and haloperidol and amlodipine were stopped. Patient was kept nothing per os with dextrose ½ normal saline 200 ml/hr was given intravenously (IV) while monitoring intake and output. Vancomycin 1 gram IV and meropenem 1 gram IV were given one time as infection could not be ruled out at that time. Dantrolene 1 mg/kg IV pushed and amantadine 100 mg per oral twice daily were given as bromocriptine was not available at that time in pharmacy. Cooling blanket was applied because patient was persistently febrile (103.6°F or 39.7°C) since admission. Enoxaparin 60 mg subcutaneously was given twice daily for three days since CT scan of chest with PE protocol could not be done due to patient's poor renal function. Head CT scan showed no acute intracranial pathology. However, lumber puncture was not done since meningoencephalitis was less likely.

After two days, mental status was improving and he opening his eyes upon calling, less muscle rigidity, total creatine kinase was trended down to 1125 IU/L and blood urea nitrogen was 5 mg/dL, creatinine was 1.1mg/dL and glomerular filtration rate (GFR) was improved to 71 mL/min. Computed tomography (CT) scan of chest with pulmonary embolism (PE) protocol was done and showed negative for PE. Enoxaparin was stopped. Dantrolene was stopped after giving one day due to deranged liver function tests. Amantadine was increased to 200 mg per oral twice daily and continued for 14 days. Patient was downgraded from ICU to medical floor after three days of ICU stay. Patient was discharged from medical service four days after admission to psychiatric ward to continue evaluation and adjustment his schizoaffective disorder. Finally, he was discharged from psychiatric service as his psychiatric symptoms were well controlled. Medications upon discharge were amantadine 200 mg per oral twice daily, carbamazepine 200 mg per oral twice daily and valproate 250 mg per oral thrice daily for seizure and divalproex 250 mg per oral three times daily to control his impulse control.

DISCUSSION

Neuroleptic malignant syndrome (NMS) a life threatening disease more often considered than truly diagnosed. Muscle rigidity and elevated total creatine kinase play an important role in considering diagnosis. Many of cases are due to change in class or dose of antipsychotic medications. However, it can also occur in long-term stable dose and sometimes it is unrelated to dose. According to the Diagnostic and Statistical Manual of Mental Disorders, (4th Edition), Washington, DC, American Psychiatric Association, 1994, diagnosis of NMS is made when the individual exhibit severe muscle rigidity and elevated temperature associated with the use of antipsychotic medication and have at least two of the following associated symptoms: (a) diaphoresis, (b) dysphagia, (c) tremor, (d) incontinence, (e) changes in level of consciousness ranging from confusion to coma, (f) mutism, (g) tachycardia, (h) elevated or labile blood pressure, (i) leukocytosis, or (j) laboratory evidence of muscle injury (e.g., elevated creatine kinase). However,

these symptoms should not be caused by neurological or a mental disorder (e.g., Mood Disorder with Catatonic Features).

Vascular dementia is the second most common type of dementia after Alzheimer disease. In subcortical pathology, patients can present with personality and mood changes, abulia, apathy, depression, emotional disturbance. And cognitive disorder characterized by relatively mild memory deficit, psychomotor retardation, and abnormal executive function. Behavioral and psychological symptoms are common in patients with small-vessel and large-vessel vascular dementia presenting with especially more apathy in small-vessel vascular dementia and more agitation or aggression in large-vessel vascular dementia [1, 2]. The prognosis of the NMS patients in presenium and senium tends to be worse. It is important to diagnose NMS early and treat them as soon as possible for better prognosis [3].

Neuroleptic malignant syndrome (NMS) is most often seen with the "typical" high potency neuroleptic agents such as haloperidol. However, every class of neuroleptic drug could be a risk factor for NMS including the newer atypical antipsychotic drugs such as clozapine and olanzapine. Although symptoms usually develop during the first two weeks of neuroleptic therapy, the association of the syndrome with drug use is idiosyncratic. Neuroleptic malignant syndrome (NMS) can occur after a single dose or after treatment with the same agent at the same dose for many months or years. It is not a dose-dependent phenomenon, but higher doses are a risk factor. NMS may not predictably develop even in predisposed individuals upon neuroleptic exposure and that additional cofactors must be present for the full syndrome to occur [4]. A significantly lower rate of mortality from haloperidol-induced NMS (7%) and a high rate of mortality (38.5%) among patients with organic brain syndrome were also noted. Myoglobinemia and renal failure are strong predictors of mortality, indicating a mortality risk of approximately 50% [5]. One study demonstrated that psychopathological features such as psychomotor agitation, confusion and disorganized behavior may be risk factors for the neuroleptic malignant syndrome [6].

Changes in either mental status or rigidity were the initial manifestations of NMS in most of cases with a single presenting sign and were significantly more likely to be observed before hyperthermia and autonomic dysfunction [7]. It is important to include differential diagnosis such as meningitis, encephalitis, systemic infections, catatonia and serotonin syndrome.

Malignant catatonia is another differential diagnosis characterized by psychosis, agitation, and catatonic excitement. The motor symptoms are also characterized by more positive phenomena (dystonic posturing, waxy flexibility, and stereotyped repetitive movements) than are described in NMS. Laboratory values are usually normal. Lethal catatonia often starts with extreme psychotic excitement, which, if persistent, can lead to fever, exhaustion, and death. NMS starts with severe extrapyramidally induced muscle rigidity. Their early clinical differentiation is important because lethal catatonia often needs neuroleptic treatment and neuroleptic malignant syndrome necessitates immediate cessation of neuroleptics [8]. In this case, patient was drowsy and did not exhibit agitation and lethal catatonia was unlikely.

Serotonin syndrome is one of the differential diagnoses and it is usually caused by use of selective serotonin reuptake inhibitors and has a similar presentation that is difficult to distinguish from NMS. Typical features in these patients that are not often found in NMS patients are shivering, hyperreflexia, myoclonus, and ataxia. Nausea, vomiting, and diarrhea are also symptoms of serotonin syndrome and are rarely described in NMS. Rigidity and hyperthermia, when present, are less prominent than in patients with NMS. In this case, it is unlikely because patient did not take selective serotonin reuptake inhibitors drugs.

Treatment NMS is mainly supportive with stopping offending neuroleptic agent, hydration to prevent kidney failure from rhabdomyolysis, cooling blankets and cardiopulmonary support. Additional treatment includes dantrolene, bromocriptine or amantadine although their efficacy is unclear and disputed [9].

CONCLUSION

Neuroleptic malignant syndrome (NMS) can be difficult to be diagnosed in the presence of baseline altered mental status. It is important to have early diagnosis of NMS in patients who presented with altered mental status and muscle rigidity with underlying dementia and psychiatric illness.

****

Author Contributions

Thein Swe – 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

Akari Thein Naing – 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 PEER REVIEWED | OPEN ACCESS

Eosinophilic syndrome with life-threatening end-organ damage

Shahd Ahmed, Erini V Kasfiki, John Smith

ABSTRACT

Introduction: Hypereosinophilic syndrome (HES) can be a multisystem disorder due to direct end-organ damage by eosinophilia, and can rarely present with life-threatening features. We present a case of multi-organ failure secondary to eosinophilia related to medications. Case report: A 66-year-old woman with a recent diagnosis of asthma on montelukast, presented with excruciating pains of sudden onset in her lower limbs, and on admission, she was found to be in multi-organ failure. After initial resuscitation, immunological investigations, including vasculitic screen were negative, and hematological investigations revealed severe eosinophilia. She was diagnosed to have systemic eosinophilic granulomatosis polyarteritis secondary to montelukast. The agent was withdrawn and the patient was started on prednisolone. The initial symptom of severe pains preventing her from mobilizing was reversed within days and the patient was cured and become steroid free after six weeks of steroid treatment with no further problems reported in subsequent follow-up. Conclusion: Eosinophilia may have a variety of causes, and montelukast is a recognized agent that can give rise to an eosinophilic syndrome. It can only be diagnosed once other systemic disorders have been excluded. The presentation can vary and can be multisystem, and rarely life-threatening, but it potentially is completely reversible, depending on the underlying diagnosis. In case of medications causing the syndrome, stopping the agent and giving a course of steroids may reverse the condition as in this case, without the need of immunotherapy in the long-term.

Keywords: End-organ damage, Eosinophilia, Hypereosinophilic syndrome, Life-threatening vasculitis

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INTRODUCTION

Eosinophilia refers to an absolute count of eosinophils >500/μl in the peripheral blood [1].

Hypereosinophilic syndrome is described when end-organ damage occurs directly because of eosinophilia, with other secondary causes having been excluded [2].

Patients may present with a variety of symptoms depending upon the end organ damage. In some patients the finding of eosinophilia is incidental, in others, as the patient described above, the initial manifestations may be severe or life-threatening.

We present a case of life-threatening hypereosinophilic syndrome secondary to medication use, which completely resolved on agent withdrawal.

CASE REPORT

A 66-year-old female presented with neuropathic pains across her right leg for two weeks. The patient had first noticed some paraesthesia on both lower limbs, which she described to feel like ''pins and needles'', with a patchy distribution from her hips to her ankles. As the days progressed, the patient described excruciating shooting pains in all muscle groups in her right leg, to the point that on presentation she was unable to weight bear, and had to be wheeled into the department.

Her documented past medical history was mild asthma of late onset for a decade, and recently diagnosed mild gastritis and osteoarthritis.

The patient was on montelukast 10 mg once daily and lansoprazole 30 mg once daily.

On further questioning, she admitted to having had recurrent chest infections and asthma exacerbations over the last few months prior to her current presentation, requiring steroids and antibiotics every 2–3 weeks. For this purpose, she was under investigation by the respiratory team. A recent computed tomography scan of thorax revealed some post-infective scarring, with nothing else of note. She also admitted to mild weight loss and drenching sweats.

She was not diabetic, or anemic, and had no thyroid disease. She denied eye, skin, bowel, bladder, sinus or joint problems. She denied cigarette smoking or alcohol consumption, and she had no allergies to any mediations.

On examination she was tachycardic, with a heart rate of 140 bpm, irregularly irregular, she was hypoxic and needed two liters of oxygen via nasal cannula to keep her oxygen saturations more than 94%. She was tachypneic with a respiratory rate of 22 beats per minute. She was apyrexial, and her blood pressure was stable.

On examination of her cardiovascular system, she had bilateral ankle pitting edema, her JVP was raised and her apex beat was displaced laterally. On auscultation of the heart there were no murmurs.

On examination of her respiratory system, she was unable to talk in full sentences. On auscultation, she had bibasal reduced breathing sounds with dullness on percussion, but no wheeze. Her peak expiratory flow was 150, which was 75% of her normal.

Abdominal examination was unremarkable. She had no rashes, lymphadenopathy, or active synovitis.

Her GCS was 15/15, and pupils were equal and reactive to light and accommodation. Cranial nerve examination revealed no abnormalities, as did peripheral neurology examination of the upper limbs.

Examination of the lower limbs was limited due to pain. Power was 5/5 on the left leg, and equally reduced to 3/5 in all muscle groups, due to pain, on the right. Reflexes were globally reduced, and patient's pain was intolerable when reflexes were tested. Vibration was normal, but proprioception was not formally assessed, as the patient had excruciating pains to even slight movement of her lower limb joints. The patient had obvious signs of small fiber neuropathy on the right lower limb.

Urine dipstick revealed proteinuria and hematuria.

The patient was adequately resuscitated with oxygen therapy and intravenous fluids, and analgesia was escalated to intravenous morphine, but with no success, as pain relief was not achieved. Routine investigations were sent. Thyroid function tests, immunoglobulin levels, complement levels, and creatine kinase were all normal. All electrolytes were within normal limits. Autoantibody screen, including ANCA, ANA and ENA, was negative. Hematinics, including vitamin B12 were normal. Liver and renal function were normal, as were clotting times. The only abnormal results from the bloods tested were her full blood count, her CRP and her serum IgE levels. The patient was anemic with hemoglobin of 10.8 g/dl (normocytic, normochromic), and her white cell count was raised to $25.2x10^9$/L, with marked eosinophilia of 17.6 ($x10^9$/L). Her platelets were raised at $507x10^9$/L. Her CRP was 120 (mg/L) (normal range 0-4 mg/L) and her IgE levels were 148 (U/L) (normal range <75U/L). Arterial blood gas was obtained, which revealed mild hypoxia. Chest X-ray revealed a small left sided pleural effusion (Figure 1).

A 12-lead ECG showed atrial fibrillation with fast ventricular response. Urgent echocardiogram showed moderate left ventricular hypertrophy, with pericardial effusion, but no echocardiographic signs of cardiac tamponade.

A diagnosis of systemic eosinophilic granulomatosis polyarteritis was made taking into account clinical and biochemical findings. The role of montelukast was questioned in the pathophysiology of the disease.

Montelukast was discontinued, amitriptyline and prednisolone were started at 25 mg and 40 mg daily respectively, and patient was put on bisoprolol and warfarin for her atrial fibrillation. DEXA scan was requested and alendronic acid was started prophylactically.

The patient's symptoms of paraesthesia and leg pains completely resolved within the next days of this admission, and her eosinophils fell to $1.6x10^9$/L within the first week of treatment. As such, nerve conduction studies and quantiferon test were both canceled, and further hematological advice was not sought.

Patient made partial recovery within three days, with only a patch of allodynia on her right lateral malleolus, and full recovery within the next six weeks, with no further episodes of pain or further exacerbations of her asthma.

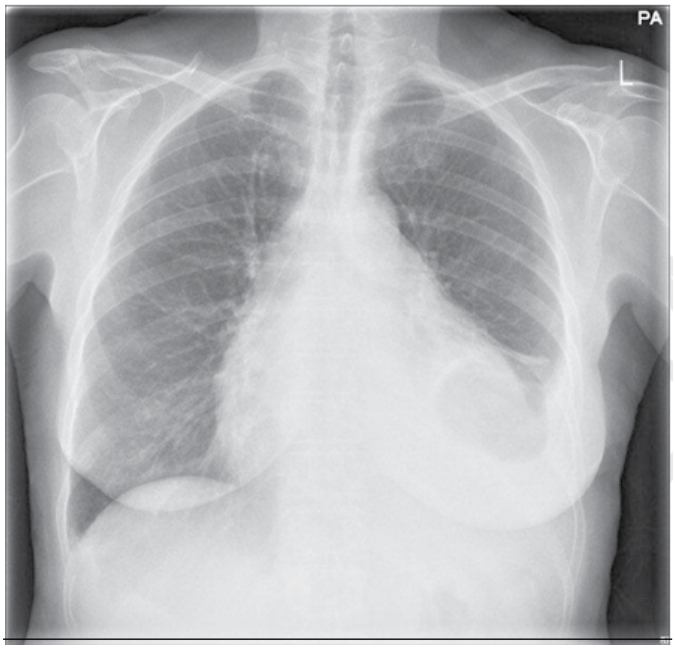

Figure 1: Chest X-ray on admission showing unilateral pleural effusion.

On further follow-up post-montelukast cessation and steroid withdraw, patient remained well and asymptomatic, with repeated bloods with normal blood count and eosinophilic values, having not required further treatment and in particular immunosuppression, making montelukast the main differential diagnosis for the patient's life threatening presentation.

DISCUSSION

Eosinophilia may have a variety of causes, such as allergic and immunologic reactions, infectious diseases, hematological disorders, drug reactions, as DRESS syndrome, connective tissue disorders. The investigations should be targeting to identifying or excluding the above conditions, and also depend on the organs affected.

Searching though EMBASE and MEDLINE, in a combined search of the terms ''eosinophilia'' ''montelukast'' and ''case report'' reveals three previous case reports of montelukast associated eosinophilic syndrome in adults in English literature, which are dated from 2002 to 2012, none of which described an English patient [3–6]. However, this is the first case report in English literature that describes a case of eosinophilia with a clinically associated significant and life-threatening syndrome and negative ANCA antibody screen vasculitis.

The treatment, as in this case, encompasses of treating the manifestations of the different symptoms derived from the offended organs, cessation of the offending agent, and oral steroids at 1 mg/kg/day. In the case of eosinophilia due to an offending agent, as in the above patient, there is no evidence in the literature suggesting the time period between the cessation of the agent and the resolution of eosinophilia and its symptoms. Our patient's symptoms started improving within the first day of montelukast cessation, even prior to starting high dose steroid treatment. The symptoms completely resolved and eosinophil number normalized within the next months.

What remains unexplained is the diagnosis of asthma prior to admission, which is the reason that the patient was started on montelukast in the first place. On subsequent follow-up, patient remained respiratory symptom free, with no variability of peak expiratory flow serial measurements and normal spirometry, and no further asthma treatment was required.

CONCLUSION

Hypereosinophilic syndrome can present with life-threatening multisystem involvement. Secondary causes, especially autoimmune and hematological conditions need to be excluded. Detailed drug history should be sought and offending agents must be stopped.

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Author Contributions

Shahd Ahmed – Group 1- Substantial contribution to conception and design, and acquisition of data, Group 2- Drafting the article, revising the article, Group 3- Final approval for publication
Eirini Kasfiki – Group 1- Substantial contribution to conception and design, and acquisition of data, Group 2- Drafting the article, revising the article, Group 3- Final approval for publication
John Smith – Group 1- Substantial contribution to conception and design, and acquisition of data, Group 2- Drafting the article, revising the article, Group 3- Final approval for publication

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Novel VPS33B mutations of G514S gene cause an arthrogryposis, renal dysfunction and cholestasis syndrome

Seçil Conkar, Ebru Yılmaz, Sevgi Mir, Afig Berdeli

ABSTRACT

Introduction: Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare multisystem disorder first described in 1979 and recently attributed to mutation in VPS33B, whose product acts in intracellular trafficking. It shows wide clinical variability. The characteristic features of ARC core phenotype include arthrogryposis, spillage of various substances in the urine, and conjugated hyperbilirubinemia. In some patients, these features are sometimes accompanied by different manifestations, such as ichthyosis, central nervous system malformation, deafness, and platelet abnormalities. Many patients with different associations of cholestasis, renal tubular acidosis, and dysmorphic morphology may be underdiagnosed. Case Report: We assessed the clinical characteristics of patients and investigated the VPS33B mutation in the gene G514S in a Turkish patient with ARC syndrome. We reported one Turkish patient with ARC syndrome, along with the presentations of renal tubular dysfunction, cholestasis, arthrogryposis, VPS33B Mutations in the gene G514S. Conclusion: This case shows that the variability of different manifestations of ARC syndrome is well described. However, the presence of the mutations VPS33B in the gene G514S has not been reported before. Our findings advance the knowledge of the molecular pathways determining cell polarity and provide new evidence on the role of intracellular trafficking proteins in regulation of epithelial polarization. Further, the fundamental defects in growth and differentiation of epithelial tissues observed in ARC and in knockdown cell lines emphasize the importance of the VPS33B pathway for organ development and function. We found a novel mutation in a Turkish patient with ARC syndrome.

Keywords: Arthrogryposis-renal dysfunction-cholestasis (ARC), Cholestasis, Renal tubular dysfunction, Mutations in VPS33B gene

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INTRODUCTION

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare autosomal recessive multisystem disorder with the association of arthrogryposis, renal

tubular dysfunction and cholestasis. It was first identified in 1973 by Lutz-Richner and Landolt, and in 1979, Nezeloff described new clinicopathologic findings [1, 2] Most cases present arthrogryposis multiplex congenita, neonatal cholestatic jaundice, mild or severe forms of renal tubular disorder, and severe lamellar ichthyosis [3]. In addition, dimorphisms, recurrent infections, platelet dysfunction, growth retardation, nephrogenic diabetes insipidus, muscular atrophy, corpus callosum agenesis and rarely deafness are among the other findings described [4]. Most patients die within the first seven months. Severe growth retardation has been observed in those living longer [5]. Recently, it has been shown that the mutation in the VPS33B gene accounts for ARC syndrome [6]. VPS33B mutation was detected in 75% of individuals with ARC syndrome [7]. So far, 35 cases with ARC syndrome with VPS33B mutation were identified. Gene regions encoded and the gene protein products of these cases show variations [8]. In our case, the mutation has been identified in G514S codon of VPS33B mutation. The present case report aims to demonstrate the phenotypic characteristics of G514S mutation in the VPS33B gene. Detecting the VPS33B mutations in the G514S gene is important since a novel mutation in the gene causes an Arthrogryposis, renal dysfunction and cholestasis syndrome.

CASE REPORT

A 2.5-month-old male neonate, 2500 grams born by cesarean section in term, was admitted to our hospital due to respiratory distress, malnutrition at 2.5 months. In his history, it was found out that the patient was hospitalized in the neonatal unit for 33 days just after the birth by reasons of respiratory distress and jaundice. In the family history, there was no kindred relationship found between the mother and father. It was also found that the other son of the family had multiple fractures of the body and died at five days old. On physical examination, atypical facial appearance, dry skin, reduced turgor tonus, icterus, dehydration, ichthyosis and muscular atrophy were observed. Severe growth retardation was observed as the body weight was 2300 g (<3p), height was 49 cm (<3p). Severe adduction deformity of the foot and callus formation in both femurs was detected. In the whole body, X-rays of the case taken for multiple fractures, diffuse reduction in the density of bone structures, thinning in the diaphysis of long bones, slight inclination in both tibia and fibula were detected. Old crack and mal callus formation at the middle part of right femur, 1/3 proximal part of the left femur were found. At the middle part of the right tibia, callus formation occurred due to an old oblique fracture was detected. In the light of these findings, the laboratory values of the patient admitted with the pre-diagnosis of ARC syndrome was given in Table 1.

Despite the high levels of serum bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), Gamma Glutamyl Transferase (GGT) was detected within the normal levels. Toxoplasmosis, herpes viruses, cytomegalovirus (CMV) and rubella screenings were found negative. Plasma amino acid profile was normal. However, increase in urine amino acids was detected. Skin biopsy performed for ichthyosis was consistent with lamellar ichthyosis. Echocardiogram performed for possible cardiac abnormalities was found normal.

In the blood biochemistry examination, the findings were: pH 7.25, bicarbonate 11.3 mmol/l, base deficit 10.3, urine pH 5, potassium 2.8 mEq/L (3.5–5.5 mEq/L), chlorine 126 mEq/L (98–106 mEq/L), phosphorus 0.7 mg/dl (1:36–2:26 mg/dl), sodium 151 mEq/L (135–148 mmol/L). In the urinalysis examined when the level of blood glucose was normal, glycosuria (1000 mg/l with dipstick) and proteinuria (22 mg/m^2/hour) were detected. Urinary electrolytes were found as Na 13 mmol/L, K 41 mmol/L, Cl 48 mmol/L, Ca 0.41 mmol/L, PO_4 18 mmol/L, and creatinine 0.9 mg/dl, TPR 57%. The patient was evaluated as Fanconi syndrome. The eye consultation requested for a possible metabolic disease was normal.

On the abdominal ultrasound, 5.5 mm hemangioma located near the capsule was detected in the liver. The shape, size and echogenicity of the kidneys were within the normal limits. Cranial magnetic resonance (MR) taken for the associated cranial anomalies was normal. During the follow-up, severe metabolic acidosis, hypernatremia (Na 155 mEq/l), and polyuria (6 cc/kg/h) developed, and urine osmolarity and blood osmolarity were detected as 124 mOsm/L and 371 mOsm/L, respectively. Desmopressin test was conducted following the development of diabetes insipidus in the patient. The patient, who was unresponsive to the desmopressin treatment, was considered as nephrogenic diabetes insipidus. The patient underwent replacement of erythrocytes due to anemia. Treatment of sodium bicarbonate and Shohl's solution were performed due to metabolic acidosis. Despite all the support therapies, the patient died of dehydration and sepsis at the age of 3.5 months. Since the permission was not obtained from the family, an autopsy could not be performed.

As a result, our patient had a severe clinical course and died at the age of 3.5 months with the clinical signs of Fanconi syndrome, arthrogryposis, cholestasis with normal GGT levels despite the elevated levels of AST, ALT, GGT and bilirubin, multiple extremity fractures, muscular atrophy, ichthyosis, anemia which required erythrocytes transfusion and nephrogenic diabetes insipidus which manifested at the final stages of the patient. The notable features of our case were exhibiting the clinical manifestations at birth, clinical worsening at the age of 2.5 months, exitus at age of 3.5 months, ARC syndrome accompanied by severe components such

as nephrogenic Diabetes insipidus (DI) and multiple fractures. We detected VPS33B mutations in the G514S gene one month after exitus of the patient. After the VPS33B mutations in the G514S gene was detected, there was no change in the clinical management of the patient when he died.

Molecular Analysis

Genomic DNA (gDNA) from 2 ml of peripheral blood samples which were collected into ethylenediaminetetraacetic acid (EDTA) anticoagulated tubes by the standard venipuncture method was extracted using the QIAmp blood DNA isolation kit following manufacturer's instructions. The DNA concentration was determined by using Thermo Scientific Nanodrop apparatus. 23 entire coding exons of VPS33B gene (Genbank NG_012162.1) were amplified by polymerase chain reaction (PCR) using flanking intronic primers (NCBI Reference Sequence NM_018668.3). All synthetic oligonucleotide primers synthesized and purchased by Invitrogen (Invitrogen, Paisley, UK) as the HPLC purification grade. Primer details are available from the authors upon request. The PCR amplification was carried out on Veriti gradient thermal cycler (Applied Biosystems, Foster City, CA) in a 25 µl reaction mixture in 0.2 ml thin-wall PCR strip tubes (Axygen Scientific, Inc., CA) containing 1 µl genomic DNA solution, 1.0 U platinium TAQ with Enhancer Buffer (Invitrogen , Paisley, UK), 50 µmol/l each of the dGTP, dATp, dTTP and dCTP (Promega, Madison, WI), 5 pmol each forward and reverse primers. The cycling conditions comprised a hot start at 95°C for 10 min, followed by 35 amplification cycles at gradient programme. Before cycle sequencing reactions the amplified PCR products were purified using Exo-SAP PCR purification Kit (Amersham Life Scince). Cycle sequencing PCR was performed with using BigDye Terminator v.3.1 kit as manufacturers. (PE Applied Biosystems, Foster City, CA). Cycle sequencing PCR products after purification with BigDye XTerminator kit (PE Applied Biosystems, Foster City, CA) were analyzed an ABI 3130xl Genetic Analyser System. The DNA sequencing was performed in both directions, initiated from the forward and the reverse primers were used in the initial PCR reaction. For sequence evaluation, the SeqScape 2.0 sequencing analysis software was used with (NP_061138.3) protein reference sequence for comparison of newly identified sequence variations.

DISCUSSION

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare autosomal recessive multisystem disorder presenting with the association of arthrogryposis, renal tubular dysfunction and cholestasis. It was first described in 1973 by Lutz-Richner and Landolt. To date, there are more than 30 patients identified with ARC syndrome. The ARC syndrome is a rare entity and has been shown as an autosomal recessive disease [5, 9]. Gisses et al. detected VPS33B gene mutation at the locus of 15q26 in 1 in 14 children with ARC syndrome [8]. It has been identified that VPS33B gene contained sec 1 protein, which plays an important role in the membrane fusion/ SNARE complex. Sec 1 protein takes part in the transport between the secretory cells. This protein is found in the kidney, liver, lung, heart, skeletal muscle and brain. It is considered that renal tubular dysfunction, cholestasis and arthrogryposis, a component of the neurogenic muscular atrophy, observed in ARC syndrome result from an incomplete function of Sec 1 protein, which is related to the VPS33B gene [1, 6, 7].

Table 1: Laboratory investigations of the patient at admission

Laboratory examination	Result	Normal range
Hemoglobin	7.6 g/dL	14–16 g/dL
Platelet	785×10⁹/L	150–400×10⁹/L
WBC	21.9×10⁹/L	4–11×10⁹/L
Total Bilirubin	10.3 mg/dL	0.3–1 mg/dL
Direct Bilirubin	5.6 mg/dL	0.1–0.3 mg/dL
ALT	44 U/L	0–35 U/L
AST	56 U/L	0–35 U/L
GGT	45 U/L	5-60U/L
Albumin	2.4 g/dL	3.5–5.0 g/dL
ALP	478 U/L	30–120 U/L
Urea	51 mg/dL	5–30 mg/dL
Creatinine	0.6 mg/dL	0.6–1.2 mg/dL

In our patient, liver function tests and GGT were found normal, while bilirubin was high. Additionally, cholestasis, ichthyosis, and renal Fanconi's syndrome, arthrogryposis, multiple fractures, and nephrogenic diabetes insipidus were observed. The presence of multiple fractures present at birth, severe respiratory distress since birth, exitus at the age of 3.5 months suggest that the clinical course may be severe in the existence of this mutation.

In literature, 62 patients, 14 different ethnic groups have been reported with the diagnosis of ARC syndrome. There are 28 cases of ARC syndrome identified with the VPS33B mutation in literature [8]. In addition, there is one Turkish patient with the VPS33B gene mutation in literature. In this patient, renal Fanconi's syndrome, arthrogryposis, ichthyosis and recurrent infections have been reported. Genetic mutation codon c.1406-1G> C was detected and the patient lived for 20 months. Another patient with ichthyosis, renal tubular acidosis, diabetes insipidus, cholestasis, hypothyroidism and large platelets was reported, but the VP33B mutation was not detected. This patient died of hypernatremia, dehydration and

sepsis at the age of seven months [1]. Unlike the cases reported in literature, our case exhibits a more severe clinical course together with the multiple fractures. We believe that the G514S mutation in the VPS33B gene may be responsible for this clinical situation. The patients with ARC syndrome usually die within the first year. In the literature, there has been only one case reported that lived until the age of three [10]. Our patient died at an earlier age and had uncontrollable dehydration.

CONCLUSION

In conclusion, the VPS33B G514S mutation must account for this clinical course. It is possible that the different mutations in this gene may cause a more severe phenotype as seen in patients with ARC syndrome. As a result, in this study, we described the phenotypic characteristics of a patient with ARC syndrome presenting with VPS33B mutation. Today, ARC syndrome is considered a rare, incurable disease that requires a genetic counseling. Identifying more serious types of mutation will conclude the diagnosis of the disease in the literature.

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Author Contributions

Seçil Conkar – 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
Ebru Yılmaz – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Sevgi Mir – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Afig Berdeli – 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 PEER REVIEWED | OPEN ACCESS

Idiopathic scrotal calcinosis: A dermatosurgical disease

Bhavinder Arora

ABSTRACT

Introduction: Idiopathic scrotal calcinosis is a dermatosurgical disorder affecting the scrotal skin and needs surgical excision. It is characterized by multiple calcified nodules on the scrotal skin. It is limited to scrotal skin and has been classified under calcinosis cutis. Although considered to be a metabolic disorder, the serum calcium remains normal in all patients. Scanty reports of idiopathic scrotal calcinosis are available in literature. Case Report: We report one such case of idiopathic scrotal calcinosis in a 65-year-old male, presenting with multiple painless nodules which were yellowish white and painless involving whole of scrotum. This patient was treated with surgical excision of the involved skin. Conclusion: This case report conveys the message that idiopathic scrotal calcinosis presentation can be large involving whole of scrotum. The picture is classical not to be confused with multiple sebaceous cysts of scrotum.

Keywords: Calcinosis, Scrotum, Idiopathic calcinosis

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INTRODUCTION

Idiopathic scrotal calcinosis is a rare and benign disease of the scrotal skin [1]. It is defined as the presence of multiple calcified and asymptomatic nodules in the scrotal skin [2]. The main controversy concerns the pathogenesis of the scrotal calcinosis [3–6]. Some authors think that it is result of dystrophic calcification of preexisting structures such as epidermal/sebaceous cyst [7], while others did not find any evidence of such preexisting disease and believe it as an idiopathic condition [8].

Histopathologically, it is characterized by presence of calcium deposits within dermis surrounded by a foreign body-type granulomatous reaction [3]. Despite the controversy about the origin of this entity, surgery is the treatment of choice.

CASE REPORT

A 65-year-old male farmer by occupation, presented with multiple, painless nodular lesion on the scrotum that had gradually increased in size and number during

the last eight years. The swelling was single and cystic to begin with that first increased in number followed by change in character from cystic to hard swelling that continues to increase till date. There was no history suggestive of metabolic, systemic, endocrine, neoplastic or autoimmune disease. Patient never experienced any local scrotal disease like trauma, infection or inflammation. General physical examination was normal. Local examination revealed multiple painless nodular swellings yellowish white in color, ranging from 1 to 5 cm in scrotal skin without any area of ulceration or discharge but had some focal areas of calcified lesions. Bilateral testes and penis were normal. Routine laboratory examination was normal. Under spinal anesthesia nodules and involved scrotal skin was excised with primary repair of scrotal skin. Postoperative course was uneventful and cosmetic results were good. Histopathological examination confirmed the diagnosis of calcinosis cutis.

DISCUSSION

Scrotal calcinosis is a rare and benign condition first described by Lewinski in 1883 [3]. It mainly appears in men aged 20–40 years age youngest being nine years and oldest being 85 years [6]. Clinically, it consists of hard yellowish white nodules within the dermis of scrotal skin. Nodules may vary in size from 1–3 cm and are usually asymptomatic. Patients usually present late in the course in Indian scenario because of social stigma and seek help mainly for cosmetic reasons. The pathogenesis of scrotal calcinosis is unclear and controversial. The most widely accepted classification of calcinosis cutis describes three types: metastatic, dystrophic and idiopathic. Metastatic calcinosis is secondary to hypercalcemia or hyperphosphatemia. Dystrophic calcinosis occurs in the dermis in which elastic fibers have been damaged. It occurs in cutaneous tumors, cysts, local trauma, burns and frost bite. Idiopathic calcinosis is used for cases in which the cause is obscure. It can be localized as in familial tumoral calcinosis, subepidermal calcified nodule, dermal calcinosis and idiopathic calcinosis of scrotum, or generalized called calcinosis universalis [9–19].

Figure 1: Showing scrotal calcinosis.

Idiopathic scrotal calcinosis is a rare clinical entity affecting the scrotal skin [19] with its counterpart vulvar calcinosis in females which is still more uncommon [11, 18]. On clinical examination, multiple hard yellowish white nodules that vary in size from 1 mm to a few centimeters, solitary or multiple, can present on scrotal skin [3]. Although these nodules are asymptomatic, itching can be predominant symptom or may discharge a chalky material. A few patients can present with prostatitis like symptoms or dysuria [19]. Clinical presentation in our patient was asymptomatic. The interval between the onset of disease and treatment may be several years. This interval was about eight years in this case.

The scrotal calcinosis is idiopathic or may be result of calcification of pre existing cyst remains controversial [3]. However, degeneration and necrosis of dartos muscle is followed by dystrophic calcification in genesis of scrotal calcinosis has been suggested by King et al. [8]. A case of scrotal calcinosis originating from eccrine epithelial cyst was reported by Ito et al. [9]. Scrotal calcinosis may be truly idiopathic [1] with normal serum calcium levels [19].

The treatment of this benign condition is for cosmetic reasons or itching. Surgical excision must be limited to scrotal skin since nodules are limited to dermis only [2]. Surgical excision is the only remedy with high probability of recurrence of scrotal calcinosis. In our case, adequate surgical excision of diseased scrotal skin was done, but with short follow up of three months, there is no recurrence till date.

CONCLUSION

Scrotal calcinosis needs identification clinically, to be differentiated from multiple sebaceous cysts of the scrotum. It may be calcium metabolism error or extravasations of calcium into skin. The extraordinary large size of disease can involve whole of scrotum. The diagnostic dilemma can be avoided by careful examination only.

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Author Contributions

Bhavinder Arora – 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

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Spontaneous rupture of a retroperitoneal extrarenal angiomyolipoma initially misdiagnosed as acute cholecystitis

Ghassan Almaimani, Thomas Zoedler, André Schneider, Bayan Almaimani

ABSTRACT

Introduction: Extrarenal angiomyolipomas are rare and tend to become clinically relevant only when hemorrhagic complications occur. Case Report: We report the case of an 81-year-old woman with a right extrarenal retroperitoneal mass initially misdiagnosed as acute cholecystitis. A definitive diagnosis of angiomyolipoma is typically made after histopathologic examination of the operative specimen, which was not possible in this case. However, modern imaging modalities, particularly CT scan and MRI scan, have made it possible to identify these lesions in vivo. Conclusion: This case highlights that the preoperative diagnosis of extrarenal angiomyolipoma can be challenging. Awareness of their clinicopathological and radiological features is essential.

Keywords: Angiomyolipoma, Computed tomography scan, Hemorrhage, Hematoma, Retroperitoneum

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INTRODUCTION

Extrarenal angiomyolipomas are extremely rare benign tumors that are sometimes difficult to diagnose preoperatively. Angiomyolipomas are most often detected incidentally during imaging for other reasons, although they occasionally present with abdominal pain when large in size or when complicated by hemorrhage [1–3]. Imaging is very useful for diagnosis and determining their characteristic composition, although histopathological assessment is ultimately necessary when possible to differentiate them from malignant fatty tumors such as liposarcomas. The exact incidence of extrarenal angiomyolipomas is unknown, but they are described in a small number of case reports. Herein, we present an educational case of extrarenal retroperitoneal angiomyolipoma with spontaneous rupture that was initially confused with acute cholecystitis.

CASE REPORT

An 81-year-old white woman with known gallstone disease presented to the emergency department with a

two-day history of right upper quadrant pain. There was no history of trauma and she was not on anticoagulant therapy. Her past medical history included myocardial infarction and stroke, but her past surgical history was unremarkable. On presentation, her vital signs were within normal limits and there was no fever. Her abdomen was tender with guarding in the right upper quadrant on examination. Murphy's sign was positive.

Blood tests indicated that she was anemic with a hemoglobin level of 9.3 g/dL, but her coagulation profile and platelet count were normal. C-reactive protein (CRP) was elevated (Table 1). Abdominal ultrasonography revealed a slightly thickened gallbladder containing small gallstones (Figure 1). The patient was admitted to hospital with a diagnosis of acute cholecystitis and initially managed with parental ampicillin/sulbactam 1.5 g 8 hourly. Despite antibiotic therapy, the clinical symptoms did not improve on day-2 and, moreover, the C-reactive protein was further elevated.

A decision was made to perform laparoscopic cholecystectomy.

On diagnostic laparoscopy, the gallbladder was found to be unremarkable, but further exploration revealed a large retroperitoneal hematoma without evidence of active bleeding. The hematoma was managed by saline lavage and drain placement. It was decided to terminate the operation without removal of the lesion due to the patient's age and comorbidities. However, postoperative abdominal computed tomography (CT) scan with intravenous contrast (Figure 2) demonstrated a right retroperitoneal fat-containing mass situated behind the liver. A diagnosis of extrarenal angiomyolipoma with spontaneous rupture was made based on: (i) direct visualization of the lesion; (ii) our prior experience with such lesions; (iii) the known propensity of angiomyolipomas to hemorrhage; and (iv) a lack of suspicious features on imaging. The patient improved over the postoperative period and she was discharged from hospital on the seventh postoperative day.

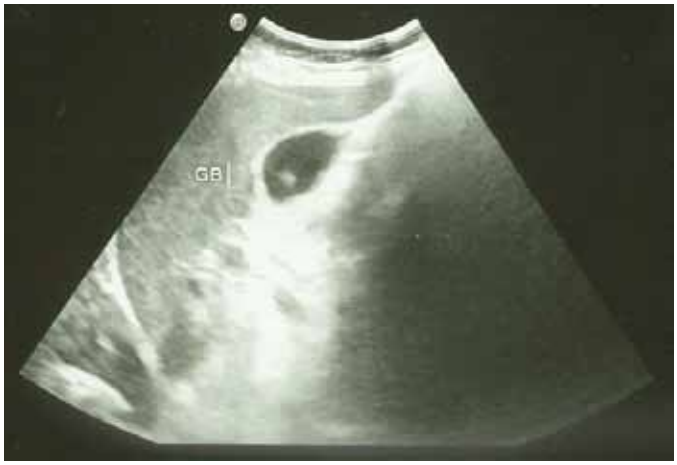

Figure 1: Ultrasound image of the gallbladder acquired at presentation in the emergency department. The gallbladder contains gallstones and has a slightly thickened wall.

The patient was managed conservatively due to the patient's age and comorbidities, the absence of active bleeding, and because there was no pressure effect on surrounding anatomical structures. She received regular follow-up every two months for half a year then yearly thereafter for two years. She remains symptom free and the lesion was sonographically stable at her last follow-up appointment, further supporting the benign diagnosis.

Table 1: Biochemistry and hematology results

Parameter	Day of presentation	Day 2 after presentation	Units	Normal range
Hemoglobin	9.3	8.9	g/dl	12–16
White cell count	9.19	7.74	1000/ul	4–10
C-reactive protein	3.95	5.13	mg/dl	0–1
Bilirubin	0.68	0.57	mg/dl	0.10–1.20
Gamma-glutamyl transferase	63	61	U/l	35–104

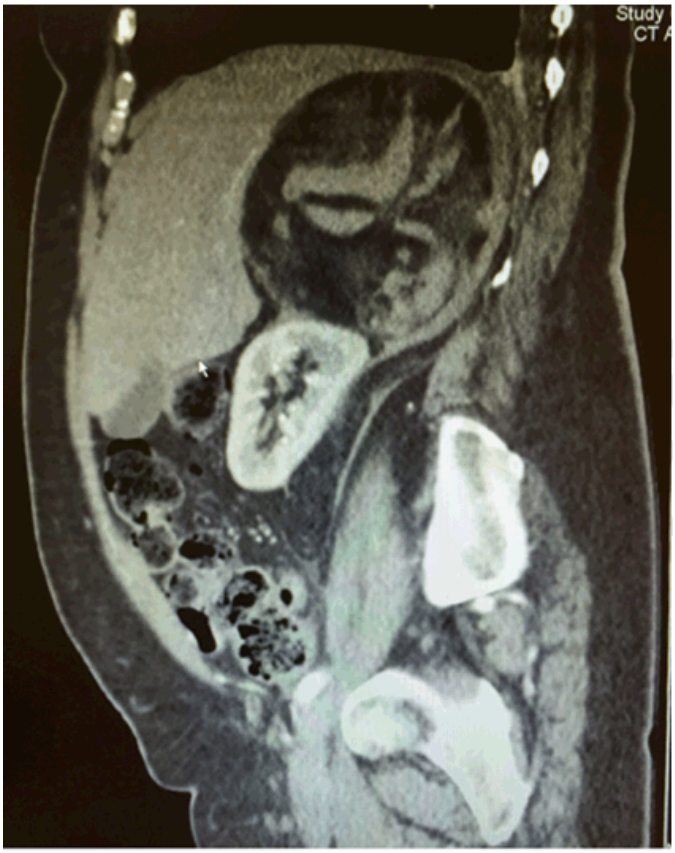

Figure 2: Sagittal abdominal computed tomography view illustrating a fat-containing retroperitoneal mass (10x11x11 cm) behind the liver.

DISCUSSION

Angiomyolipomas are uncommon benign neoplasms with a characteristic composition of blood vessels, smooth muscle, and mature fat. The majority of angiomyolipomas are sporadic (80%) and most commonly found in adult women (mean age of presentation 43 years; F:M 4:1). The remaining 20% are seen in the hereditary setting of tuberous sclerosis, Von Hippel-Lindau (VHL) syndrome, and neurofibromatosis type 1 [1]. Angiomyolipomas are typically found in the kidney but are also commonly found in the liver and, less commonly, retroperitoneum, ovary, fallopian tube, spermatic cord, palate, and colon [2]. Although most angiomyolipomas are asymptomatic, 68–80% of patients develop symptoms when the tumor grows to 4 cm or more [3]. The most severe symptoms are associated with tumor rupture, with patients presenting with acute onset pain due to hemorrhage; up to 20% are in shock at the time of presentation. Although hemorrhage is a frequent complication, necrosis and calcification are rare [4].

A definitive diagnosis of angiomyolipoma is typically made after histopathologic examination of the operative specimen. However, modern imaging modalities, particularly CT scan and MRI scan, have made it possible to identify these lesions in vivo [4], with MRI most suitable for assessing the distinctive vascular and adipose components of these lesions [2]. In our case, the most important differential diagnosis was liposarcoma, which is characterized on CT scan by the presence of non–fat attenuating intratumoral nodules and calcifications, especially multiple, globular calcifications, which were not seen in our case [5–7]. Furthermore, angiomyolipomas are known to have a propensity for hemorrhage, unlike liposarcomas, which are hypovascular; we note that a single case of retroperitoneal liposarcoma complicated by hemorrhage is reported in the literature [8]. Angiomyolipomas are primarily treated by surgery or tumor embolization based on tumor size and symptoms. Many cases of renal angiomyolipoma with spontaneous rupture are reported in literature but, to date, only three cases of retroperitoneal extrarenal angiomyolipoma with spontaneous rupture (including our case) are described [9, 10].

CONCLUSION

This case highlights the need to be vigilant and aware of this infrequent entity, whose presentation can mimic other common conditions. A high index of suspicion is required for effective treatment of this lesion.

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Author Contributions
Ghassan Almaimani – 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
Thomas Zoedler – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
André Schneider – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Bayan Almaimani – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
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Conflict of Interest
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CASE REPORT PEER REVIEWED | OPEN ACCESS

Disseminated tuberculosis: Challenges in diagnosis

Catarina Assis Cardoso, Teresa Filomena Garcia,
Patricia Raimundo Cachado

ABSTRACT

Introduction: Disseminated tuberculosis is difficult to identify and probably underdiagnosed. Its prevalence in non-HIV patients is rising and a high index of suspicion must always be present, especially when other diseases are present, because there is usually considerable signs and symptoms overlap between them. Also, difficulties in obtaining adequate tissue specimens and body fluids is frequent not only because the patient may not be able to undergo some procedures but also adequate biological samples amount and material processing in high quality laboratories is needed to reach a definitive diagnosis. Case Report: A case of a 67-year-old male with a past medical history of alcoholism and diabetes presented with cachexia, right pleural effusion, abdominal ascites and bilateral leg edema. Isolated thrombocytopenia was present. Heart failure was first diagnosed, but thrombocytopenia worsening led us to a high suspicion for tuberculosis. A series of factors such as heart failure treatment and restraints on adequate tissue biopsy specimens for histopathological and microbiological evidence delayed diagnosis. Bone marrow biopsy was the key for a conclusion. However, despite therapy, the patient's condition did not improve and he passed away. Post-mortem examination revealed the extension of the disease. Conclusion: Late diagnosis and treatment is one of the reasons why disseminated tuberculosis has such high rate mortality, so our aim is to raise awareness for its early identification with appropriate use of invasive procedures and also provide an example of some restraints that might preclude diagnosis, which physicians should pay attention to.

Keywords: Bone marrow, Biopsy, Diagnosis, Disseminated tuberculosis

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INTRODUCTION

Tuberculosis is a highly prevalent disease in Portugal (incidence of 187 per 100,000 population) but disseminated form is rare (1%), especially in non-HIV patients. Although there have been some unusual case presentation reports, it is probably underdiagnosed in most of the patients and means a challenge for physicians because symptoms and signs may overlap other diseases,

sometimes with difficulties in establishing the diagnosis due to the fact that patients may not be able to undergo some invasive procedures.

CASE REPORT

A 67-year-old man born in Mozambique with Goa ancestry, living in Portugal for 30 years without any abroad trips, currently unemployed, with a past medical history of alcoholism, type 2 diabetes under control with metformin 850 mg twice daily and stage three chronic kidney disease, was admitted in the emergency department with a four-month history of anorexia, weight loss of 10 kg (previous weight: 60 kg), adynamia and dry cough. On physical examination the patient was emaciated. Lung auscultation revealed diminished sounds in the lower right hemithorax and the abdomen showed shifting dullness to percussion. There was discrete bilateral leg edema and doubtful hepatojugular reflux. Blood laboratory workup revealed chronic renal failure (creatinine 1.54 mg/dL, urea 87 mg/dL) a cyto-cholestatic pattern without hyperbilirubinemia (aspartate aminotransferase/alanine aminotransferase 70/89 U/L respectively, alkaline phosphatase 312 U/L), discrete International Normalized Ratio elevation to 1.5 and thrombocytopenia (78,000/mm^3) without additional cytopenias.

Thoracic X-ray showed a unilateral right effusion (Figure 1). We decided to hospitalize the patient for further investigation.

We considered the following differential diagnosis: neoplasia, tuberculosis or chronic hepatic disease.

Infectious serologies, namely HIV and hepatitis were non-reactive. Tuberculin test was negative.

Blood smear did not show significant abnormalities.

Imaging exams such as abdominal ultrasound showed no signs of chronic hepatic disease but moderate ascites was noticed (Figure 2).

Non-enhanced (due to renal failure) chest and abdominal computed tomography scan revealed mediastinal perihilar right adenopathies with a unilateral moderate right pleural effusion, cardiomegaly and moderate ascitic fluid (Figures 3 and 4).

Thoracentesis and closed pleural biopsy were not possible at the same time so they were scheduled in the following week. Meanwhile, transthoracic echocardiography revealed global hypokinesia with severe left systolic dysfunction, low ejection fraction of 17% with impaired right ventricle function. Brain natriuretic peptide was strongly elevated with 1,200 pg/mL. We considered a heart failure diagnosis, so treatment with diuretics, beta blockers, angiotensin II receptor blockers and small dose digoxin were started.

There was a gradual improvement of both pleural effusion and ascites, but on the other hand, a progressive decrease in thrombocytopenia to 55,000/mm^3 and after a few additional days to 18,000/mm^3 was noticed without additional explanation. Thoracic X-ray showed a marked decrease in right pleural effusion making closed pleural biopsy a high risk procedure, even with coagulopathy correction, so it was not performed. Meanwhile, a second abdominal ultrasound also showed very small ascites with significant diffuse bowel distension making the patient unfit for paracentesis.

Bone marrow biopsy was performed and few epithelioid non-caseous granulomas were identified with a negative acid-fast bacilli smear. Unexpectedly, myeloculture and blood culture showed the presence of a nosocomial bacteria *Serratia marcescens*, which contaminated the sample for mycobacterial growth. We decided to treat this infection with piperacillin-tazobactam according to antimicrobial susceptibility testing.

A second bone marrow biopsy attempt was made and this time significant stromal fibrosis due to Langhans giant cell granulomas, one with caseous necrosis, was identified.

Considering the patient's history and bone marrow findings, disseminated tuberculosis was very likely, so we decided to add anti-tuberculosis drugs while the sample

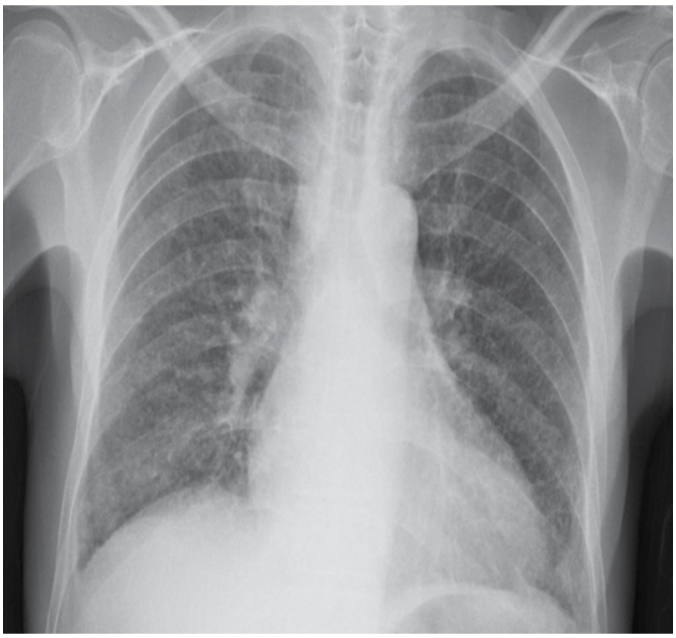

Figure 1: Thoracic X-ray showing unilateral right-sided effusion.

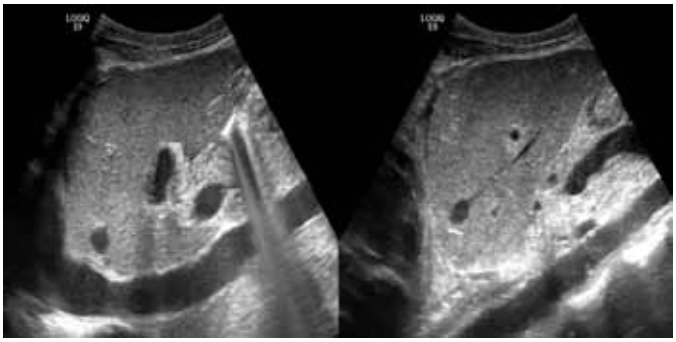

Figure 2: Abdominal ultrasound identified moderate ascites with a normal-sized homogeneous texture liver.

was being decontaminated for mycobacterial growth culture. The patient was started on a four drug therapy with isoniazid, rifampicin, pyrazinamide and ethambutol. Eventually there was a discrete improvement on platelets counts, but the patient died due to progressive malnutrition after one week of therapy.

Post-mortem examination revealed green ascites with identification of yellowish granulomas present in mesentery and subdiaphragmatic peritoneum. Mediastinal adenopathies were present bilaterally. Liver had a granular surface texture. Acid-fast bacilli were identified with Ziehl-Neelsen technique in granulomas, adenopathies and liver myeloculture was positive for mycobacterium tuberculosis. Final diagnosis was disseminated tuberculosis with miliary bone marrow, abdominal and thoracic involvement.

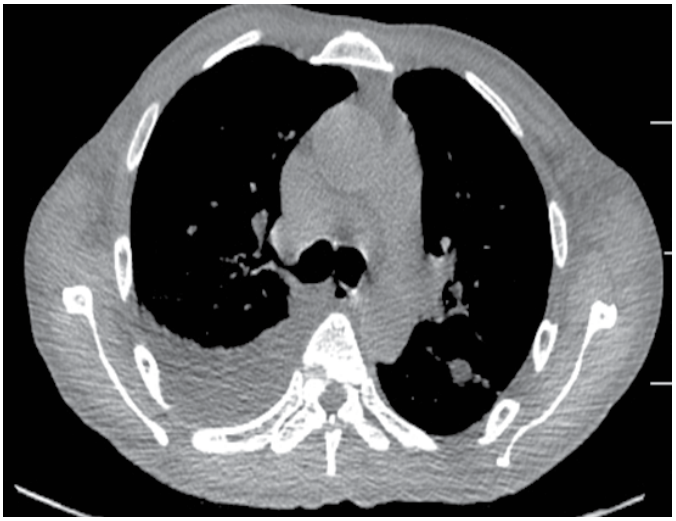

Figure 3: Non-enhanced chest computed tomography scan showing unilateral right sided pleural effusion with small mediastinal right-sided lymphadenopathy and cardiomegaly.

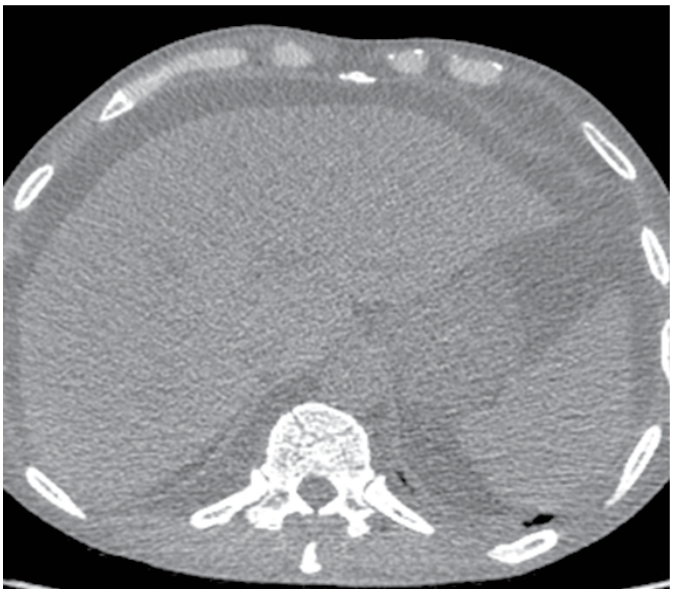

Figure 4: Non-enhanced abdominal computed tomography scan showing moderate free-fluid ascites.

DISCUSSION

Disseminated tuberculosis, especially miliary form, accounts for less than 2% of all cases and up to 20% of all extra-pulmonary cases in various clinical series. Classic presentation is seeding in the lung, as evidenced on chest radiography or computed tomography scan. But individual organ involvement, although unusual, is possible [1].

Also, it is more difficult to diagnose. Conventional acid fast bacilli smears have low sensitivity and require a long time for *Mycobacterium tuberculosis* to become evident during culture. As a result, diagnosis mostly depends on histological evidence.

Our case is different from other reported disseminated tuberculosis diagnosis [2–6] because we had to endure considerable difficulties on acquiring biological material for the final diagnosis. Heart failure first diagnosis and treatment decreased pleural and ascitic fluid, which together with coagulopathy made closed pleural biopsy a high risk procedure. Moreover, even if we tried paracentesis in a small amount of ascitic fluid, acid fast stained smear has a disappointingly low yield and not only the frequency of a positive culture is less than 20% [7, 8] but we also need to consider the usual four to six weeks delay of microbiological culture results.

Since the key to diagnosis was finding a few caseating granulomas in bone marrow histopathology. We call attention for bone marrow biopsy as a high profitable and less prone for complications invasive procedure whenever disseminated tuberculosis is suspected, especially when cytopenias are present [8].

Another problem was the identification of *Serratia marcescens* in myelocultures, which precluded mycobacteria growth. As far as literature reviews, no case of bone marrow culture with nosocomial bacteria isolation has been reported. Positive cultures from bone marrow have a low yield as described in literature [1, 9] but they remain the gold standard for tuberculosis diagnosis, especially in an era of multidrug resistance disease.

Mortality, in disseminated tuberculosis, is high in the range of 50 to almost 100%. Certain factors are thought to contribute to the variable outcome such as disease severity and underlying comorbidities, but delay in initiation of appropriate treatment is probably the most important. These two latter conditions were indeed present in our patient; he was extremely malnourished and treatment was started in a disease probably present for more than four months [10].

CONCLUSION

In conclusion, miliary tuberculosis still faces diagnostic difficulties. Our aim is to show and discuss diagnostic issues in acquiring appropriate tissue and body fluids since they must be obtained in the first place with

adequate amount and appropriate analysis in high quality laboratories whenever tuberculosis is to be considered.

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Author Contributions

Catarina Assis Cardoso – 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
Teresa Filomena Garcia – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Patricia Raimundo Cachado – 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 PEER REVIEWED | OPEN ACCESS

Healthcare-associated necrotizing cutaneous mucormycosis: A case report

Oleksandra Lupak, Kassem Bourgi, Tricia Stein

ABSTRACT

Introduction: Mucormycosis is becoming a challenging problem as the number of immunocompromised patients is increasing. Historically, the primary presentation of the disease was rhinocerebral. However, other manifestations are becoming more prevalent. Case Report: We report a case of healthcare cutaneous mucormycosis in 51-year-old female initially presenting as cellulitis. The patient subsequently had worsening necrotizing infection and required multiple extensive intra-operative debridement procedures along with right arm amputation. Histopathology later confirmed by tissue cultures, revealed evidence of *Rhizopus*. The patient was then started on lifelong isavuconazole therapy. Conclusion: Healthcare associated mucormycosis is a growing problem that requires high index of suspicion to ensure early diagnosis and prompt treatment.

Keywords: Amphotericin B, Immunocompromised patients, Isavuconazole, Mucormycosis

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INTRODUCTION

Mucormycosis is an aggressive opportunistic fungal infection caused by filamentous Mucorales [1]. It commonly affects immunocompromised patients and is associated with high morbidity and mortality. While rhino cerebral and pulmonary mucormycosis are the most common forms of the disease; cutaneous, gastric, and intestinal manifestations are becoming more prevalent as the numbers of immunocompromised hosts expands [1]. Cutaneous mucormycosis is less common than other clinical forms, however, it can be lethal if not identified and treated early [2].

CASE REPORT

Our patient is a 51-year-old African-American female with multi-system sarcoidosis and steroid-induced hyperglycemia. She was hospitalized, prior to current presentation, for a neurosarcoid flare requiring pulse dose of IV steroids. At the time of discharge the patient noted mild erythema on the right forearm, at the site of intravascular catheter placement. On a follow-up

appointment with her primary care physician, one week post-discharge, the erythema was worsening. She was started on a 7-day course of cephalexin for treatment of presumed cellulitis. Despite the antibiotic therapy, her symptoms progressed as she developed purulent bloody discharge. On initial evaluation in the emergency department, the patient had no complaints of fevers, chills, numbness or pain. The right forearm appeared swollen, red, and tender to palpation. Superficial eschar was visualized over the medial aspect. Initial laboratory results were significant for leukocytosis of $12.8x10^9$ per liter. A computed tomography (CT) of the right forearm reveled diffuse soft tissue swelling of the ulnar aspect with scattered subcutaneous gas. There was evidence of small focal fluid collection with no gas seen within deep muscular compartment.

The patient was diagnosed with right forearm abscess and started on IV vancomycin. Plastic surgery team performed an intraoperative right forearm superficial debridement. Intraoperative wound cultures grew *Escherichia coli*, *Enterococcus faecalis*, and *Morganella morganii*. Based on the results of in vitro susceptibility, antibiotics were then escalated with the addition of intravenous meropenem.

The patient continued to deteriorate despite aggressive therapy. On day-five of her hospitalization an extensive debridement of the forearm was performed. Histopathology of muscular and subcutaneous tissue revealed necrotizing infection with angioinvasion, surrounding infarction as well as perineural invasion secondary to zygomycetes (mucormycosis) (Figure 1). Liposomal amphotericin B was then initiated. Rhizopus subsequently grew on the intraoperative cultures 72 hours later. A full body CT ruled out any evidences of disseminated infection. The patient continued to have extensive muscle and tissue necrosis requiring right arm amputation with shoulder disarticulation to prevent systemic dissemination of the infection.

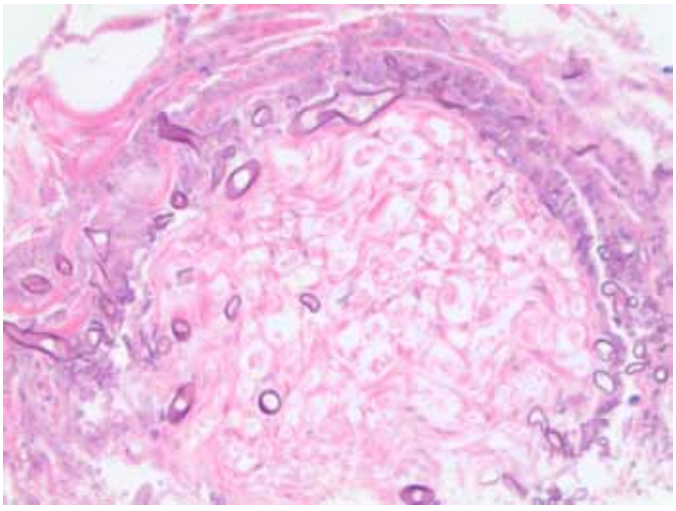

Figure 1: Histopathology from debrided tissue showing angioinvasian and perineual invasian with broad thin-walled zygomycetes (H&E stain, x200).

Hospital course was complicated by acute renal failure that was attributed to the amphotericin B. At that time, she was switched to oral isavuconazole and discharged home to continue a prolonged course of therapy. On follow-up with infectious disease clinic at 2 and 4 weeks post-discharge she had no evidence of disease recurrence. It was decided to continue the patient on lifelong treatment with isavuconazole.

DISCUSSION

Healthcare associated mucormycosis is a growing concern as the number of immunocompromised patients increase [3]. Necrotizing infection secondary to cutaneous mucormycosis is an infrequent presentation of a relatively rare infection. Reports have associated cutaneous mucormycosis to minor skin breaks and trauma resulting in spore inoculation into the dermis [4, 5]. The entry site of the fungi in the health care setting has been previously associated with an intravenous catheters [3], as appears to be the case with our patient.

The diagnosis of mucormycosis relies upon the identification of organisms in tissue by histopathology with culture confirmation. As our case demonstrates, culture often yields no growth initially, and histopathology identification may be the only evidence of infection. High clinical suspicion coupled with early identification is crucial as treatment of mucormycosis involves a combination of aggressive surgical debridement with adjunctive antifungal therapy and decreased in immunosuppressive therapy [6]. Lipid formulation of amphotericin B is currently the recommended first-line antifungal [6]. However, as in our case, it is often associated with dose-related toxicity resulting in renal damage limiting its use. Isavuconazole is a newly approved extended spectrum triazole with activity against mucormycosis [7]. Advantages of using isavuconazole include great oral bioavailability, predictable pharmacokinetics in adults, and availability of a water-soluble intravenous formulation [8, 9]. Recent open-label case control trial have showed isavuconazole was similar in efficacy to amphotericin B and posaconazole for mucormycosis primary and salvage treatment [10]. Recent data also shows that isavuconazole is well tolerated, has fewer serious side effects and less drug-drug interaction when compared to amphotericin B [9].

CONCLUSION

In summary, mucormycosis emerges as concerning infection especially in the immune suppressed population. Our case demonstrates the need for prompt diagnosis and early treatment of mucormycosis, especially for the less common clinical form. The availability of new broad-spectrum antifungal antibiotics provides more

options for patients in whom amphotericin B is not well tolerated.

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Author Contributions

Oleksandra Lupak – Substantial contributions to conception and data acquisition, Analysis and interpretation, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Kassem Bourgi – Substantial contributions to data acquisition, Analysis and interpretation., Revising article critically for important intellectual content, Final approval of the version to be published

Tricia Stein – Substantial contributions to conception, Revising article critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Aspergillus as a rare cause of non-healing traumatic breast wound

Sana Zeeshan, Syed Faisal Mahmood, Abida K. Sattar

ABSTRACT

Introduction: *Aspergillus* is an opportunistic fungal infection in immunocompromised hosts with a very rare occurrence in breast tissue. Case Report: We report a case of *Aspergillus flavus*, identified within a non-healing ulcer in the breast of an immunocompromised host. The patient was a 63-year old lady with diabetes mellitus and severe rheumatoid arthritis requiring oral prednisolone therapy. She had developed a pressure ulcer on her right breast secondary to an upper extremity cast placed for conservative management of a humerus fracture. This pressure ulcer failed to improve despite multiple debridements, local wound care and antibiotic treatment. Tissue biopsy from the debridement specimen revealed fungal hyphae without evidence of malignancy. Formal fungal cultures confirmed this to be *Aspergillus flavus*. She was started on oral Itraconazole along with local wound care. She later succumbed to gram negative sepsis and Disseminated intravascular coagulation (DIC). Extensive literature search to identify causes of non-healing traumatic breast wounds revealed a few case reports only. Conclusion: *Aspergillus* can present with extensive soft tissue or breast involvement in immune suppressed individuals and should be considered in patients with a non-healing breast wound with a high index of suspicion.

Keywords: *Aspergillus*, Breast wound, Immune compromised, Non-healing

How to cite this article

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INTRODUCTION

Invasive fungal infections in healthy individuals are very rare due to competency of immune system against such infections [1]. Opportunistic fungal infections in immunocompromised hosts have been reported and seem to be increasing over time merely due to increasing number of susceptible hosts, greater laboratory expertise in the detection and identification of fungi, use of new transplantation modalities and use of antimicrobial prophylactic practices. Among them, *Aspergillus* and *Candida* have a higher prevalence [2]. Immunocompromised patients are equally at risk of developing soft tissue fungal infections as they are at risk of acquiring other types of infections [3–6]. In breast, soft tissue fungal infections have been reported in

association with prosthetic breast implants [1, 7–9]. They are considered to colonize via airborne dissemination, contamination of implants during manufacture, hematogenous dissemination or nosocomial spread from the operating room environment or instruments during surgery [10, 11]. In most patients, the source was presumed to be airborne infection during a surgical procedure [10]. *Aspergillus* is an ubiquitous saprophytic fungus with more than 200 recognized species that may cause allergic bronchopulmonary aspergillosis, pulmonary aspergilloma, paranasal sinus infection, endocarditis, implant infections [10,12,13]. Few cases of aspergilloma of breast tissue have been reported in literature so far. We describe the case of *Aspergillus flavus* infecting breast tissue of an immune compromised host resulting in a non-healing wound.

CASE REPORT

A 63-year-old lady, known case of long standing diabetes mellitus with acceptable glycemic control and rheumatoid arthritis, on oral prednisolone therapy for five years, with normal white count, was admitted to our hospital with a non-healing fracture of the proximal shaft of right humerus. A road traffic accident two-months prior resulted in the upper extremity fracture that had been managed conservatively with a cast at an outside institution. This cast rested against her right breast and resulted in pressure necrosis. At the outside facility, she underwent two formal wound debridements for this necrotic breast wound resulting in a large ulcer. Without much improvement over a two-month period, frustrated, the patient transferred care to our institution that serves as a tertiary care referral center.

Examination at presentation showed a large ulcerated area in the lower half of the right breast with unhealthy edges. The base was heavily coated with necrotic tissue and fibrin. There were multiple dry scabs on the skin of the remaining breast (Figure 1). Neither purulent drainage nor cellulitis was seen. Examination did not identify a lump and the contralateral breast was normal. Mammogram and ultrasound of both breasts were negative for malignancy. Routine tissue culture did not grow any organism and histology showed dense acute and chronic inflammatory infiltrate with fat necrosis and microabscesses (Figure 2). Special stain PAS+D highlighted fungal hyphae (Figure 3). For the identification of fungal strain, a formal fungal culture of breast tissue revealed moderate septate hyphae on smear and heavy growth of *Aspergillus flavus* on culture.

The right humerus fracture was surgically managed with open reduction and internal fixation. Her breast wound was debrided down to healthy tissue. She was started on oral itraconazole 200 mg q 12 hourly along with local wound care and discharged home. 10-days after her discharge, she returned to the emergency Room with DIC secondary to *E. coli* septicemia from pyelonephritis.

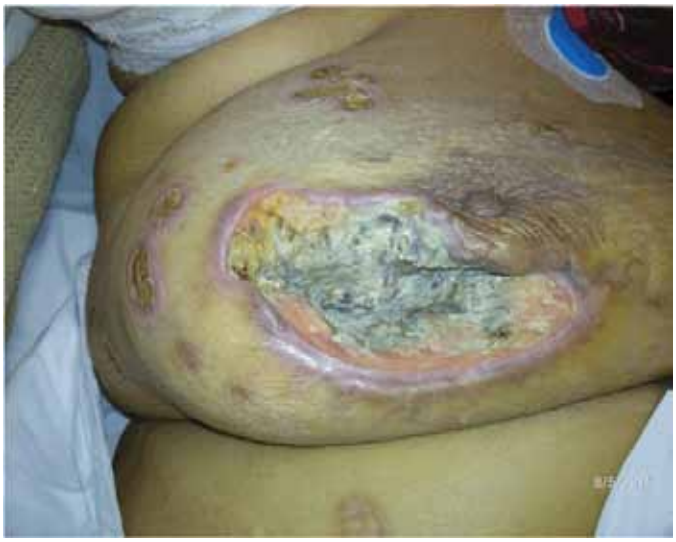

Figure 1: Ulcerated wound with necrotic tissue over lower half of right breast.

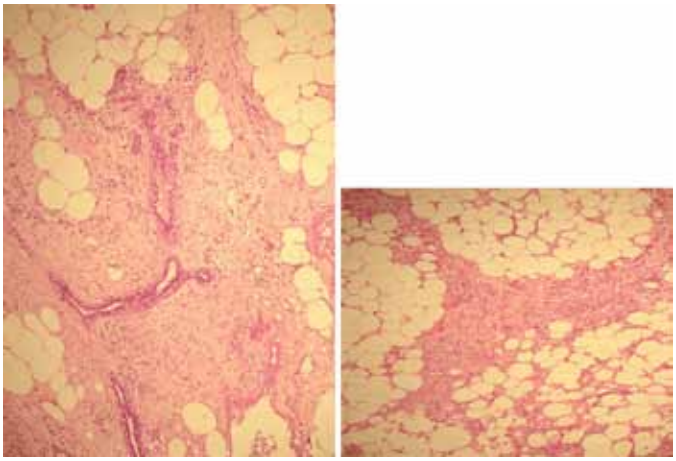

Figure 2: Breast tissue showing breast ducts and surrounding moderate degree of lymphocytic, plasma cell and eosinophilic infiltrate (H&E stain, x100).

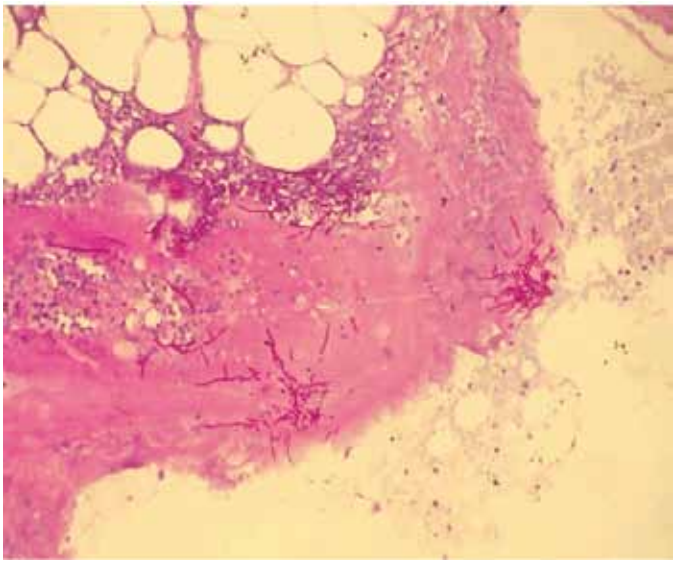

Figure 3: Breast tissue showing necrosis with collections of septate, branching fungal hyphae highlighted by PAS+D special stain (H&E stain, x400).

She was admitted to the intensive care unit and given supportive therapy along with culture specific antibiotics. Despite local wound care at home and itraconazole, her breast wound failed to improve and was once again covered with fibrinous exudate and necrotic tissue. Due to elevated bilirubin and deranged renal function, itraconazole was switched to oral voriconazole. Due to her overall status, further debridement of breast wound was deferred. Her septicemia resulted in multi system organ failure and due to their inability to pay in a self-pay system, the patient elected to leave against medical advice and passed away shortly after.

DISCUSSION

Fungal infections of the breast are very rare [1, 3]. They are usually present in relation to breast malignancy and implants in otherwise immunocompetent individuals [1, 3, 7]. Patients who are severely immunocompromised can present with fungal infections involving virtually any organ of the body such as lungs, skin, gastrointestinal tract, etc. with the breast being a very rare site of involvement [3, 8, 10]. Until 2013, only 13 cases of fungal infection of breasts were reported in literature [8]. These were reported in patients with diabetes mellitus [4], postoperative status for breast carcinoma [4], acute myeloid leukemia [5], transplantation [6] and breast implants [1, 7]. Few cases of fungal infection of breasts and chest wall are also reported in immunocompetent individuals and also in male breasts [8, 9].

Aspergillus is an opportunistic mold, the virulence of which depends on the biological features of the fungus and the immune status of the host [3]. There are more than 200 recognized *Aspergillus* species. Among them, *A. fumigatus* is the most common form, followed by *A. flavus* and *A. terreus* [3, 10, 12]. *A. fumigatus* and *A. flavus* are also the most common cause of cutaneous manifestation of locally invasive aspergillosis [8]. The production of conidia characterizes the infectious life cycle of *Aspergillus* [3, 8]. These conidia are easily dispersed into the air and when they reach a permissive environment such as the lung of an immunosuppressed host, they germinate and become hyphae, which is the invasive form of *Aspergillus*. The hyphal growth invades the blood vessels, resulting in hemorrhagic necrosis, infarction, and potential dissemination to any other organ in susceptible patients [3, 8, 14]. It most commonly affects the lungs and paranasal sinuses, less frequently, the brain, skin, gastrointestinal tract, heart, or kidney may show extra-pulmonary manifestations [3–5]. Over 90% of patients who develop aspergillosis have at least one of the following factors: cytotoxic chemotherapy, corticosteroid therapy, solid organ or bone marrow transplantation, AIDS or prolonged neutropenia [15].

Our case of culture proven *Aspergillus flavus* was seen in an immunocompromised host with diabetes mellitus and long-term steroid therapy without neutropenia. An additional factor promoting initial colonization may have been indiscriminate use of multiple antibiotics over a two-month period for a conservatively managed humerus fracture. It is postulated that *Aspergillus* may have inoculated the breast wound from the cast that initiated the ulcer from pressure necrosis or possibly during surgical debridements at outside facilities.

The purpose of presenting this case is to highlight fungal infections as one of the rare causes of a non-healing breast wound, other being mycobacteria [16]. The surgeon should have a high index of suspicion for diagnosis [15]. Fungal infections should be suspected in a non-healing breast wound especially in the absence of malignancy, with appropriate wound therapy and negative routine cultures. Smears, tissue cultures, histopathology and special stains for fungi and mycobacterium should be ordered to establish the diagnosis. To the best of our knowledge, this is the only reported case of aspergillosis in a non-healing breast wound from Pakistan.

Recommended treatment for aspergillosis of the breast comprises voriconazole, itraconazole and amphotericin b. Dose adjustment may be necessary with certain inhaled steroids. Surgical excision of partial or entire breast may be necessary as blood vessel involvement can lead to extensive soft tissue necrosis rendering the breast non-salvageable [17,18].

CONCLUSION

Aspergillus can present with extensive soft tissue or breast involvement in immune suppressed individuals and should be considered in patients with a non-healing wound. High index of suspicion is necessary to send appropriate cultures. Infected patients should receive early, aggressive combined medical and surgical therapy.

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Author Contributions
Sana Zeeshan – 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
Syed Faisal Mahmood – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Final approval of the version to be published

Abida K. Sattar – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Pediatric traumatic pulmonary herniation: A case report

Robert Vezzetti, Peter Cosgrove, Julie Sanchez, Gael Lonergan

ABSTRACT

Introduction: Blunt thoracic trauma is not common in the pediatric population and usually results in pulmonary contusion, but other injuries may be present, especially in the presence of rib fractures. Case Report: We describe a case of blunt thoracic trauma that was complicated by rib fractures and associated lung herniation, which is a rare complication of such an injury. Imaging modalities as well as repair options are discussed. Conclusion: Thoracic trauma in children, while rare, can be associated with significant injury. Often, associated clinical symptoms may be subtle in children, making detection difficult. Recognition of injuries associated with non-penetrating thoracic trauma is critical to ensure proper treatment and recovery in children.

Keywords: Lung herniation, Pediatrics, Thoracic injury, VATS

How to cite this article

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INTRODUCTION

Thoracic trauma in children is rare, accounting for 4–6% of children presenting to trauma centers [1]. This trauma mechanism, however, can be significant and is second to head injury as a cause of significant morbidity and mortality among the pediatric population [2, 3]. The majority of cases in children are due to blunt injury, although penetrating injury occurs more frequently in the adolescent population. Blunt thoracic trauma typically does not result in clinically significant injury but when present can be associated with other intrathoracic injuries, including rib fractures, pneumothorax, hemothorax, and pulmonary contusions. Infants often are exposed to thoracic trauma through motor vehicle crashes or non-accidental trauma; in school-age children, this trauma often is due to bicycle accidents, scooters, etc.

In adolescents, motor vehicle crashes or gunshot injuries predominate [2]. The data regarding the use of imaging in the pediatric patient with thoracic trauma is sparse and the method of repair of pediatric thoracic injuries is evolving.

CASE REPORT

An 11-year-old girl was brought to the pediatric emergency department after falling off of her bicycle. She was riding when she turned suddenly and, in the process of falling, her left chest struck the handlebar. On physical exam, her vitals include a heart rate 103 bpm, respiratory rate 24 bpm, blood pressure 110/70 mmHg, and an oxygen saturation of 98% on room air. She was conversing and stated that she had some left sided anterolateral chest pain. Physical examination demonstrated a small visible bruise at the anterolateral portion of the mid-left chest. There was mild palpable tenderness and she complained of pain with inspiration; breath sounds were mildly decreased on the involved side. She had no abdominal pain. At the conclusion of the physical examination she was found not to have any further injuries. Laboratory evaluation, including complete blood count, liver function tests and urinalysis were normal. Chest radiograph demonstrated rib fractures and there were also thickening of the periaortic tissues, possibly consistent with a small effusion, and the left lung base was hazy (Figure 1). These findings prompt a CT scan, demonstrating rib fractures and lung herniation. Additionally, there was a small pulmonary contusion of the affected lung (Figure 2). The pediatric trauma team was consulted and the child was taken to the operating room for repair, using video-assisted thoracoscopic repair (VATS) technique (Figures 3–5). She had an uneventful hospital course and does well.

DISCUSSION

Blunt thoracic trauma in most children typically results in pulmonary contusion [4]. The anatomic properties of the pediatric chest play a significant role in the injury sustained from this type of trauma mechanism. Principally, the pediatric thorax is more pliable, allowing for compression of the ribs, which results most commonly in contusions rather than fractures [2]. Indeed, the presence of rib fractures has been shown to be associated with other pathology, including intracranial and intra-abdominal injuries, [5] and their presence should alert the clinician to this possibility. The presence of multiple rib fractures has been shown to correlate with increasing mortality [6].

Identification of thoracic injuries in children who have sustained blunt thoracic trauma is critical to ensure a reduction in morbidity and mortality. There is a dearth of clinical decision rules for identifying thoracic injuries due to blunt chest trauma in pediatrics. One prospective study identified six clinical findings to help predict injuries: abnormal chest auscultation, low systolic blood pressure, Glasgow Coma Scale (GCS) <15, abnormal thoracic examination, elevated respiratory rate, and femur fracture [4]. Of the six criteria, abnormal chest auscultation, hypotension, and elevated respiratory rate had the highest specificity, while a GCS <15, abnormal thoracic examination, and elevated respiratory rate had the highest sensitivity [4]. Interestingly, our patient met

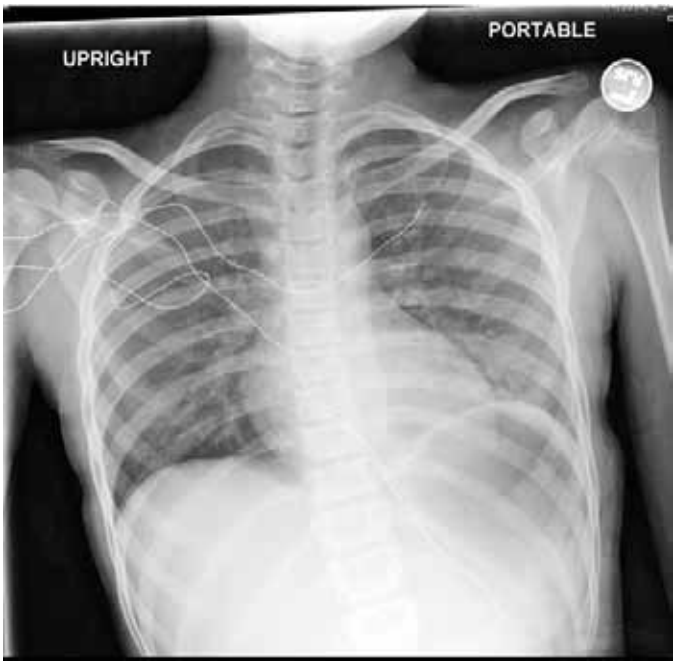

Figure 1: Chest X-ray demonstrating rib fractures and subtle left pulmonary hazziness.

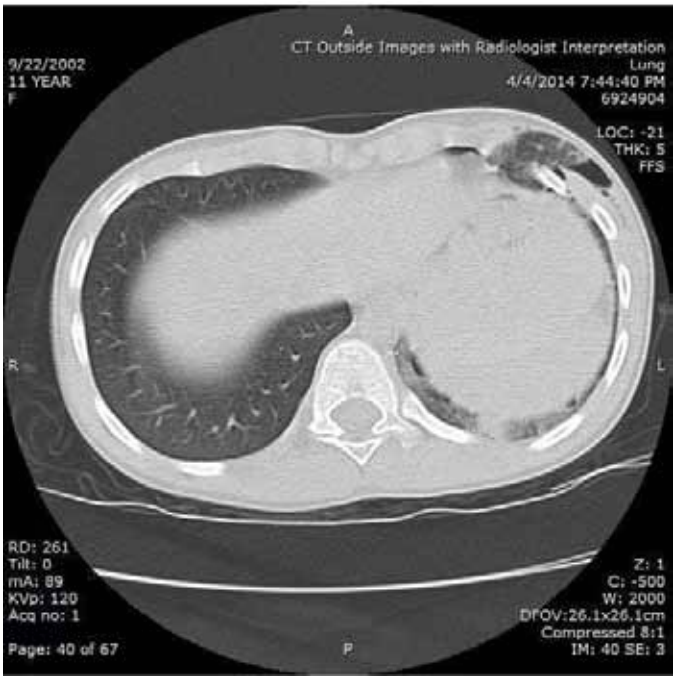

Figure 2: Chest computed tomography scan demonstrating rib fractures and lung herniation.

several of these criteria, including elevated respiratory rate, abnormal chest auscultation findings, and abnormal thoracic examination.

Plain chest radiography is a common study to obtain when evaluating children with blunt thoracic trauma. This imaging modality can identify rib fracture, pneumothorax, hemothorax, and pulmonary contusion. The identification of a pneumothorax or other findings on plain radiography and correlation to more significant thoracic injury has been studied. A multicenter retrospective cohort identified the presence of a hydrothorax and/or pneumothorax; isolated subcutaneous emphysema on CXR and off-road vehicle incidents, as statistically significant variables associated with significant thoracic injury [7]. In this study, 7 of 396 "unremarkable" chest radiographs were found to have occult pneumothoraces. Although none of these required chest tube placement, this questions a normal chest radiograph's negative predictive value. Prospective data evaluating the predictive value of chest radiographs in pediatric thoracic trauma are currently lacking.

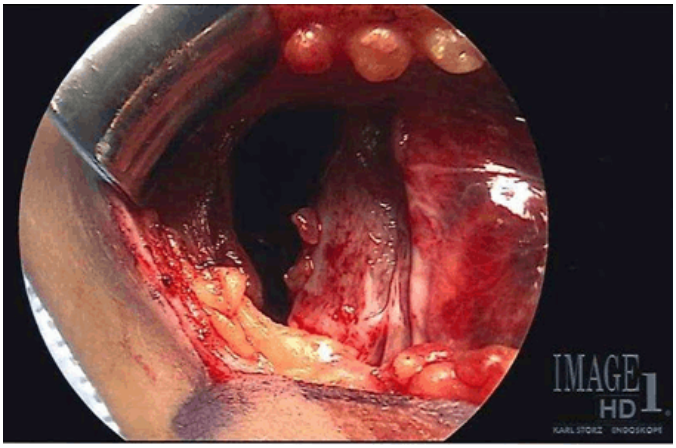

Figure 3: Operative photo of chest wall defect.

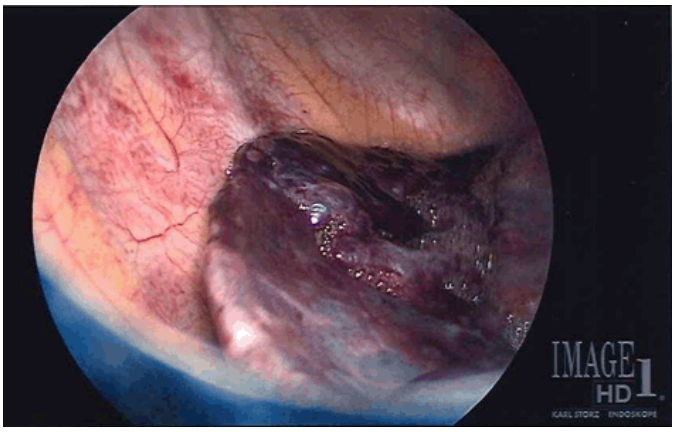

Figure 4: Operative photo of contused lung.

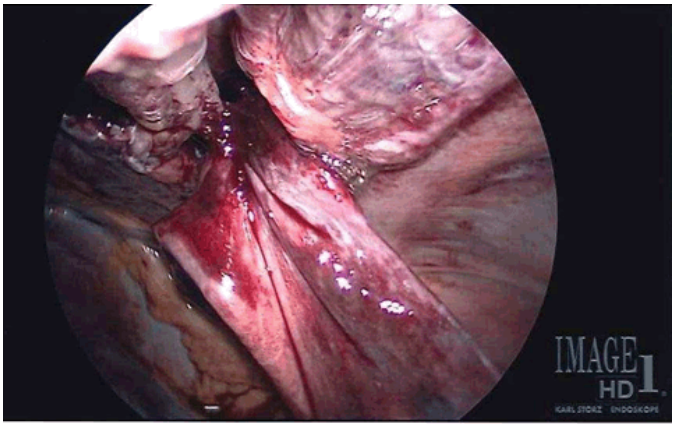

Figure 5: Operative photo of lung herniation.

The role of computed tomography (CT) imaging in pediatric blunt thoracic trauma is unclear. Smaller observational studies note that typical indications for CT imaging were thoracic injury on chest radiograph and high impact force, with few relying solely on physical examination findings. In one study, of 45 children identified at a level 1 trauma center who all had both plain radiographs and CT, 18 patients had findings on CT not seen on chest radiograph [8]. However, only six patients had a change in therapy based on CT results. Power was lacking to determine the presence of non-radiologic predictive variables that may have otherwise identified the need for thoracic CT scan . One large observational study of 235 children presenting to a level 1 Trauma Center noted that of 145 reportedly "normal" chest radiographs, the chest CT scan was abnormal in 47.6% [8]. Computed tomography scan was superior at identifying pneumothorax/hemothorax and bone/vertebral fractures when compared to portable chest radiograph. Although 47 hemothoraces or pneumothoraces were identified on CT scan only four of these required chest tube placement [9]. Whether a combination of plain radiographs and physical examination is sufficient to detect significant injury in pediatric thoracic trauma, or if CT is required, remains to be determined. In the majority of studies, CT findings did not change patient management. It would seem that in most situations plain radiography and physical examination are a reasonable first step in thoracic trauma, with CT imaging reserved for those patients with significant historical, clinical, or plain radiographic findings.

Children with lung herniation from blunt thoracic trauma require evaluation by a pediatric surgeon. The majority of children with this injury are surgically repaired. Traditionally, this is primary closure with open repair which is associated with longer hospital stays, post-operative pain/discomfort, and the potential for infection. While primary closure remains an option, Hebra et al. advocated for a GORE-TEX (Gore Medical, Flagstaff, Arizona, USA) pericardial patch mesh repair, citing shorter hospital stay and reduced postoperative pain [10]. The advent of video-assisted thoracoscopic surgery (VATS) provides a less invasive method of repair. VATS, though, may have limitations in patients with more extensive pleural disease or difficult anatomical sites not amenable to thoracoscopy. While surgical repair is the usual treatment modality and these hernias rarely

resolve on their own, they have also been described to spontaneously resolve which may support the option for clinical observation in selected patients [4]. However, the length of time to resolution is unknown and data are lacking in the pediatric population [11].

CONCLUSION

Pediatric thoracic trauma is most often associated with blunt injury. A rare complication of pediatric blunt thoracic trauma is lung herniation. Imaging options include chest radiographs and, in select patients, chest CT scanning. In most clinical settings, good quality chest radiographs are all that are indicated, with chest CT reserved for those patients with significant chest trauma, multiple injuries, or where there is a high index of suspicion for significant thoracic injury. Open, primary repair is often done, but the VATS technique is also a viable option.

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Author Contributions

Robert Vezzetti – 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
Peter Cosgrove – 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
Julie Sanchez – 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
Gael Lonergan – 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

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Antinuclear antibodies positive patient with splenic infarct a diagnostic dilemma

Sabina Langer, Ravi Daswani, Rahul Arora, Nitin Gupta, Anil Arora, Jyoti Kotwal

ABSTRACT

Introduction: Presence of autoimmune phenomenon along with splenic infarct made clinician relate the two considering the splenomegaly as a consequence of splenic vein thrombosis and autoimmune myelofibrosis as a cause of pallor and repeated blood transfusions. The presence of near normal counts masked the underlying myeloproliferative neoplasm which led to the patient wrongly being treated as autoimmune myelofibrosis. This case highlights the need to keep a high level of suspicion for chronic myeloproliferative neoplasms in all cases of splanchnic vein thrombosis. The autoimmune phenomenon including Antinuclear antibodies (ANA) positivity is incidentally found to coexist with the primary myelofibrosis. Case Report: A 69-year-old male presented with splenic infarct and ANA positivity. The splenomegaly was initially attributed to the splenic vein thrombosis and autoimmune phenomenon like Raynaud's phenomenon and skin rash bought clinician's attention. The presence of splenic vein thrombosis, near normal counts with mainly pallor the patient was been treated on the lines of autoimmune myelofibrosis. The bone marrow done pointed towards the diagnosis of primary myelofibrosis which was confirmed by molecular studies positive for JAK-2 mutation. Conclusion: Autoimmune phenomenon can coexist with the chronic myeloproliferative neoplasms like primary myelofibrosis. All patients presenting with splanchnic vein thrombosis should be investigated for underlying myeloproliferative neoplasms especially molecular studies like JAK-2 V617F mutations.

Keywords: Primary myelofibrosis, Splenic infarct, Thrombosis

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INTRODUCTION

Splanchnic vein thrombosis with near normal white blood counts can mask an underlying myeloproliferative

disorder which needs to be investigated and is confirmed by molecular studies [1]. We present here a case of splenic vein thrombosis leading to splenic infarct with autoimmune phenomenon like skin pigmentation, Raynaud's phenomenon and ANA positivity. This had created confusion in the minds of clinician attributing splenomegaly to thrombosis and both as the consequence of autoimmune condition. The patient was therefore wrongly treated for three months. However, on bone marrow examination and molecular studies this turned out to be a case of primary myelofibrosis. The autoimmune process is an incidental finding in this case which is reported in literature to be associated with primary myelofibrosis [2]. It is important to diagnose correctly as both conditions have distinct prognosis and course of disease [3].

CASE REPORT

A 69-year-old male, presented to gastroenterology department with hyperpigmentation, pallor, history of itching and hematemesis. He was transfused five units of packed red cells and was on azathioprine and prednisolone since last three months. On examination there was pallor, spleen 10 cm below costal margin and ascites. There was no lymphadenopathy and no icterus. On investigation he had hemoglobin 9.0 g/dl, white blood cell count 12,100/µl, platelet 2,16,000/µl and serum creatinine 1. 6 mg/dl. His liver function test was near normal. The β2 GPI-IgM and anticardiolipin antibodies were negative. Ultrasound abdomen had shown splenomegaly with infarct and splenic vein thrombosis and left kidney atrophy with right normal kidney. Upper gastrointestinal endoscopy showed mild linear fundal varices and fibroscan was 13.4. The patient had Raynaud's phenomenon while admitted in hospital along with history of darkening of skin of the abdomen and lower limbs. Antinuclear antibody (ANA) done by immunofluorescence which was strongly positive, ANA profile revealed JO1 and centromere positivity. The splenomegaly was attributed to splenic vein thrombosis this together with significant autoimmune phenomenon like skin rash, Raynaud's phenomenon and joint pains. The clinician considered autoimmune myelofibrosis as the diagnosis, bone marrow was done to confirm this. The patient was investigated for inherited thrombophilia disorders all the tests were found to be negative.

In the post-transfusion peripheral blood smear (PBS) (Figure 1) there were normocytic normochromic to microcytic hypochromic red cells with a fair number of tear drop cells, polychromasia and presence of nRBCs (25/100 WBCs). The differential count on the PBS was neutrophils 80%, lymphocytes 11%, myelocytes 3%, metamyelocytes 3% and eosinophils 3%. The bone marrow aspirates were hemodilute, with a leukoerythroblastic blood picture. Due to the presence of tear drop cells in parent cells and marked splenomegaly the possibility of myeloproliferative neoplasm/myelofibrosis as primary etiology to splenomegaly were suggested and need to be ruled out on bone marrow biopsy. The bone marrow biopsy (Figure 2) was adequate with 50% of marrow spaces showing severe fibrosis and others showing mild fibrosis. It showed panmyelosis with myeloid preponderance, increase in number of megakaryocytes with clustering showing nuclear atypia, cloud like and hyperchromatic nuclei. Micromegakaryocytes were also seen with focal areas of clustering. In many areas, new bone formation was also seen. The special stains of reticulin and Masson's trichrome (Figure 3) revealed grade 3 fibrosis which commensurate with findings on bone marrow biopsy. Together with bone marrow morphology, significant splenomegaly the final impression of primary myelofibrosis was given. The splanchnic vein thrombosis is also reported in many cases of underlying philadelphia negative chronic myeloproliferative neoplasms. The molecular studies for bcr-abl, and JAK-2 V617 F mutations were done, which showed JAK-2 positive and bcr-abl negative hence commensurate with the diagnosis of primary myelofibrosis. This patient was later started on lenalinomide, steroids and acenocoumarol (3 mg). He responded well to treatment and his hemoglobin was improved

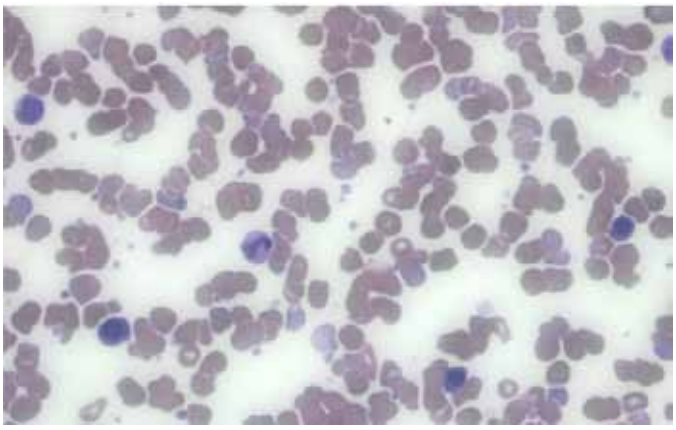

Figure 1: Peripheral blood picture showing, nucleated red cells and tear drop cell.

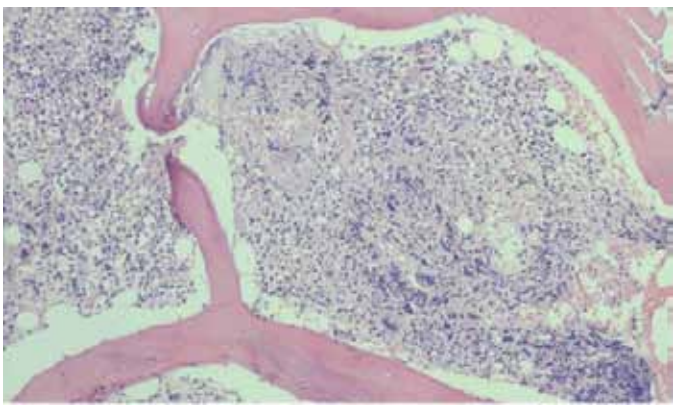

Figure 2: Bone marrow biopsy showing marrow fibrosis and megakaryocytes showing nuclear atypia and clustering.

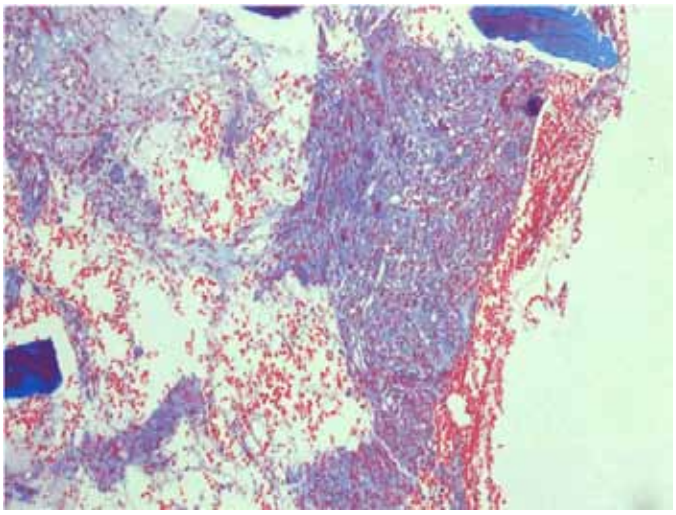

Figure 3: Masson's trichrome showing blue bundle of collagen.

DISCUSSION

As this patient had presented with skin hyperpigmentation, Raynaud's phenomenon and joint pains and pallor, therefore, he was investigated for autoimmune condition and was found to have strong ANA positivity. Computed tomography scan had revealed splenic vein thrombosis, despite the presence of normal counts. The clinician attributed the presence of splenomegaly to splenic vein thrombosis and autoimmune etiology.

The hematopathologists on examining bone marrow aspiration and biopsy correlated with marked splenomegaly and refuted the diagnosis of autoimmune myelofibrosis considering the diagnosis of primary myelofibrosis. The splenic vein thrombosis leading to splenic infarct is found in cases of chronic myeloproliferative neoplasms. The ANA positivity is reported as coexisting finding in some cases of primary myelofibrosis. These cases can also have underlying inherited thrombophilias like protein C, protein S deficiency or factor V Leiden mutations. However, in this case these investigations turned out to be negative.

Primary autoimmune myelofibrosis is now defined as a distinct steroid-responsive clinicopathologic entity with excellent prognosis [3]. The neoplastic cause of primary myelofibrosis can sometimes have overlapping features with non-neoplastic causes like autoimmune myelofibrosis, secondary to SLE or primary autoimmune myelofibrosis. The features of primary autoimmune myelofibrosis have been well elucidated by Pullarkat et al. include

(i) grade 3 or 4 reticulin fibrosis of the bone marrow;
(ii) lack of clustered or atypical megakaryocytes;
(iii) lack of myeloid or erythroid dysplasia, eosinophilia, or basophilia;
(iv) lymphocyte infiltration of the bone marrow;
(v) lack of osteosclerosis;
(vi) absent or mild splenomegaly;
(vii) presence of autoantibodies; and
(viii) absence of a disorder known to cause MF

In our patient, only 3 out of 8 criteria were present. The features favoring primary myelofibrosis over autoimmune myelofibrosis (AIMF) were presence of significant splenomegaly and leukoerythroblastic blood picture with several tear drop cells, presence of osteosclerosis, presence of megakaryocyte clustering.

The molecular reports confirmed this case to be philadelphia negative and JAK-2 mutation positive. The review of literature showed that ANA positivity is also reported in some sporadic cases of primary myelofibrosis (PMF), such cases were also shown to respond well to steroids [2]. Thus this case demonstrates the difficulty posed due to overlapping features of AIMF and PMF creates possibly indicating an associated etiology. It is pertinent to be able to distinguish between the two as they have differences in therapy, also whereas PMF has limited survival other causes including AIMF have a favorable clinical outcome.

The neoplastic cause of primary myelofibrosis can sometimes have overlapping features with non-neoplastic causes like autoimmune myelofibrosis, secondary to SLE or primary autoimmune myelofibrosis. The portal vein thrombosis (PVT) or splanchnic vein thrombosis can be the sole or chief presenting symptom of an underlying myeloproliferative neoplasms (MPN) with normal or near normal peripheral blood cell counts due to hemodilution, iron deficiency or splenomegaly. The JAK2V617F mutation contributes to detection of MPNs as it is present in ~95% polycythemia vera close to 50% of the cases with essential thrombocythemia or primary myelofibrosis therefore is an important part of the work-up of patients presenting with PVT in the absence of cirrhosis or hepatobiliary malignancies. However a bone marrow biopsy is often required as absence of the JAK2 mutation does not exclude the presence of MPN. The presence of portal vein thrombosis with underlying MPN is associated with high rate of recurrence and frequent extension of thrombosis into the splenic vein or superior mesenteric vein they require anticoagulation or antiplatelet therapy [4].

CONCLUSION

This case has highlights the need to have high level of suspicion of underlying myeloproliferative neoplasms in cases of splanchnic vein thrombosis. These cases should be systematically investigated including bone marrow examination and molecular studies to confirm. It should be kept in mind that Antinuclear antibodies (ANA) positivity and autoimmune features can superimpose or coexist with myeloproliferative neoplasms.

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Author Contributions

Sabina Langer – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Ravi Daswani – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Rahul Arora – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Nitin Gupta – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Anil Arora – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Jyoti Kotwal – 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 PEER REVIEWED | OPEN ACCESS

A case study of paraneoplastic cauda equina syndrome caused by a gastric adenocarcinoma

Debbie Hunt, Shomari Zack-Williams, Anita Hargreaves, David Monk

ABSTRACT

Introduction: Cauda equina syndrome results from dysfunction of multiple sacral and lumbar nerve roots in the lumbar vertebral canal, leading to impairment of bladder, bowel, or sexual function, and perianal or "saddle" numbness. The most common cause of cauda equina syndrome is disc herniation resulting in compression at L4/5 and L5/S1. However, we will discuss the case of cauda equine syndrome with a paraneoplastic cause. There are only a handful of cases in literature of paraneoplastic cauda equine syndrome, and none specifically as a result of gastric adenocarcinoma. Paraneoplastic neurological syndromes (of which paraneoplastic cauda equine syndrome is one) are described as remote effects of cancer on the neurological system. They are rare, affecting less than 1/10,000 patients with cancer. In this case, the cauda equina was the target for an autoimmune response directed against antigens common to both the cancer and the nervous system. Case Report: A 71-year-old female was admitted with a two-month history of lumbar back pain, radiating down her thigh, progressive weakness of both legs, numbness of the sacral area, urinary incontinence and 6.4 kilogram unintentional weight loss within 2 months. Abdominal radiograph, breast examination, lumbar puncture, and autoantibodies screens were all negative. Abdominal and pelvic CT, spinal MRI, radioisotope scan and abdominal USS still did not demonstrate any malignant process. One month after admission, the patient deteriorated with sudden abdominal peritonism, tachycardia and hypothermia. An urgent CT was performed, which demonstrated a gastric perforation. A laparotomy was undertaken which demonstrated a 4-cm gastric perforation. Biopsies were taken and the histology subsequently demonstrated a high grade, poorly differentiated adenocarcinoma. From this diagnosis, it was ascertained that she had been suffering from secondary paraneoplastic neuropathy, caused by the gastric adenocarcinoma in the body of the stomach. This specific case has not been reported in literature within the last 10 years. Conclusion: In conclusion, an unusual presentation of acute and progressive neuropathy without obvious spinal/ cranial aetiology and associated cachexia should prompt thorough investigation to exclude a neoplastic process, as paraneoplastic syndromes may be the first sign of malignancy.

Keywords: Gastric adenocarcinoma, Neurological syndromes, Paraneoplastic cauda equina syndrome, Sacral and lumbar nerve

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INTRODUCTION

Cauda equina syndrome is described as dysfunction of multiple sacral and lumbar nerve roots in the lumbar vertebral canal, which can result in a combination of clinical features. However, the term cauda equina syndrome is used only when these include impairment of bladder, bowel, or sexual function, and perianal or "saddle" numbness.

The most common cause of cauda equina syndrome is compression at L4/5 and L5/S1 from large central lumbar disc herniation. Less common causes include spinal fractures or subluxation, spinal neoplasms of metastatic or primary origin and infective causes.

In this report, we will discuss the case of cauda equina syndrome with a paraneoplastic cause. There are only a few cases in literature of paraneoplastic cauda equine syndrome, and none specifically as a result of gastric adenocarcinoma.

CASE REPORT

A 71-year-old, previously healthy woman, was admitted to the orthopedic ward with a two month history of lumbar back pain, right groin pain radiating down the front of her thigh and progressive weakness of both legs. There was also a seven-day history of numbness of the sacral area and urinary incontinence. In addition, it was also noted that the patient had undergone a 6.4-kg unintentional weight loss within two months, with a current BMI of 16.8.

On examination, the abdomen was soft with generalized tenderness in the lower abdomen and also a localized tenderness is the lumbosacral area. There was no sensory deficit of the legs, normal tone, normal co-ordination and no pain at this stage. However, there was reduced power in the right hip flexors. There was obvious cachexia with marked muscle wasting. Spinal examination was normal. On rectal examination, there was found to be poor anal tone and dubious saddle sensation. These neurological signs fluctuated throughout the course of the patient's stay.

At this stage, an MRI scan was taken of lumbar spine, showed multilevel degeneration, with disc disease and facet joint osteoarthritis. However, it was thought that the degree of narrowing did not appear severe enough to cause the present symptoms. The bladder scan confirmed acute urinary retention, showing a residual volume of 999 ml, and the patient was subsequently catheterized (which stayed in situ for the duration of the patient's stay). An abdominal radiograph also confirmed significant fecal loading. The lumbar back pain worsened over the next week requiring increasing amounts of oral morphine. The patient's weight did not improve either, despite a high protein, high calorie diet. She also experienced worsening abdominal pain and constant nausea.

Over the next three weeks, the patient also suffered from a number of falls, and progressive loss of sensation in her feet. At this stage the patient was also incontinent of feces, there was a loss of reflexes in both legs and the weight loss had progressed to 13 kilograms, even with enteral feeding. There were also increasingly frequent episodes of confusion. This was thought to be due to a UTI as her urine dipstick was positive for ketones, leucocytes, nitrites, protein and blood and cultured positive for *E.coli*, and she was therefore started on appropriate antibiotics.

Breast examination and mammography did not demonstrate any pathology. Blood tests demonstrated an increased CRP (284 mg/L), increased LDH (717 U/L), increased ferritin (761.4 ng/ml), neutropenia ($1.5x10^9$/L), deranged urea and electrolytes (urea 10.5 mmol/L, Na 124, K 3.2 mmol/L) and normal calcium (2.4 mmol/L), phosphate (1.1mmol/L) and tumor markers (including Ca19-9, Ca15-3 and Ca125). A lumbar puncture showed clear and colorless cerebrospinal fluid with low glucose, high protein and no organisms. Autoantibodies and ANCA were negative. Electrophoresis did not demonstrate any monoclonal bands. Abdominal and pelvic computed tomography, spinal MRI scan (Figure 1), and abdominal USS still did not demonstrate any malignant process. The isotope scan demonstrated increased uptake from the right femoral neck only (there was no known pathology in this region).

One month after admission, the patient deteriorated with sudden severe right upper quadrant and right flank pain, abdominal peritonism, tachycardia and hypothermia. Bowel sounds were no longer present. It was noted that the NG tube feed had been increased that day and the patient had been taking non steroidal anti-inflammatories. There was no previous history of gastric pathology.

An urgent CT scan was performed, which demonstrated a gastric perforation (Figure 2). A laparotomy was undertaken which demonstrated a 4-cm gastric perforation and extensive contamination of the abdomen. Biopsies were taken and the perforation was closed with the Graham Patch. (Radical treatment was initiated as it is known that perforation can occur even in the early stages and seems not to be a negative prognostic factor itself for adenocarcinoma [1]. Drains were inserted in each paracolic gutter. The histology subsequently demonstrated a high grade, poorly differentiated adenocarcinoma.

Postoperatively the patient was transferred to the intensive care unit where she was given both cardiovascular and respiratory support, intravenous tazocin and metronidazole, and total parenteral nutrition feed. She was also maintained on the Hong Kong regime which involves a COX-2 inhibitor and a PPI. While on ITU, the patient suffered from episodes of significant tachycardia and low hemoglobin (7.4 g/L), for which she required two transfusions. The CRP (276 mg/L) and WCC ($17.2\ 10^9$ /L) remained high despite her intravenous antibiotics.

Subsequently, due to the patient's general health, it was decided that the patient was for palliation of symptoms only and she was put on the Liverpool Care Pathway.

The final diagnosis given was that of secondary paraneoplastic neuropathy, caused by a gastric adenocarcinoma in the body of the stomach, which, in this case, caused a cauda equina syndrome. This specific case has not been reported in literature.

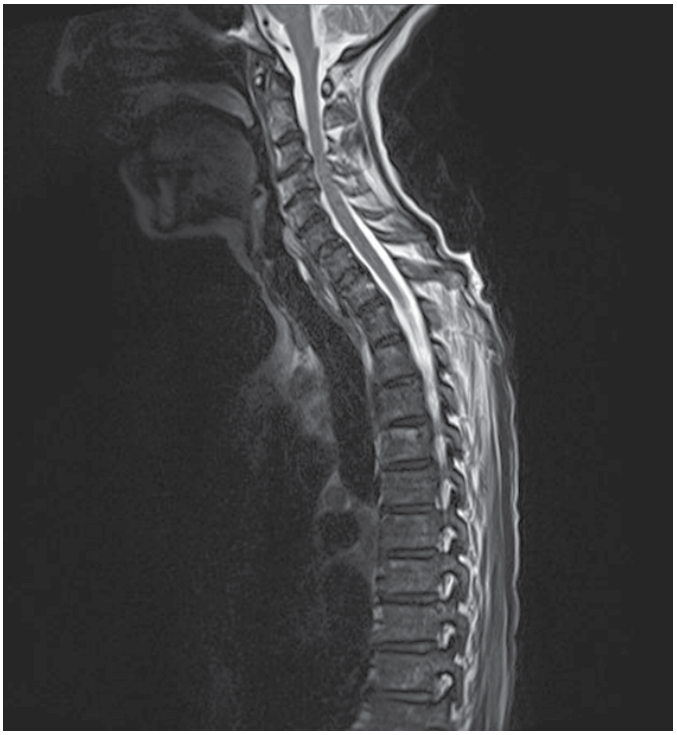

Figure 1: Magnetic resonance imaging showing no intrinsic cervical/thoracic cord abnormality. There are, however, spondylotic changes in the mid-cervical spine resulting in spinal canal narrowing – although not deemed to be extensive enough to cause the symptoms discussed. There is also a small central disc protrusion at T5/6.

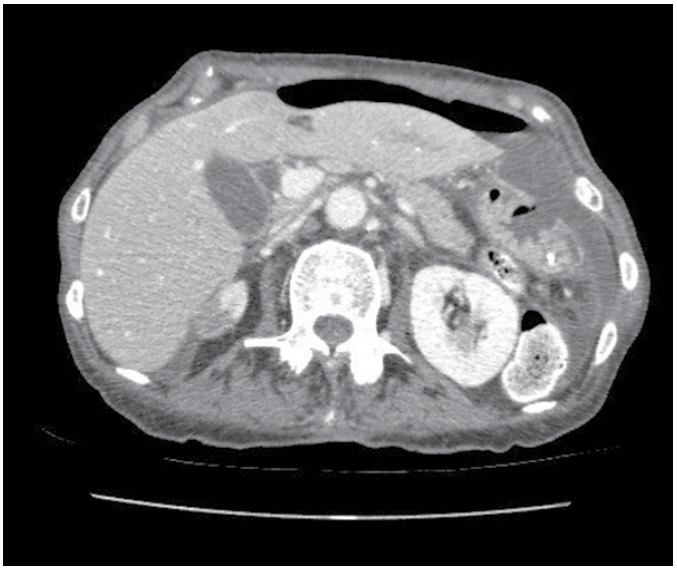

Figure 2: Computed tomography image showing marked ascites, free intraperitoneal gas as a result of a large perforated gastric ulcer along the anterior wall of the stomach body.

The diagnosis of paraneoplastic cauda equine was a presumptive diagnosis based on the extensive negative findings and final histology. There was not enough time preoperatively (between the finding of the adenocarcinoma on computed tomography and the emergency laparotomy) to perform onconeural antibodies. Furthermore, postoperatively, the patient deteriorated very quickly, giving little time for either, assessment of the effects of treatment of the gastric adenocarcinoma on the cauda equina syndrome (a condition to be satisfied for a conclusive diagnosis of paraneoplastic syndrome to be made), or for testing of onconeural antibodies (another condition).

Furthermore, computed tomography, magnetic resonance imaging and isotope bone scanning showed neither evidence of an abnormality of the spine (for example any evidence of spinal metastasis/sufficient disc protrusion to produce the symptoms) or abnormality of the cauda equina itself. This led us to the conclusion that the symptoms were caused by a paraneoplastic phenomenon as all other plausible causes had been excluded.

DISCUSSION

Paraneoplastic neurological syndromes, of which cauda equina syndrome in one, are defined as the remote effects of cancer that are not caused by the tumor and its metastasis, or by infection, ischemia or metabolic disruptions. These cases are rare, affecting less than 1/10,000 patients with cancer [2]. In 2007, criteria were developed for diagnosing PNS. In short, the criteria include

(i) a classical neurological syndrome is observed (one of which is sensory neuropathy);
(ii) the condition improves after cancer treatment;
(iii) or if non-classical neurological syndrome, that onconeural antibodies are present [3].

There have been cases of PNS reported from metastatic breast cancer [4–5] prostate cancer, small cell lung cancer [6] and lymphoma and it is thought that these tumors secrete a protein, which is taken up by the nerves, causing them to hypertrophy due to osmotic retention of water, causing compression leading to the neurological symptoms described [7]. There are also cases described in literature where the cauda equina is a target for an autoimmune response directed against antigens common to both the cancer and the nervous system, designated as onconeural antigens [2]. Therefore, the best way to diagnose these cases is to identify one of the anti-onconeural protein antibodies. These antibodies can guide the search for the primary malignancy (when often these are not clinically overt). This is important as the best way to stabilize the paraneoplastic syndrome

is to treat the primary cancer. However, other papers refute this, claiming that less than 50% of patients with paraneoplastic syndromes have paraneoplastic antibodies [3].

Similar cases of paraneoplastic neuropathy affecting the cauda equina describe progressive distal limb paresthesia, weakness, heaviness and gait difficulty. There was also loss of vibration and proprioception. Nerve conduction studies showed evidence of axonal peripheral neuropathy and somatosensory evoked potential studies showed impaired conduction [7, 8].

Similar to our case, these patients described symptoms which progressed over many months to years. In a case report of a 45-year-old woman with a metastatic cauda equina tumour from breast cancer [5], the patient presented four years after she had undergone resection, without spinal column or brain metastasis. This particular case however, in contrast to our case with generalized hypertrophy of the cauda equina, demonstrated a well enhanced intradural extramedullary mass. In contrast to our case however, these patients showed diffuse abnormal thickening and enhancement of the cauda equine nerve roots on MRI scan [8], whereas in our case, there was no abnormality of the cauda equina on any imaging modality.

Additionally, while there have been no reports of gastric cancers causing a cauda equine syndrome specifically, there have been cases described in literature of other paraneoplastic neurological manifestations of gastric carcinoma, including one case of Stage 1b gastric cancer associated with spontaneous muscle atrophy of both hands. The cause of the atrophy was not apparent with neurologic diagnostic modalities, and therefore the case was assumed to be due to a paraneoplastic manifestation [9]. There is also a case report of systemic polyarteritis nodosa leading to the discovery of an asymptomatic, surgically curable gastric adenocarcinoma, and a diagnosis of paraneoplastic systemic angiitis was given [10].

CONCLUSION

In conclusion, an unusual presentation of acute and progressive neuropathy without obvious spinal/ cranial aetiology and associated cachexia should prompt thorough investigation to exclude a neoplastic process, as paraneoplastic syndromes may be the first sign of malignancy.

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Author Contributions

Debbie Hunt – 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
Shomari Zack-Williams – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Anita Hargreaves – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
David Monk – 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 PEER REVIEWED | OPEN ACCESS

Glandular odontogenic cyst of posterior maxilla: A rare entity

LiFeng Li, Pradeep Singh, Ji Ping, Xian Li

ABSTRACT

Introduction: Glandular odontogenic cyst (GOC) is uncommon jaw cyst of odontogenic origin with unpredictable and potentially aggressive behavior. It is a rare developmental cyst with relatively low frequency of just 0.012–0.03%. Very limited cases of GOC have been reported in literature since it was first described by Gardner et al. in 1988. GOC is found to occur in fifth decade of life and the most common site of occurrence is mandible, especially the mandibular anterior region with slight predilection for males. However, its occurrence in the maxillary posterior region of a 23-year-old female with associated symptoms of pain is quite rare. Case Report: This case report presents one such rare case of GOC in right maxillary region of a 23-year-old female who was primarily diagnosed as a radicular cyst. Later, due to recurrence of the lesion, patient had to undergo enucleation and partial resection of posterior maxilla, and after a comprehensive histopathological analysis, it was finally diagnosed as GOC. Conclusion: In conclusion, Glandular odontogenic cyst being such a rare entity, this paper may enhance the existing knowledge about GOC and may guide readers and clinicians to pay special attention to similar cases when encountered in clinical work.

Keywords: Cytokeratin, Glandular odontogenic cyst (GOC), Ki-67, p53, Radicular cyst

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INTRODUCTION

Glandular odontogenic cyst (GOC) is a rare developmental cyst of odontogenic origin. Padayachee and Van Wyk initially reported it as a sialo odontogenic cyst in 1987 [1] but its odontogenic origin was first described by Gardner et al. in 1988 who also proposed the name 'GOC' [2]. The term 'polymorphous odontogenic cyst' for this cyst was proposed by High et al. in (1996), because of its aggressive growth pattern [3]. Sadeghib in 1991 used the term mucoepidermoid cyst or mucous producing cyst due to the microscopic findings of mucus producing cells and squamous cells [4]. Moreover, WHO

histological typing of odontogenic tumors also includes glandular odontogenic cyst under the terms, GOC or Sialo odontogenic cyst. Magnusson et al. observed that only 0.012% of the cysts seen on the oral cavity have fulfilled the criteria of GOC microscopically [5].

The GOC is a rare developmental cyst with relatively low frequency of 0.012–0.03% and prevalence rate 0.17%. 'High recurrence rate" and an "aggressive growth potential [6] are considered to be the most important clinical characteristics of GOC. The following three possibilities can be attributed to the development of GOC:

(a) Odontogenic primordial origin, wherein epithelial lining undergoes prosoplasia into glandular epithelium.

(b) As a low-grade mucoepidermoid carcinoma that appears as a single cystic space as opposed to usual multicystic spaces.

(c) As a true cyst of glandular origin, in which the entrapped salivary gland primordia or undifferentiated primitive epithelial rests differentiate into glandular epithelium [7].

Clinically, the most common site of occurrence is mandibular anterior region [8], where it presents as a slow growing intraosseous lesion. The GOC occurs primarily in middle-aged patients (mean age of 49.5 years) [9, 10] with slight male predilection [11]. Radiographically, the lesion can be described as a unilocular or, more commonly, multilocular radiolucency with well-defined sclerotic margins [12]. Histologically, GOC is characterized by a non-keratinized stratified squamous epithelial lining with papillary projections, focal plaque like thickenings within the lining, microcysts or intraepithelial crypts containing mucin, 'mucous lakes' and hyaline bodies. It also includes cuboidal basal cells, sometimes vacuolated and absence of inflammation in the subepithelial connective tissue [12, 13]. The relative rarity of this lesion is the reason behind presentation of this case. In this paper, we present one such unique case of a GOC and its clinic-histopathological features.

CASE REPORT

A 23-year-old female patient presented to the department of oral and maxillofacial surgery, with the chief complaint of pain in the right upper back tooth region of jaw since four months. Pain was mild and recurrent in nature. There were no associated symptoms apart from mild tenderness of the maxillary right buccal region. Meticulous dental history with patient revealed that he had a previous history of swelling and intermittent pain in the same region five years ago, for which she was diagnosed with radicular cyst in 16, and had to undergo surgery for enucleation of the cyst. One year post operatively, patient underwent extraction of upper right first molar at some other dental facility, because of continuous pain. Four months ago she underwent root canal therapy for 17, at some other dental facility. Past medical, and family history were noncontributory and there was no previous history of trauma.

Clinical examination

Extra-orally there was no apparent facial asymmetry. On intra-oral examination any significant mass and swelling was non-apparent, except mild tenderness of the maxillary right posterior buccal region, extending from 15 to 18 tooth region. The associated teeth were tested vital. Cystic fluid was reddish in color on needle aspiration. There were no obvious signs of infection, and limitation of mouth opening. Preoperatively panoramic radiograph was taken and postoperatively histologic examination was done.

Radiological examination

Panoramic radiograph revealed a large oval well-circumscribed multilocular radiolucent lesion measuring around 3.00x1.80 cm, located under the maxillary sinus region and extending from the root apices of 15 to 18 tooth region (Figures 1 and 2). 3D cone beam computed tomography (CBCT) reconstruction image showed perforations of the cortical bone extending from the periapical region of 15 to 18 (Figure 3).

Initial Histological examination

Microscopic examination of H&E stained section of the specimen revealed non-keratinized stratified squamous epithelial lining of varying thickness with

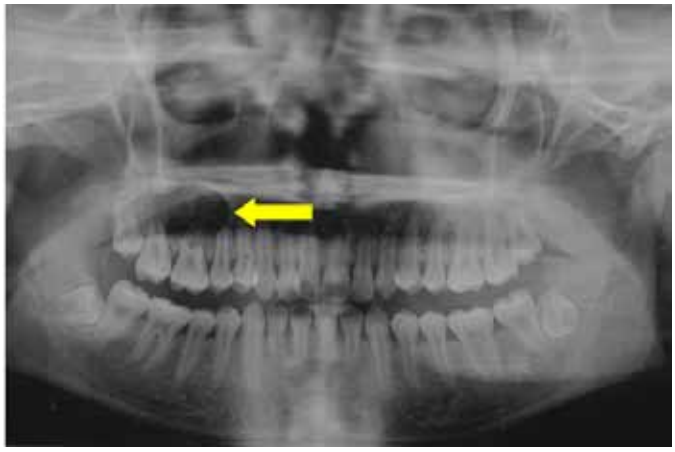

Figure 1: Initial preoperative panoramic radiograph (five years ago) showing 3.00x1.80 cm oval well-circumscribed multilocular radiolucent lesion (arrow) near the root apices of 15 to 18.

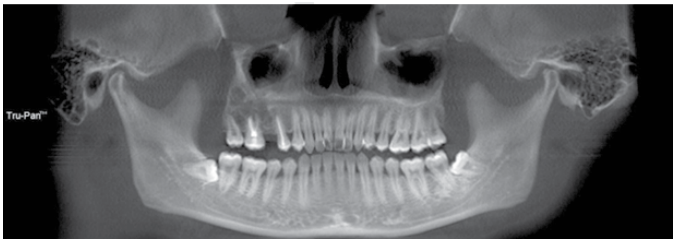

Figure 2 : Recent preoperative panoramic radiograph showing cystic lesion near the root apices of 15 to 18, extraction socket of 16, and R.C.T treated 17 can be well appreciated.

epithelial hyperplasia (irregular proliferation and elongation). However, some mucus gland-like cells were also observed within some selective areas which were not so typical (Figure 4A–B). The nature, anatomical location, radiographic findings, and histopathological findings of the lesion were compatible with the diagnosis of radicular cyst. Ameloblastoma and odontogenic keratocyst were considered for the differential diagnosis of the same.

Current Operative Procedure

Considering the age and subjective requirements, and with patient's full consent, it was finally decided to treat the case with enucleation and block resection of the maxilla, simultaneously extracting 15, 17 and 18. The surgery was performed under general anesthesia and during the surgery some thick cystic lining was found which could be easily enucleated from the bony cavity (Figures 5 and 6). In order to further elucidate the nature of the lesion and to provide final diagnosis, we carried out an incisional biopsy and a part of cystic lining was excised through the perforations of cortical bone and the specimen was subjected to histopathological and immunohistochemical examination.

Recent Histopathological examination

Microscopic examination of the specimen showed, glandular structures lined by mucous cells within the non-keratinized squamous epithelium. Spinous cell layer appeared as vacuoles (Figure 7A–B). No single mucinous cell was observed in the epithelium. No significant signs of mucoepidermoid carcinoma were seen in the sections examined.

Immunohistochemical examination

To assess the proliferate nature of the cyst in the present case, an immunohistochemistry (IHC) staining was done using Ki-67, p53 and cytokeratin (CK) was found to be positive for p53 (Figure 8A), Ki-67 (Figure 8B) and CK (Figure 9). However, the expression of CK was moderately positive in the basal layer and slightly positive in the parabasal and surface layers and duct forming cells.

Histopathological and immunohistochemical examination findings were indicative of 'glandular odontogenic cyst' thus a final diagnosis of GOC was

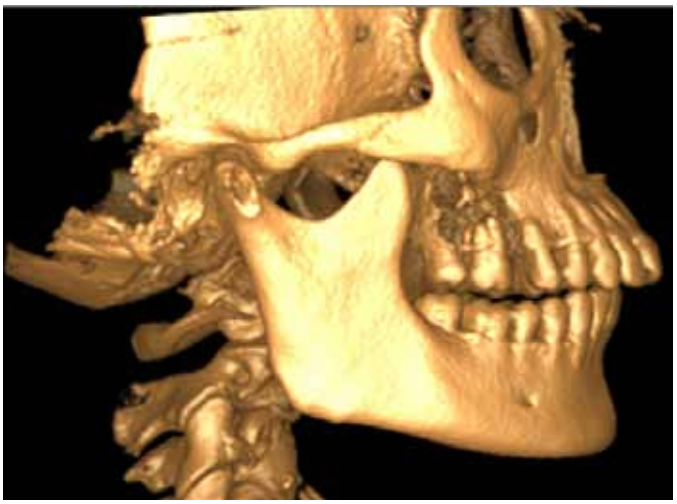

Figure 3: Recent preoperative 3D CBCT reconstruction image showing perforations of the cortical bone extending from the periapical region of 15 to 18.

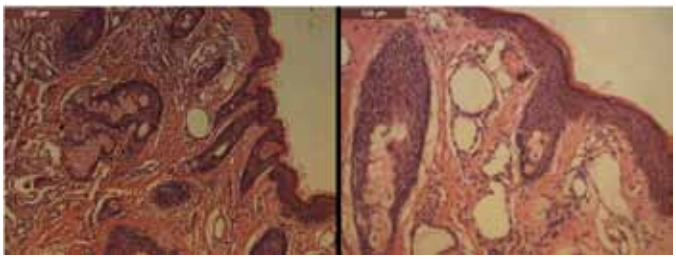

Figure 4: (A, B) Photomicrograph of the initial specimen showing non-keratinized stratified squamous epithelial lining of varying thickness with epithelial hyperplasia. Some mucus gland-like cells can also be seen in selective areas (Magnification Figure 4A: H&E stain, x100, Figure 4B: H&E stain, x200).

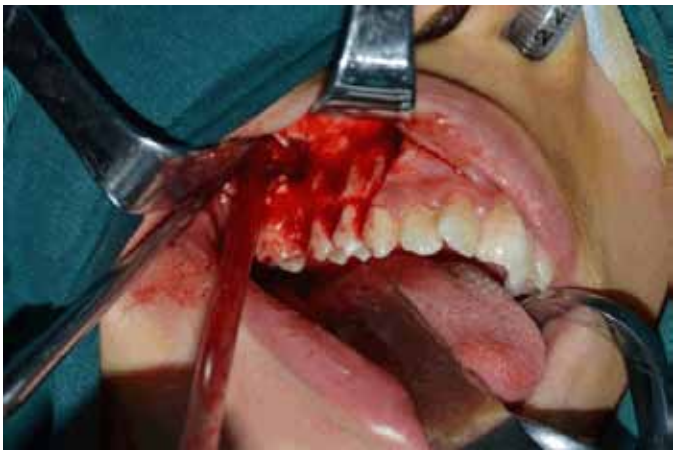

Figure 5 : Intraoperative image showing cystic enucleation.

Figure 6 : Enucleated specimen from the bone cavity.

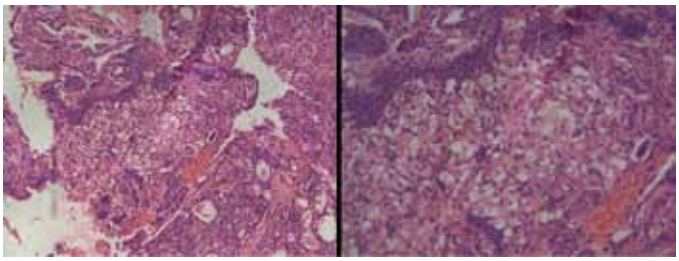

Figure 7 (A, B) : Photomicrograph of the specimen (recent) showing non-keratinized squamous epithelium and glandular structures, lined by mucous cells. Spinous layer cell appeared as vacuoles. (Magnification: Figure 7A: H&E stain, x100, Figure 7B: H&E stain, x200).

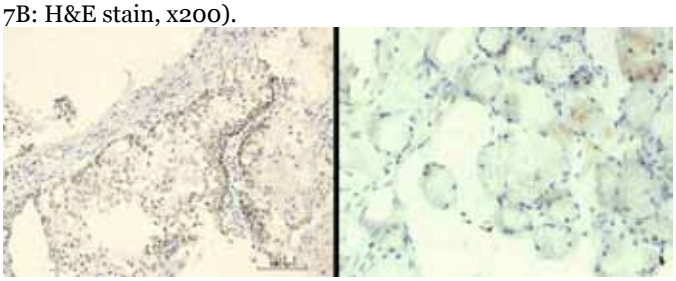

Figure 8 (A, B): Immunohistochemical findings for p53 and Ki-67 in the lining epithelia of Glandular odontogenic cyst of the maxilla. Photomicrograph of immunohistochemically stained (A) p53 and (B) Ki-67 showing scattered positive cells in GOC lining (IHC stain, x 200).

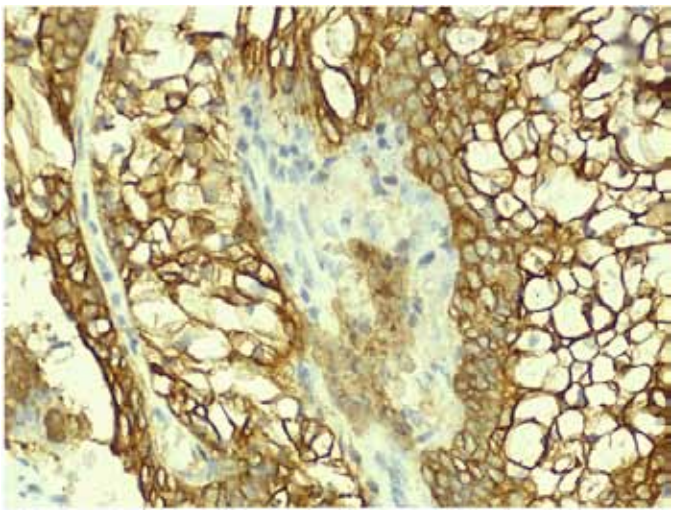

Figure 9: Immunohistochemical findings for cytokeratin in the lining epithelia of glandular odontogenic cyst of the maxilla. Photomicrograph showing positive immunoreactions to CK protein (IHC stain, x200). The CK was positive in the whole layer of the lining epithelia.

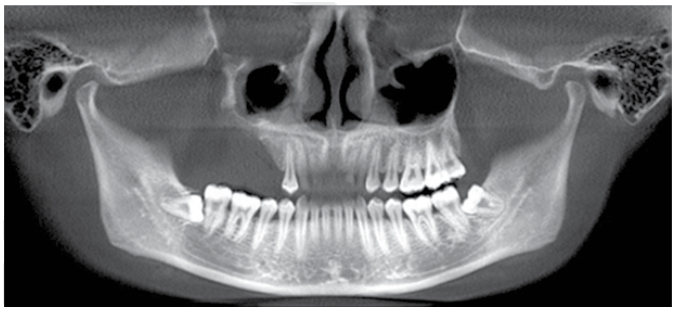

Figure 10: Postoperative panoramic image after partial maxillary resection.

made. Postoperative recovery was uneventful (Figures 10 and 11). Patient is currently subjected under a long-term follow-up. One year follow-up showed improved bone healing with no signs of relapse.

DISCUSSION

The GOC is a rare entity with relatively low frequency of 0.012–0.03% [5] and prevalence rate 0.17%. Magnusson et al. in their study evaluated 5900 cases of jaw bone cysts and found only seven cases of GOC, i.e, about 0.12% [5]. In an another similar study by Van Heerden et al., only 1.3% cases were reported [14]. Literature review showed that GOC may mimic a wide clinicopathologic spectrum ranging from LPC to a destructive malignant neoplasm such as central mucoepidermoid carcinoma (CMEC) [15].

As there are very few cases of GOC reported in English literature, its incidence, clinical manifestations, radiological findings, histological features, treatment and prognosis has no unified opinion. Clinically, GOC is often manifested as a slow growing painless mass, few accompanied by pain, paresthesia and numbness. The lesion may cause pain due to compression of a neurovascular bundle or secondary infection [16]. In the present case the patient is a middle-aged female with recurrent pain in right maxillary posterior region, However existing literature reports, slight male predilection and, mandibular anterior being the most common site of occurrence. In this case, the recurrent pain the patient complained of is considered to be due to compression of the posterior superior alveolar nerve by the lesion.

Lack of consistency in the clinical manifestations, and the intraosseous development of these lesions, and similarities with various other intrabony pathologies demonstrate the importance of radiographical and histopathological evaluation. Radiographically, GOC

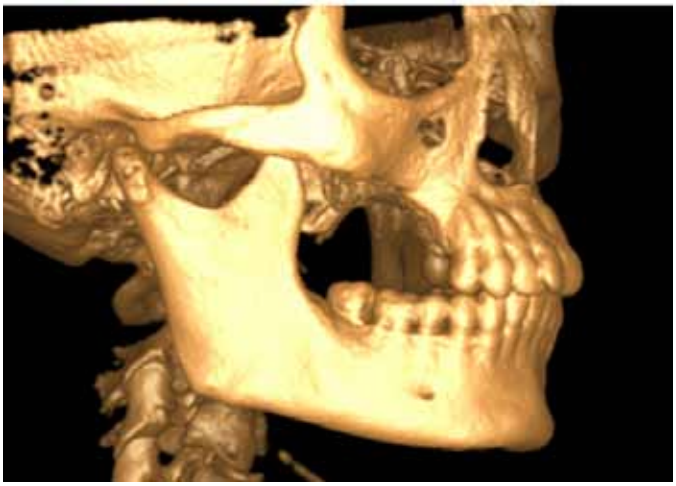

Figure 11: 3D cone beam computed tomography (CBCT) reconstruction image after partial maxillary resection.

may appear as intraosseously localized, multilocular or unilocular radiolucent lesion with well-defined borders. In some instances it may also present scalloped, and peripherally osteosclerotic borders, together with root resorption and displacement of the teeth. In the presented case, radiographic examination shows unilocular multilocular radiolucencies with well-defined margins. It is often diagnosed as an odontogenic cyst or a tumor because this disease has no special characteristics.

Histologically the presented case consisted of certain characteristic features of GOC like non-keratinized squamous epithelium varying in thickness and cuboidal or ciliated epithelium with mucus-producing cells on the surface. Owing to the fact that lateral periodontal cyst (LPC) and CMEC exhibit substantial overlap between histological features, their histopathological differentiation becomes difficult and must be performed with considerable care. In particular the differentiation of low-grade CMEC from GOC is more important and difficult. However, the identification of intraepithelial microcysts or duct-like structures, epithelial whorls, ciliated cells, and superficial cuboidal cells in GOC differentiates it from low-grade CMEC [17]. Likewise, the absence of duct like spaces with mucous cells and ciliated epithelium in the histological sections of LPC, favors the diagnosis of GOC [18].

While some authors believe the distinction between GOC and central mucoepidermoid carcinoma depends largely on the degree of epithelial proliferation [19] others have recommended the use of immunohistochemical markers to distinguish these two diseases [20]. Immunostaining with Ki-67, p53, CK-19 and their positivity in GOC may help in differentiating GOC from Mucoepidermoid carcinoma (MEC). Certain studies have reported an increased Ki-67 index and decreased P53 positivity suggesting that GOC lining displays increased proliferation, but not malignant transformation potential. Kaplan et al. found that GOC showed lower p53 immunoreactivity but significantly higher Ki-67 proliferative index than MEC [21]. Besides, cell kinetics in the lining epithelium might be associated with the tendency for recurrence and aggressive nature of GOC. Furthermore, Tosios et al. demonstrated increased Bcl2 (an anti-apoptotic protein) in their study and suggested dysregulation of cell death in lining epithelium to be associated with the biological behavior of GOC [22].

Several treatment options including curettage, enucleation, en block resection and partial osteotomy are available for the treatment of GOC but the treatment of choice is still controversial. Another factor is, treatment by enucleation or curettage alone is associated with a high recurrence rate. Multicystic lesions treated by curettage or enucleation demonstrated increased recurrence rate of 55% with an average of 4.9 years [23]. In this case, en block resection was considered to be the treatment of choice in order to cure the disease and avoid further surgery. The cyst has an aggressive behavior and a high recurrence rate, so follow-up during three to five years should be carried out.

Reviewing the histologic examination of radicular cyst, we can find some mucus gland-like cells within some selective areas, although these cells are not so typical. Analyzing the clinical features, radiological and histological examination of the two lesions (GOC and Radicular cyst), it is questionable to diagnose whether this is actually a GOC evolving from a radicular cyst or just a new lesion arising from the same area. Review of literature has shown that in one of the case reports GOC presented as dentigerous cyst. At this point, both alternatives are possible and more case reports and studies should be encouraged to support these possibilities.

CONCLUSION

In conclusion, glandular odontogenic cyst (GDC) being such a rare entity, this paper may enhance the existing knowledge about GOC and may guide readers and clinicians to pay special attention to similar cases when encountered in clinical work. Mucus gland-like cells found in the histological examination of radicular cysts should draw particular attention to the lesion, whether leading to recurrence or evolving to GOC. Close follow-up must be put in schedule.

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Author Contributions

LiFeng Li – 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

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

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

Xian Li – 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

The authors Li LiFeng and Singh Pradeep contributed equally to this case report, and the authors Li LiFeng and Singh Pradeep should be regarded as first joint authors.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Redistribution of pericardial effusion during respiration simulating the echocardiographic features of cardiac tamponade

Raymond Maung M. Khin Hou, Angel I. Martin, Emmanuel A. Bassily, G. Joseph Coffman, Maqsood A. Siddique, David M. Whitaker

ABSTRACT

Introduction: The aim of the study was to identify the significance of pericardial effusion and physiology of cardiac tamponade. Case Report: We used cardiac imaging with echocardiography and cardiac computed tomography (CT) in a patient with pericardial effusion. Two-dimensional transthoracic echocardiography was used to identify the significance of pericardial effusion and 64 multi-slice, ECG retrospectively gated cardiac CT was used to confirm the physiology of cardiac tamponade. On follow-up of serial echocardiograms, there was a development of pericardial effusion and possible signs of cardiac tamponade. To confirm the significance of these findings, a cardiac CT scan was performed which showed redistribution of the pericardial effusion with respiration causing transient echocardiographic features mimicking cardiac tamponade. Conclusion: The cardiac CT scan is helpful in cases of pericardial effusion with equivocal echocardiographic features of cardiac tamponade. In asymptomatic patients, small to moderate effusions can be followed with serial echocardiograms to evaluate progression and signs of hemodynamic compromise. Although some echocardiographic features may mimic signs of cardiac tamponade, cardiac CT scan can be used to rule out hemodynamic compromise.

Keywords: Cardiac computed tomography, Cardiac tamponade, Echocardiography, Pericardial effusion

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INTRODUCTION

Pericardial effusion is normally located along the pericardial space of the inferior wall of the heart when standing and posterior wall when supine. As the pericardial effusion increases, it becomes more circumferentially distributed. Though the pericardial sac may be compliant when accommodating a small to moderate effusion, distribution changes can be seen with normal respiration.

The management of pericardial effusions depends on the size, etiology, rate of progression, as well as signs and symptoms suggesting the clinical presence of cardiac tamponade. Asymptomatic small to moderate effusions can be followed with serial echocardiograms to evaluate progression and early signs of hemodynamic compromise. However, some echocardiographic features may mimic the early appearance of cardiac tamponade or pericardial constriction. Further testing with a different imaging modality such as, cardiac computed tomography scan, is useful to evaluate for the presence of hemodynamic compromise. This has a great impact on clinical decision-making regarding the timing and urgency of pericardiocentesis or other surgical interventions.

CASE REPORT

A 67-year-old male presented for preoperative evaluation of cataract surgery. His medical history included squamous cell carcinoma of the left lung with mediastinal involvement, diagnosed two years prior requiring partial resection, chemotherapy, and radiation. On presentation, the patient had a functional capacity of more than four metabolic equivalents with no chest pain, dyspnea, or any other complaints. Physical examination revealed no evidence of jugular venous distention, Kussmaul sign or pulsus paradoxus. Lung fields were clear to auscultation. Heart sounds were normal without murmurs, rubs or gallops. The electrocardiogram (ECG) showed normal sinus rhythm, no evidence of low voltage or electrical alternans. Transthoracic echocardiogram showed normal left ventricular systolic function and a small pericardial effusion (inferoposterior effusion; <10 mm pericardial space thickness) without echocardiographic evidence of cardiac tamponade. The patient remained asymptomatic, however follow-up echocardiogram three months later revealed moderate size inferoposterior pericardial effusion (10–20 mm thickness), which was larger than the previous study. There was possible early systolic inversion of the right atrium (RA) as shown in Figure 1 and early diastolic collapse of the right ventricle (RV) during inspiration as shown in Figure 2b. These findings were concerning for early cardiac tamponade. A cardiac CT was subsequently done to further evaluate this significant change in pathophysiology of the pericardial effusion. The cardiac CT images obtained during inspiration and expiration, showed no pericardial thickening, calcification, constriction or cardiac tamponade physiology. However, marked redistribution of the pericardial fluid was noted with each respiratory cycle.

Clinically, the patient continued to remain asymptomatic. Due to concerns for malignant pericardial effusion, he was monitored with periodic physical examinations as well as follow-up echocardiograms. For three months, no changes in the pericardial effusion were noted. Four months later, the patient developed pleuritic chest pain with dyspnea. The pericardial effusion had grown in size (>20 mm thickness) as confirmed by echocardiogram with Doppler evidence of hemodynamic significance. As a result, he underwent a right anterior thoracotomy, creation of pericardial window and drainage of 400 mL of pericardial fluid. He remained asymptomatic postoperatively with only a trace residual amount of pericardial fluid noted.

DISCUSSION

During inspiration, the pulling of the diaphragmatic parietal pericardium makes the inferior pericardial space adjacent to the RV larger, while the heart remains in the same position due to its superior attachments to the diaphragmatic base (Figure 3a, lower panel). This allows for the pericardial fluid from other parts of the heart to shift, or redistribute to the inferior space (Figure 3a, upper panel, adjacent to the RV wall). The reverse of this process occurs during expiration as the inferior space becomes smaller, thus allowing the fluid to shift back to other parts of the pericardial space (Figure3b, upper and lower panels). In addition, during inspiration, the increase in diastolic filling of the RV also leads to more fluid accumulating in this inferior space [1]. During this process, the intra-cardiac pressure of the RV becomes the lowest, temporarily leading to RV collapse (Figure 2b).

Studies have been done in normal subjects without pericardial effusion and have demonstrated an increase in RV diastolic filling and decrease in left ventricle (LV) diastolic filling during inspiration. Reciprocal effects occur during expiration, referred to as ventricular interdependence [1]. The net effect of these changes on pericardial fluid during respiration is neutral in the normal population [1]. However, the ventricular interdependence is more pronounced in cases of cardiac tamponade or pericardial constriction where the intra-pericardial pressure exceeds the intra-cardiac pressures [2]. Abnormal inspiratory increase of right ventricular dimensions and abnormal inspiratory decrease of left ventricular dimensions are suggestive features of cardiac tamponade [3].

In our case, there were no significant changes in RV and LV end diastolic dimensions during inspiration and expiration (Figure 4). Similarly, non-significant changes were seen in LV volumes and LV systolic functions with respiration. This suggests that neither RV and LV

diastolic fillings nor systolic functions are affected by respiration. Therefore, changes in ventricular volumes during respiration play a minor role in redistribution of pericardial effusion.

Acute and rapid accumulation of a small amount of pericardial fluid can cause a sudden increase in intra-pericardial pressure causing cardiac tamponade. Chronic accumulation of a pericardial effusion does not result in cardiac tamponade until the pericardial effusion is large enough to increase intra-pericardial pressure beyond the pericardium's compliance. Collapse of the lower pressure chambers (RA and RV) occurs first when the intra-pericardial pressure exceeds the intra-cardiac pressures. The RA inversion is not a very specific sign for cardiac tamponade and observed in approximately 18% of patients with pericardial effusion without clinical cardiac tamponade (82% specificity) [4]. During late diastole or early systolic phase of the cardiac cycle, the intra-cardiac pressure of the RA is the lowest and its thin wall is most vulnerable to invagination. This effect is most prominent in the supine position when posterior redistribution of the effusion accumulates around the RA. Narrowing or compression of the RV in diastole during expiration is strongly associated with cardiac tamponade [5, 6]. The echocardiogram of our patient showed RV collapse during inspiration but no RV collapse during expiration. This phenomenon is due to the inferior redistribution of pericardial fluid during inspiration as demonstrated by cardiac CT scan. These mimicking features of RA and RV collapse were observed in our patient's simulated cardiac tamponade physiology. Other characteristic two dimensional echocardiographic signs such as inferior vena cava plethora with blunted response to respiration (dilated inferior vena cava with lack of inspiratory

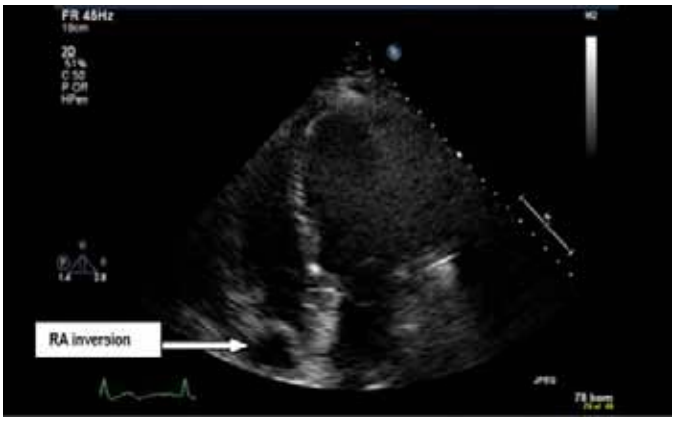

Figure 1: Long-axis (apical 4-chamber) echocardiographic view of the heart in early systole during normal respiration. Short duration (< 1/3 of cardiac cycle) of RA inversion (white arrow) in early systole (indicated by the ECG) without significant pericardial effusion was seen in this view.

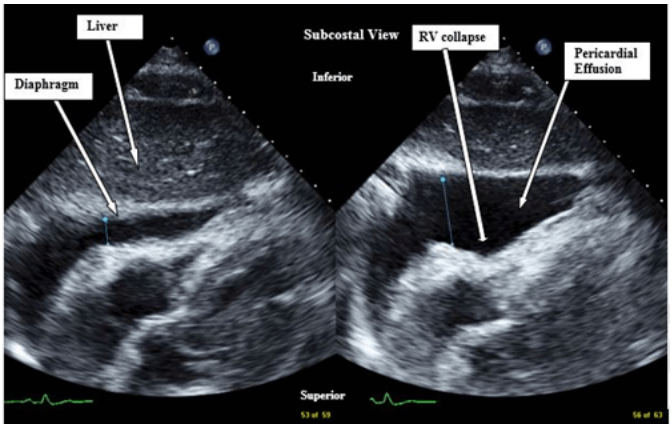

Figure 2: Subcostal long-axis (4-chamber) echocardiographic view of the heart with pericardial effusion during early diastole of cardiac cycle (indicated by the ECG) with expiration (Figure 2a) and inspiration (Figure 2b) on the same study. Moderate amount of fluid measuring 12 mm (line in Figure 2a) at tricuspid annulus, adjacent to the inferior wall of RV with normal RV excursion during expiration and apparent large pericardial effusion measuring 31 mm (line in Figure 2b) at tricuspid annulus with RV collapse (white short arrow) during inspiration. The long white arrows indicate tissues inferior to the heart in Figure 2a and the larger size of pericardial effusion and the collapse of RV wall in Figure 2b.

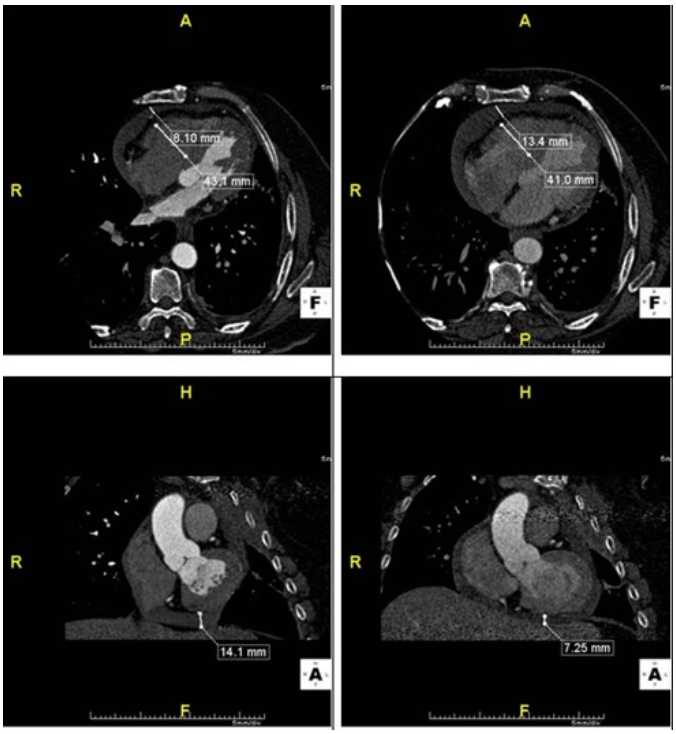

Figure 3: Cardiac CT demonstrates redistribution of pericardial effusion in diastole during inspiratory and expiratory breath holding. Antero-lateral pericardial effusion (at the level of RV free wall on axial views in top panel) measures 8.1 mm during inspiration (Figure 3a, upper panel) and 13.4 mm during expiration (Figure3b, upper panel). Inferior pericardial effusion (adjacent to the RV and LV inferior wall on coronal views in bottom panel) measuring 14.1 mm during inspiration (Figure3a, lower panel) and 7.25 mm during expiration (Figure 3b, lower panel). RV diastolic diameters show 43.1mm during inspiration (Figure 3a, upper panel) and 41.0 mm during expiration (Figure 3b, upper panel).

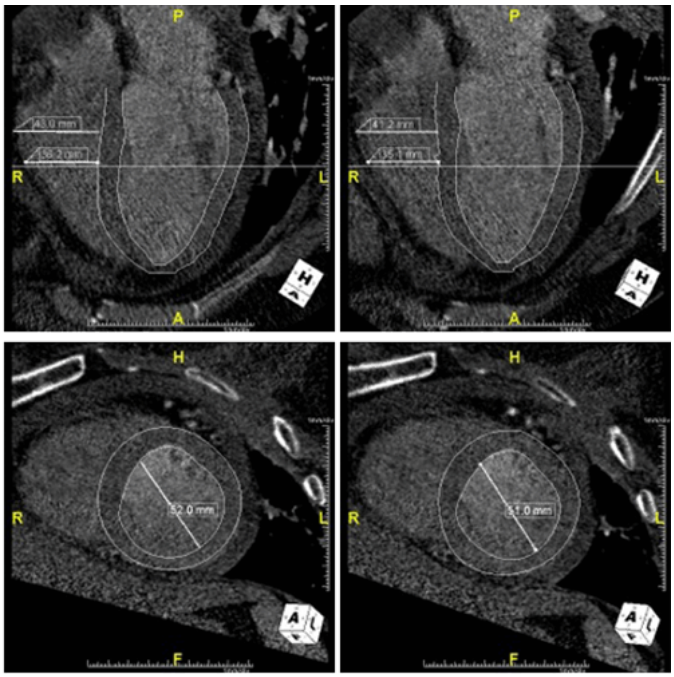

Figure 4: Cardiac CT (4-chamber long-axis views in top panel and mid-LV short-axis view in bottom panel) shows RV and LV measurements in end diastole during inspiratory and expiratory breath hold. The RV end diastolic diameter measures 43.0 mm in maximal diameter and 36.2 mm in mid cavity during inspiration (Figure4a, upper panel) and 41.2 mm in maximal diameter and 35.1mm in mid cavity during expiration (Figure 4b, upper panel). The LV end diastolic diameters measure 52.0 mm in mid cavity during inspiration (Figure 4a, lower panel) and 51.0 mm in mid cavity during expiration (Figure 4b, lower panel).

collapse) [7] and abnormal ventricular septal motion [8] are useful in supporting cardiac tamponade, but often seen in patients with congestive heart failure and with constrictive pericarditis. Doppler echocardiographic evidence of abnormal inspiratory increase of blood flow velocity through the tricuspid valve and decrease of mitral valve flow velocity may be too sensitive to indicate hemodynamically significant cardiac tamponade [9]. These abnormal flow velocity findings are non-specific, and seen in obstructive airway disease, pulmonary embolism, acute cardiac dilatation, pleural effusion, constrictive pericarditis, or in right ventricular infarction. Moreover, these signs may be exaggerated in dehydration or hypovolemic states where intra-cardiac pressures are relatively lower than intra-pericardial pressure. On the other hand, the signs of RA or RV diastolic collapse may be blunted, masked or absent in conditions where right sided intra-cardiac pressures are chronically elevated, with decreased compliance, or hypertrophy of these chambers.

The diagnosis of cardiac tamponade by echocardiographic features alone is not sufficient in supporting hemodynamic significance in some cases where cardiac CT scan may be useful [10]. In addition, constrictive pericarditis can complicate chronic pericardial effusion, causing an effusive constrictive pericarditis. This can pose a diagnostic dilemma and multimodality imaging may play a role in diagnosing these complex diseases [11, 12].

CONCLUSION

Small and moderate sized pericardial effusions are usually asymptomatic and can be managed conservatively with follow-up echocardiograms to monitor their progression. The smaller pericardial effusions may resolve. However they may become larger, leading to cardiac tamponade requiring pericardial drainage, window or pericardiectomy. When echocardiographic features are inconclusive or equivocal for hemodynamic significance or compromise, advanced cardiac imaging with cardiac CT or magnetic resonance imaging may be useful. Advances in ECG gated cardiac CT technique allows clinicians, to not only evaluate pericardial pathology, but also cardiac function and dynamic changes in pericardial effusion during respiration. Our case provides insight into this area of research thus prompting further investigation which can allow these imaging modalities to serve as new diagnostic tools for clinical decision making. In summary, non-invasive cardiac imaging can provide the diagnosis, the early detection of hemodynamic significance, and the assistance in timing for pericardiocentesis or surgery of pericardial effusion in asymptomatic patients.

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Raymond Maung M. Khin Hou – 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 PEER REVIEWED | OPEN ACCESS

A case of an *Ureaplasma* infection causing significant soft tissue destruction to the vagina, perineum and abdominal wall in a patient with hypogammaglobulinemia

Debbie Hunt, Shomari Dotun Lee Zack-Williams, Janet Purcell, John Cheesbrough, Jeyramam Srinivasan

ABSTRACT

Introduction: *Ureaplasma* species make up part of the normal genital flora and rarely penetrate the submucosa, except in the case of immunosuppression/instrumentation. However, so far in literature, there is no cases of *Ureaplasma* causing significant tissue loss. We present a case of significant tissue destruction of the abdominal wall and perineum caused by *Ureaplasma*. Case Report: A 23-year-old female with B lymphocyte deficiency presented with a urinary tract infection (UTI) which quickly progressed into recurrent abscesses and then widespread infection of the pubic region and genitalia, requiring multiple surgical debridement. This leads to a significant soft tissue defect producing complex reconstructive challenges. A distally based rectus abdominis turn down flap and skin graft was used to reconstruct the pubic defect. However, despite the flap being viable and no outward evidence of infection, the healthy tissue did not heal. In addition, the surgical wound used to raise the flap broke down and the anterior rectus sheath disintegrated. Despite multiple wound swabs and cultures the cause could not be isolated. Numerous broad spectrum antibiotics were trialed, yet the wound persisted for over a year, with recurrent admissions and operations. Finally, specific viral transport medium and PCR identified *Ureaplasma* and after starting doxycycline, the patient drastically improved within weeks. Conclusion: It is important to suspect mycoplasma when the clinical picture indicates infection, but the infectious agent cannot be isolated on standard culturing methods. Involving support from microbiologists early would be helpful in such cases.

Keywords: Abdominal wall, Destruction to the vagina, Hypogammaglobulinemia, Perineum

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INTRODUCTION

Ureaplasma species make up part of the normal genital flora and rarely penetrate the submucosa, except

in the case of immunosuppression/instrumentation. However, so far in literature, there are no cases of *Ureaplasma* causing significant tissue loss. We present a case of significant tissue destruction of the abdominal wall and perineum caused by *Ureaplasma*.

CASE REPORT

A 22-year-old female with agammaglobulinemia due to absent B lymphocytes had been receiving regular immunoglobulin replacement therapy since childhood. She maintained good health until early 2012, when, aged 20, she developed cystitis and a vaginal discharge. An initial diagnosis of urinary tract infection was made which failed to respond to antibiotics. Pelvic inflammatory disease (PID) was then suspected and in March 2012 she had a laparotomy at which multiple intra-abdominal abscesses were found. These failed to yield any growth on routine culture. Her symptoms improved following surgery and antibiotics. However, her vaginal discharge and abdominal pain returned and she received several further courses of antibiotics for PID over the next 15 months. In May 2013, she developed a swelling of the left vulva, initially felt to be a Bartholin's abscess which spontaneously discharged. Anaerobes were isolated on culture and metronidazole given. Failure to improve resulted in an admission for drainage in July, at which time enterococci were isolated from pus. By this time the vulva was ulcerated. A diagnosis of genital herpes was made and aciclovir given but this was not confirmed by polymerase chain reaction (PCR). By November 2013, she had a large vulvar ulcer with widespread soft tissue infection of the pubic and genital region requiring multiple wound debridements and packing under general anesthetic due to the severe pain. Magnetic resonance imaging showed two abscesses deep to the left vulva/labia which required further drainage. Biopsy of the ulcer margin showed chronic inflammation with no evidence of malignancy or vasculitis. Mycobacterial culture was negative and PCR was negative for HSV 1 and 2. HIV and syphilis were not detected by PCR in plasma. A Plastic surgery opinion was sought for the resultant complex wound management and the patient transferred to the regional centre.

Reconstructive surgery

The degree of soft tissue loss involving vagina and perineum in such a young lady required multi-disciplinary input from plastic surgery, urology, immunology, microbiology and caring nursing support. In addition, the patient was malnourished after prolonged hospitalization and frequent visits to theatre. These nutritional and psychological aspects were further handicap to the reconstructive efforts, and treatment as a whole (Figure 1).

The aim of the reconstructive surgery at this stage was to provide a healed wound first in order to turn the tide of ongoing catabolism in this individual. A distally based rectus abdominis flap and skin graft was used for reconstruction of the pubic defect and vaginal roof (Figure 2). Despite the flap being viable, the healthy tissue did not show any healing with the vaginal vault tissue. In addition, the abdominal wound used to harvest the rectus abdominis flap also started to break down showing further loss of healing between abdominal skin flap and the rectus sheath. In fact, the entire anterior rectus sheath completely disintegrated exposing the inlay prolene mesh, despite the administration of Tazocin and later meropenem and clindamycin (Figure 3).

Further surgical interventions were stopped at this stage and vacuum assisted dressing were applied to manage this total wound break down. Infection with *Mycoplasma* and/or *Ureaplasma* was suspected due to the background of hypogammaglobulinemia and lack of response to previous antibiotics. Doxycycline was commenced after collecting samples for *Mycoplasma*/*Ureaplasma* culture and PCR in viral transport medium. A non-specific 16S eubacterial PCR was also requested. *Ureaplasma urealyticum* was confirmed by both methods and azithromycin and moxifloxacin added to optimize anti-*Ureaplasma* activity and reduce any risk of resistance emerging. The CRP fell rapidly and wound healing improved dramatically allowing the abdominal wall and the pubic/vaginal area showing satisfactory healing around the rectus muscle flap.

This patient was eventually discharged from the hospital with well healing perineal region and abdominal wall. She was able to pass urine per urethram despite a long period of catheterization and supra pubic urine diversion during multiple surgical procedures. Her nutritional status also improved dramatically leading to weight gain. She has resumed most of her social activities, studies, etc. Her ongoing concerns are related to the appearance of the vaginal introitus and her ability to have normal sexual relationship in future.

This young woman was posing many challenges – in identification of the cause and the management of the soft tissue defect. Conventional wound cultures did not reveal any definite pathogens and many courses of antibiotics with activity against this colonizing flora did not help in reversing the trend of continuing infection, delayed tissue healing and ongoing catabolic state for this individual. The need for a MDT approach was identified very early on from the Plastic surgery care and was instrumental in managing this difficult condition.

DISCUSSION

The family Mycoplasmataceae consists of two genera: Mycoplasma and Ureaplasma. They are the smallest free living organisms and are classified as bacteria since their cultivation does not require cells. They are the only prokaryotes that lack a cell wall— a feature that is largely responsible for their biologic properties, including lack of a Gram stain reaction and non-susceptibility to many

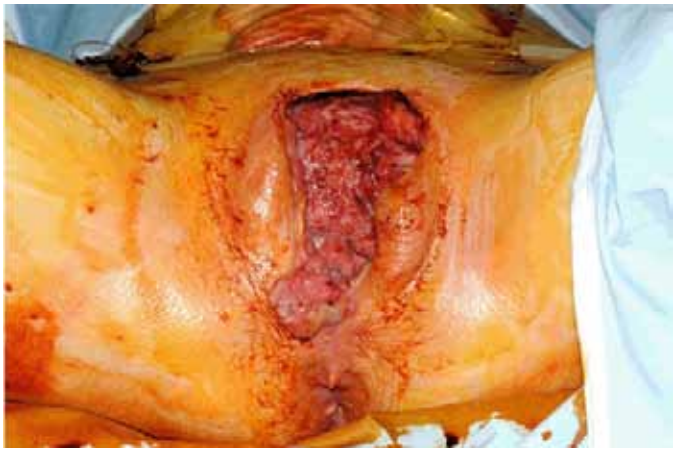

Figure 1: Loss of soft tissue of the perineum – a clinical photograph taken at initial debridement under Plastic surgery.

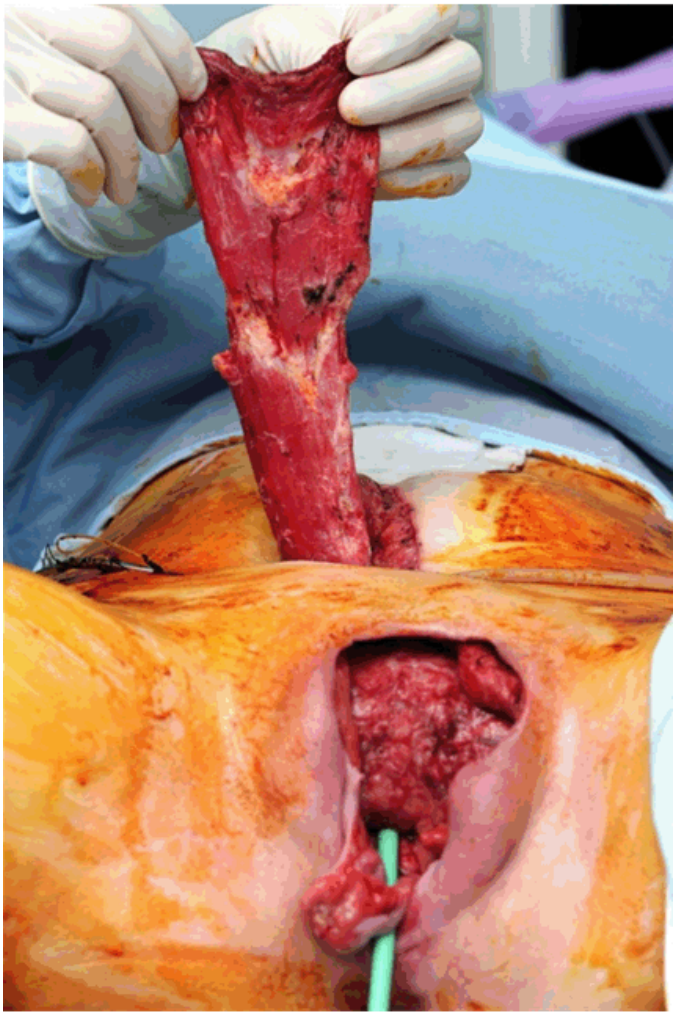

Figure 2: A clinical photograph to show the construction of a rectus abdominis turn down flap.

commonly prescribed antimicrobial agents, including beta-lactams. They are commonly associated with mucosae, residing extracellularly in the respiratory and urogenital tracts and rarely penetrate the submucosa. *Ureaplasma sp*. (*U. urealyticum* and *U. parvum*) along with *Mycoplasma hominis,* make up part of the normal

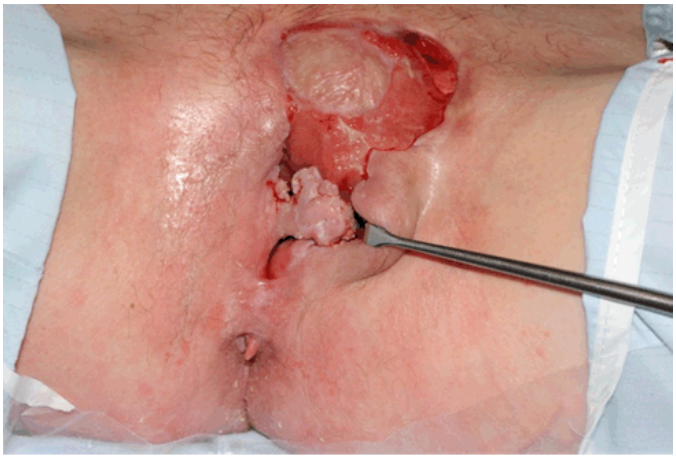

Figure 3: Wound breakdown and loss of integrity of the vagina and clitoris.

genital flora of both men and women and at least one of these organisms is found in about 70% of sexually active humans [1–3].

Occasionally *U. urealyticum* has been shown to have a causal role in a spectrum of urogenital diseases in women including urinary calculus formation, nonspecific urethritis, pyelonephritis, bacterial vaginosis, pelvic inflammatory disease, infertility, chorioamnionitis, spontaneous abortion, prematurity and intrauterine growth retardation. Extragenital infection is rare and often in the context of underlying immunosuppression [4] or a prosthetic device. Site of infection may include; arthritis, meningitis, brain abscess, sternal wound infection, mediastinitis and aortic graft infection and an abscess in a transplanted kidney (Jof Infection Ref) [5–8]. However, their role in localized genital disease is still unclear given their low pathogenic potential and high background prevalence.

Despite the above, an extensive review of literature, has shown that here were no cases of ureaplasma causing such significant tissue loss in adults. It is known however, to cause sepsis in neonates [9]. Reports have also shown that mycoplasma hominis, another commensal of the urogenital tract, can cause extensive and sometimes even life-threatening, slow healing infections [10]. However, there have been no reports specifically for *Ureaplasma urealyticum*.

Treatment

Doxycycline is the drug of choice in the treatment of ureaplasma. Azithromycin can also be used as can the fluoroquinolones, especially moxifloxacin [11]. Resistance has been reported to all these agents. This risk of this should be reduced with combination treatment. Sensitivity testing can be technically difficult and was not undertaken in our case. The prompt response to doxycycline monotherapy indicates that the isolate was sensitive in our case and the subsequent addition of other

agents aimed to reduce risk of late relapse rather than hasten clinical response penicillins are ineffective as *U. urealyticum* does not have a cell wall [12, 13].

The learning points from this case are two-fold. Firstly, it is imperative to involve the microbiology and immunology specialists early in cases when there is an underlying immune defect that might render the patient susceptible to infection with microbes not detected by routine culture. It is important for practitioners to bear in mind that samples from open skin sites will always grow microbes, and while some may be potential pathogens and reported with sensitivities, the same microbes often just represent colonizing flora. Suspicion that microbes isolated on culture may be irrelevant should be heightened when antibiotics with in vitro activity confer no clinical benefit. Good communication and teamwork are essential to manage the patient as effectively as possible. It is important both for doctors, and for microbiologists to suspect mycoplasma when the clinical picture indicates infection, and the infectious agent cannot be isolated on standard culturing methods [14].

Secondly, surgical attempts to debride and reconstruct the defect would not have been successful till the source of the infection has been identified and adequately treated. When a healthy muscle flap such as rectus abdominis was not healing as expected, the index of suspicion was raised and further attempts of reconstruction were with held till the wound healing was restored by appropriate antibiotics. With a collaborative working pattern among the varied specialties —surgical and medial teams— the situation was brought under control.

CONCLUSION

While rare, *Ureaplasma* can have potentially devastating consequences in the immunocompromised and therefore needs to be tested for early in a case of soft tissue infection resistant to standard treatment.

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Author Contributions

Debbie Hunt – 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

Shomari Dotun Lee Zack-Williams – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

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

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Jeyramam Srinivasan – 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 PEER REVIEWED | OPEN ACCESS

Perventricular device closure of post-myocardial infarction ventricular septal defect: Can it combine best of both worlds!

Alok Ranjan, Kalpesh Malik, Manik Chopra, Arool Shukla, Kanaiyalal Patel

ABSTRACT

Introduction: Post-myocardial infarction ventricular septal defect (VSD) is a rare but dreadful complication of acute myocardial infarction. Current management of this complication has high morbidity and mortality rates. A hybrid approach (perventricular device closure) to high risk congenital muscular VSD has shown promising results. We report first case of a perventricular device closure of post infarct VSD by Amplatzer post-infarct muscular VSD device. Case Report: A 52-year-old male was referred to us for rapidly progressive dyspnea. He had anterior wall myocardial infarction, complicated by post-infarct VSD. His coronary angiography revealed 90% lesion in left anterior descending (LAD) artery. Perventricular device closure of VSD (Amplatzer post-infarct muscular VSD device) and graft to the LAD were performed using a beating heart technique. His postoperative stay was complicated by an enlarged secondary post-infarct VSD. It was closed by percutaneous technique. He was discharged in stable condition. He is in compensated heart failure at 1 year follow-up. Conclusion: Perventricular approach to congenital muscular VSD is an established procedure. Applying this approach to post-infarct VSD can also effectively manage this dreadful complication. The combination of surgical and percutaneous techniques might be less traumatic with better outcome.

Keywords: Closure, Device, Myocardial infarction, Perventricular device, Ventricular septal defect (VSD)

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INTRODUCTION

Acquired ventricular septal defect (VSD) is one of the three major mechanical complications of acute myocardial infarction (AMI), the other two being acute mitral regurgitation and rupture of the ventricular free wall. With the advent of early reperfusion strategies and

adjunct medical therapy, the incidence of this complication has significantly decreased to < 1% of cases but remains associated with a high morbidity and mortality. Although this decrease is encouraging, both early and long-term prognosis after AMI-related VSD remain unsatisfactory. Medically managed patients with post-myocardial infarction VSDs (PI-VSD) have 30-day mortality rates as high as 94% [1]. Given this high mortality rate, surgical closure has traditionally been advocated as the preferred treatment strategy. But even in surgically treated patients, mortality remains high, with reported rates ranging from 23–81% [1–3]. Even the incidence of a large residual shunt and re-rupture after surgery reaches up to 10–20% [3]. With advances in cardiac interventional techniques and devices, transcatheter closure of PI-VSD has become an alternative or bridge to surgical repair for patients with PI-VSD in the last decade [1, 3, 4]. However, both these methods do have their limitations in management of PI-VSDs [4]. A hybrid approach (perventricular device closure), performed both by surgeons and cardiologists has been described for congenital muscular VSDs [5, 6]. Although it is safe and effective in high risk cases, it has not been widely tried in PI-VSD cases. Only two cases of PI-VSD have been managed with hybrid approach till date [7]. We report a case of perventricular closure of PI-VSD with an Amplatzer post-infarct muscular VSD device. To the best of our knowledge this is the first reported case of perventricular device closure of PI-VSD by an Amplatzer post-infarct (PI) muscular VSD device.

CASE REPORT

A 52-year-old male without previous history of hypertension, diabetes mellitus and smoking, was referred to our hospital for rapidly progressive dyspnea. He was symptomatic for last 15 days, symptoms started with chest pain and shortness of breath. His dyspnea gradually worsened to NYHA class IV at the time of admission.

Clinically, he was in congestive heart failure with a pulse rate of 110/minute, blood pressure of 100/70 mmHg, a respiratory rate of 30 per minute, bilateral basal crepitations in lungs and a grade III pan systolic murmur at left lower parasternal area.

Investigations: Blood investigations showed mildly deranged renal and liver function tests. His electrocardiogram (ECG) was consistent with evolved anterior wall myocardial infarction. Transthoracic echocardiogram (TTE) showed mid and distal interventricular septal akinesia and hypokinesia in apex and anterolateral segments, moderate left ventricular dysfunction and a large muscular VSD of 10 mm size in the distal part of the septum. One additional small muscular VSD was seen anterosuperior to the larger VSD. Coronary angiography (CAG) was performed next day which revealed 90% lesion in left anterior descending (LAD) artery involving ostium and proximal part. Other vessels were normal.

Treatment: The medical treatment was optimized with inotropic support, vasopressor drugs and diuretic therapy. He was put on intra-aortic balloon pump (IABP) support post coronary angiography. Perventricular device closure of VSD and graft to LAD were planned next day. Next day, for the procedure, the patient was anesthetized as per coronary artery bypass graft surgery (CABG) protocol and the chest and pericardium were opened in operation theatre. Using a beating heart technique, a Teflon pledgeted purse-string suture with Ethibond 2/0 (Johnson and Johnson, USA) was taken on right ventricle (RV) free wall, about one and half inches away from the RV apex. The site was selected using transesophageal echocardiography (TEE) guidance and after discussion with surgeon. A direct puncture was made in the middle of the purse-string with an 18-gauge Jelco (Smiths Medical, Italia) in the direction of VSD. The needle was removed and a 0.035" short wire (Terumo, angled tip, RADIFOCUS, Terumo Corporation, Tokyo) was positioned in the left ventricle (LV) under TEE guidance (Figure 1). A 10-French (Fr) Terumo sheath (RADIFOCUS, Terumo Corporation, Tokyo) was advanced to the LV over the wire. The dilator and wire were removed. A 16-mm Amplatzer post-infarction muscular VSD device (St. Jude Medical, Inc., USA) was selected and was advanced through the sheath. The left sided retention disc was delivered in the mid LV cavity. The waist was then delivered and the entire assembly (sheath, device and cable) was pulled back to the interventricular septum. The right ventricular disc was delivered by active pushing as there was no sufficient space to passively deliver it, as the distance between septum and right ventricular free wall was short. These steps were performed under TEE guidance (Figure 2). The position of the device and residual shunt were checked on TEE. There was no significant shunt across the device and the position of the device was stable. There was no significant shunt across the additional VSD site at this point of time. The device was released from the delivery cable with counter clockwise rotation of pin vise. Thereafter a saphenous venous graft to LAD was performed using a beating heart technique. The absence of residual shunt was reconfirmed and the purse-string was tied after removal of Terumo sheath. The Ethibond purse-string suture was reinforced with a Prolene 3/0 (Johnson and Johnson, USA). The sternal wound was closed as per standard technique. The patient was shifted to intensive coronary care unit (ICCU) with IABP and ventilatory support. He was extubated on 2nd day and gradually weaned off from IABP support in next 4 days. A grade III pan systolic murmur persisted. There was no residual shunt across the device but shunt across the additional VSD was present. He had hepatic and renal dysfunction which required intensive treatment and he was shifted to ward on 5th postoperative day. His renal parameters gradually returned to normal and hepatic enzymes showed gradual downward trend. He required intravenous diuretics apart from usual postoperative medicines. However on 20th postoperative day, his

clinical condition deteriorated considerably. He was put on intravenous inotropic and noninvasive ventilatory (BIPAP) support again. A repeat TTE revealed an enlarged VSD (size 10 mm) anterosuperior to the device. In view of rapidly deteriorating symptoms, percutaneous device closure of VSD was planned and was performed on the same day. The VSD was closed using an 18 mm Amplatzer muscular VSD (St. Jude Medical, Inc., USA) device using standard technique (Figure 3A–B). There was a residual shunt across the VSD but the step up in oxygen saturation was less than 5%. He was then shifted to ICCU and thereafter to the wards next day. He was discharged in stable condition after five days on aspirin, statin, warfarin and anti-failure treatment.

A 12-month follow-up has been completed. The patient remains in NYHA class II symptoms with LVEF 30%. He has a small residual shunt and has two devices across the interventricular septum (Figure 3C–D).

DISCUSSION

The PI-VSD is a rare but serious complication of AMI. PI-VSD usually occurs 2–8 days after the infarction and often precipitates cardiogenic shock. The size of the defect determines the magnitude of the left-to-right shunt and consequently the hemodynamic deterioration, which affects survival. Compared to patients with AMI without VSD, patients with VSD are older, more likely to be women, has increased the rate of chronic renal disease, congestive heart failure and cardiogenic shock, the absence of a history of angina or myocardial infarction, and severe coronary stenosis or total occlusion without compensatory collateral circulation and are less likely to be hypertensive or diabetic [3].

The pathogenesis of PI-VSD reflects two different types of rupture. The first, a simple rupture, is a direct through-and-through defect. Conversely, complex ruptures are believed to result from tracking of blood as it dissects through the septum with left ventricular entry sites remote from right ventricular exit sites – these tracks then enlarge over time due to the pressure gradient between the left and right ventricle. Multiple defects are found in 5–11% of cases [2, 8]. Incomplete closure of residual or secondary defects can account for postoperative recurrences. Fortunately, most residual shunts tend to be physiologically tolerated and spontaneous closure has been reported. Operative re-intervention is associated with a >60% mortality [2] and surgery is reserved for patients in heart failure failing medical management or those with large shunts (Qp:Qs > 2.0) [2, 8].

The mortality of PI-VSD is very high. 50% of these patients die within one week and about 85% within two months [2, 9]. Attempts to stabilize the patient's condition with medical therapy often fail because most patients have a rapid deterioration and subsequently die [3]. The dismal prognosis of this subgroup of patients with AMI has elicited aggressive surgical intervention. The mere presence of

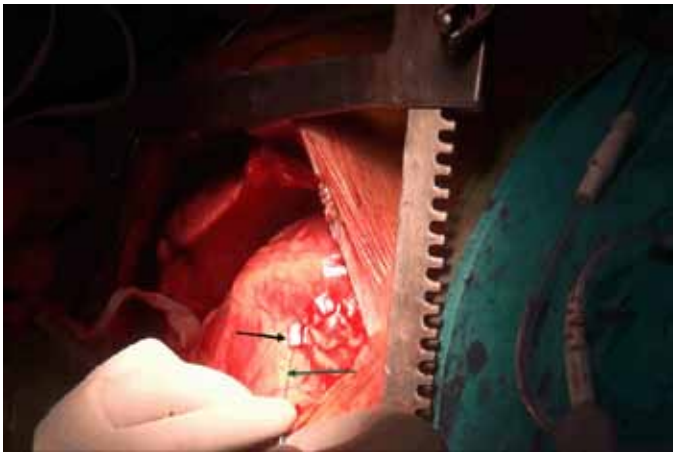

Figure 1: Puncture site on RV (Black arrow) with Terumo wire (green arrow).

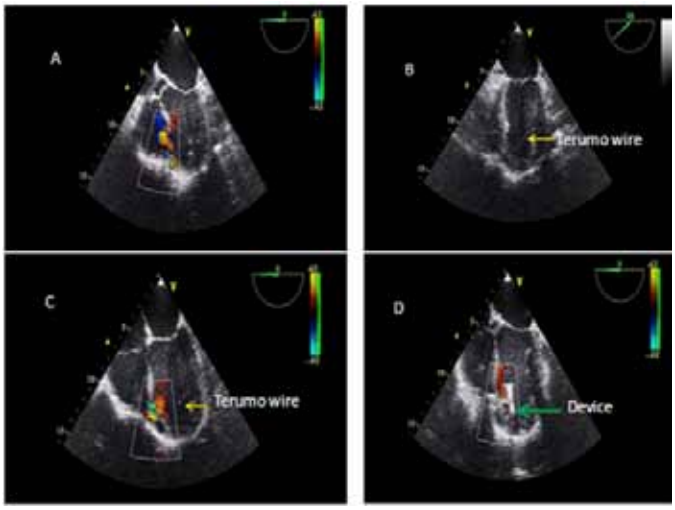

Figure 2: Deployment of Amplatzer post-infarct muscular device by perventricular approach under transesophageal echocardiography (TEE) guidance. (A) Left to right shunt across the ventricular septal defect (VSD), (B) Terumo wire in left ventricle (yellow arrow), (C) Terumo wire in left ventricle across the defect (yellow arrow), and (D) No left to right shunt across the defect after device deployment (Device: green arrow)

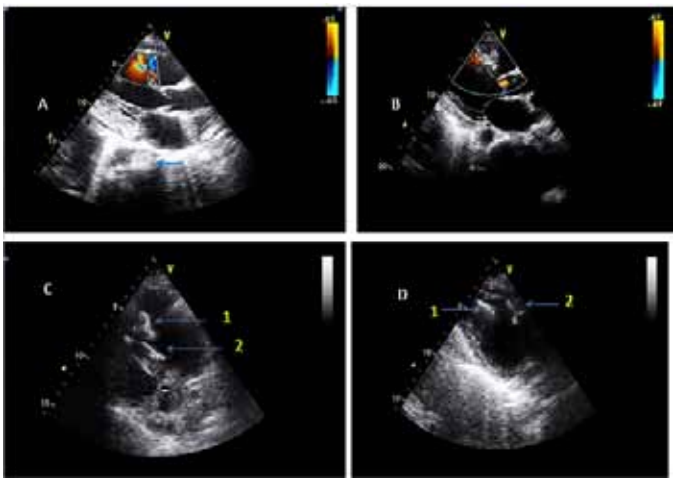

Figure 3: (A) Left to right shunt across the secondary VSD, (B) No significant shunt after percutaneous device closure, and (C, D): 1: Device deployed by perventricular approach. 2: Device deployed by percutaneous approach.

a PI-VSD is considered an indication for surgery with the majority of patients undergoing urgent or emergent operative intervention. The primary goal of VSD closure is to reduce the end-organ damage from the combined insults of acute right ventricular overload/failure and systemic cardiogenic shock [2]. The joint American Heart Association/American College of Cardiology (AHA/ACC) 2004 Guidelines recommend emergent repair of the VSD with concurrent coronary artery bypass grafting, as indicated, irrespective of hemodynamic status, with no change in this class I recommendation in the 2011 ACC/AHA guideline for coronary artery bypass surgery [1, 10]. Current surgical management of this uncommon catastrophe includes: 1) deferring operation, if possible, until three weeks after infarction, 2) cardiac support with intra-aortic balloon pump insertion to allow preoperative definition of coronary and ventricular anatomy of patients with hemodynamic deterioration, and 3) a transinfarct incision with prosthetic replacement of excised ventricular free wall or septum, if necessary, and 4) possible repair of associated coronary or mitral valve pathology [8, 9]. Cardiac surgery is considered the gold standard in the management of these defects. However, its main limitation is that it carries a high risk of perioperative mortality and postoperative morbidity.

Percutaneous transcatheter closure of PI-VSD is an alternative method of repair [1, 3]. It is a less invasive option and allows immediate complete closure after initial hemodynamic stabilization. It has become an alternative or bridge to surgical repair for patients with PI-VSD. Immediate reduction of the left-to-right shunt, even if the VSD is not completely closed, may stabilize the patient enough to function as a bridge to surgery [1]. Specially designed devices for the closure of PI VSDs have also become available. The difficulty of transcatheter closure of ventricular septal rupture is how to push the catheter through the septum defect without injuring the surrounding friable myocardium [3]. As the site of septal rupture in patients with AMI is surrounded by fragile necrotic tissue, attempts to pass the closure device though the site may increase the size of rupture [8]. In addition, the occluders are usually difficult to fix because of the presence of the friable necrotic myocardium tissue around the defect [3]. Moreover, current interventional reports are mainly restricted to VSD closure in the sub-acute or chronic setting, or for residual shunts after initial surgical closure [1]. Due to scarcity of reports in literature, there is limited data regarding survival data; however, the few reported series have shown an overall mortality rate of 44–60% within one year [11]. Furthermore, non-inferiority to surgery has been demonstrated in one case series [4]. Long-term follow-up studies are lacking, and thus long-term mortality has yet to be discerned.

Perventricular device closure for congenital muscular VSD (m-VSD) is a new approach. It is performed by both surgeon and cardiologist in hybrid suit or operating room combining catheterization and surgical techniques [5, 6]. Thakkar et al. concluded in their series of 24 infants who underwent perventricular device closure of mVSD that in selected high-risk infants, perventricular device closure of isolated mVSD is effective and may either substitute or complement the conventional surgical closure depending on the performance of institutional pediatric cardiac surgery program. The procedural safety can certainly be improved with more precautions for preventable complications. Until specifically designed hardware is available, very large defect or defects extending into inlet, posterior or apical septum are not suitable for perventricular closure [5]. The major advantages of hybrid approach are: from surgeon's view; i) easy accessibility of m-VSD even in difficult locations ii) no palliative pulmonary artery banding or ventriculotomy required to close the apical m-VSD iii) no ill effects of CPB (cardiopulmonary bypass); from cardiologist's view; i) no limitation for vascular access and sheath size ii) no hemodynamic instability due to arterio-venous looping iii) septum can be approached from anterior (perpendicular angle) but, not from a lateral (tricuspid valve) plane [6]. Thus, this hybrid approach appears to combine the positives from both surgical and percutaneous methods. Although this approach has become popular to close high risk congenital muscular VSDs, it has not been attempted extensively for PI-VSD. Only 2 cases of PI-VSD have been closed by this approach till date. Love et al. has used this approach to close PI-VSD by Amplatzer septal occluder [7]. In our case, the PI-VSD was closed with an Amplatzer post-infarct muscular VSD device. Previous experience with congenital VSDs has found the Amplatzer system to have a higher success rate than other devices and extrapolation of this experience has led to the tendency to also use this family of devices for the closure of acquired post-AMI ventricular septal ruptures [1]. The Amplatzer muscular VSD occluder is a self-expanding, single-unit Nitinol device with incorporated polyester fabric that comprises two discs connected by a 7-mm long waist portion, compared with a 4-mm waist in the atrial septal defect (Amplatzer septal occluder) device. The device is sized between 4 and 18 mm by the diameter of the central waist, with the discs being 8 mm larger than this segment. The disc sizes are larger in Amplatzer septal occluder; 14 mm on left atrial side (distal disc) and 10 mm on right atrial side (proximal disc). These devices are secured onto a delivery cable and implanted via a 5-Fr to 12-Fr diameter sheath. It is self-centering and permits several positioning attempts because it is retrievable before release. Specially designed devices for the closure of post-AMI VSDs have also become available. The Amplatzer PI muscular VSD device has larger disks and a longer waist (10 mm) than the muscular VSD Amplatzer device to accommodate the thicker adult interventricular septum. It is available in sizes of 16 to 24 mm in 2-mm increments, as determined by the diameter of the waist section. The size of the device in our case was 50% more than the size of PI-VSD as measured on TEE.

The device closure in our case was performed with standard technique but our deployment method of the

device was different from Love et al. Love et al. deployed the proximal disc on the exterior surface of RV to ligate RV free wall to VSD. It minimized the residual shunt across the PI-VSD in their cases. The RV puncture site was closed with pericardial patch in these 2 cases [7]. In our case, the proximal disc was deployed inside the RV cavity by active pushing of the device. There was no residual shunt on TEE in our case. The puncture site on RV was closed with Ethibond purse-string sutures with reinforcement from Prolene 3/0 sutures. Thereafter, graft to LAD and wound closure was performed with standard technique. The patient showed gradual stabilization in clinical status after the procedure.

During postoperative period, our patient deteriorated due to increase in size of the additional VSD. As there was no flow across it on the day of hybrid procedure, it was not closed at that time. During early postoperative period, the pan systolic murmur was present. However as the patient was clinically stable, he was managed conservatively. Intervention was needed as there was sudden increase in size of VSD. This second VSD was closed using transcatheter technique. The second VSD was closed with Amplatzer muscular VSD device. The patient improved considerably and was discharged in stable condition. He has completed one year follow-up and he is in NYHA class II.

CONCLUSION

Perventricular device closure of post-myocardial infarction VSDs (PI-VSD) appears to be a safe and effective method to close PI-VSD. This approach has established itself for management of high risk congenital muscular VSDs. It has advantages over both surgical and transcatheter techniques. With this approach, immediate complete closure of PI-VSD with complete coronary revascularization is feasible without the ill effects of cardiopulmonary bypass or challenges of arterio-venous looping. However, many more cases will be required before this hybrid procedure becomes as established a procedure as it has become for congenital muscular VSD closure.

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Author Contributions

Alok Ranjan – 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
Kalpesh Malik – Acquisition of data, Drafting the article, Final approval of the version to be published
Manik Chopra – Acquisition of data, Analysis and interpretation of data, Final approval of the version to be published
Arool Shukla – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Dr. Kanaiylal Patel – Acquisition of data, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Massive chylous ascites following an elective repair of an abdominal aortic aneurysm: A case report

Al-Khusheh M., Blach O., Button M.

ABSTRACT

Introduction: Symptomatic postoperative chyloperitoneum is a rarely reported complication of elective abdominal aortic aneurysm surgery (AAA). Treatment, conservative versus invasive, could be challenging. Case Report: We present a case of severe chyloperitoneum following seemingly uncomplicated elective repair of an 8 cm infra-renal AAA, in a 69-year-old male. Patient presented with a progressively increasing abdominal distension and small amount of milky white discharge around the transverse incision wound three weeks postoperatively. We discuss the diagnostic process, different management strategies attempted and outcome in light of the existing literature and our own experience. Conclusion: While an adequate trial of conservative measures should precede any surgical intervention, our case report shows that early consideration of peritoneovenous shunt insertion for refractory chyloperitoneum provides excellent and sustained results.

Keywords: Aortic aneurysm, Chylous, Chyloperitoneum, Peritoneovenous shunt

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INTRODUCTION

Chylous ascites is a rare complication of abdominal aortic aneurysm (AAA) surgery with a few cases reported in literature. Due to their anatomical relation with the abdominal aorta, cisterna chyli injury is more common following open AAA repairs when compared to other surgeries.

We present a case of severe chylous ascites following elective AAA repair in a 69-year-old male who gradually developed abdominal distension following discharge from hospital. A conservative approach was followed by a successful peritoneovenous shunt insertion. This less invasive treatment avoided the patient having relaparotomy and ligation of leaking lymphatic vessel.

CASE REPORT

A 69-year-old male presented three weeks post-seemingly uncomplicated elective open repair of an 8-cm infra-renal AAA, with progressively increasing

abdominal distension and small amount of milky white discharge around the transverse incision wound. Computed tomography angiogram (CTA) showed minor fatty stranding around the aneurysm sac suspicious of graft infection, treated with a course of tazocin and teicoplanin, a superficial abdominal wall collection and extensive ascites (Figure 1). The collection was drained.

Blood tests were grossly normal, except for hypoalbuminemia. An ascitic tap showed fluid triglycerides level of 36.4 mmol/L (3224.1 mg/dL), confirming a diagnosis of chylous ascites. No dietary changes were recommended by the dietician and the patient was discharged with an outpatient follow-up.

The patient was then re-admitted a month later for USS guided drainage of the worsening abdominal chyle collection; 20.7 liters of chyle were drained in total and a drain was left in situ. He was put on a high protein/ medium TAG diet and advised to reduce oral fat intake. Patient was then discharged home. However, here-presented within two weeks with dyspnea, decreased drain output, abdominal distension and CT scan showed re-accumulation of ascites (Figure 2). Further four liters of chyle were drained under USS guidance. In view of the chylous ascites refractory to conservative treatment, and to avoid major operation which has considerable risks to this patient with high body mass index (BMI) and several comorbidities, a peritoneovenous shunt was inserted, with no further complications or re-accumulation of ascites, and no need for lymphangiography or re-operation, result sustained 6 months later, where patient was asymptomatic at the follow-up clinic and ultrasound scan showed no reaccumulation of the ascites.

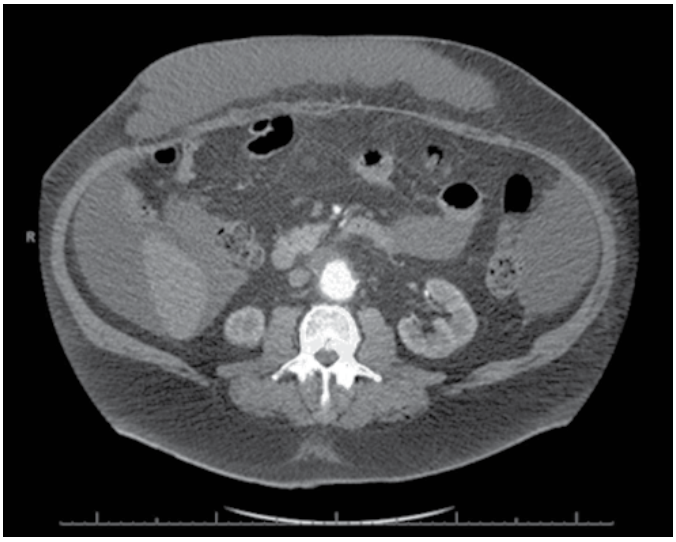

Figure 1: Enhanced computed tomography scan of the abdomen three weeks postoperatively showing subcutaneous abdominal wall collection and ascites.

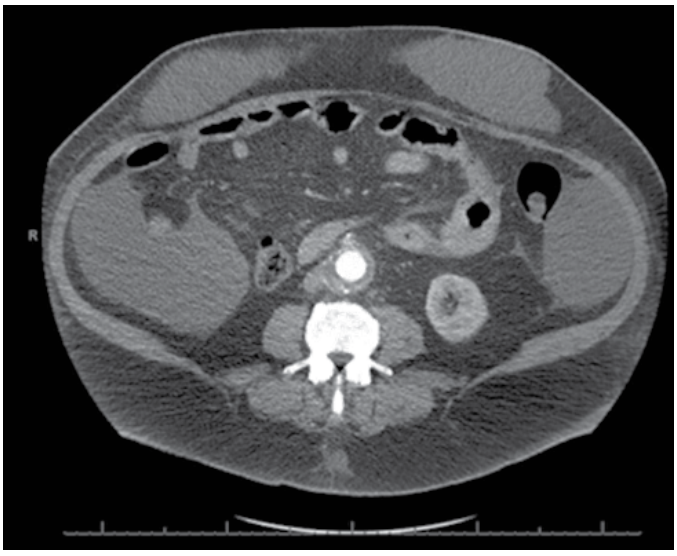

Figure 2: Enhanced computed tomography scan of the abdomen six weeks postoperatively showing reaccumulation of ascites in spite of the per-cutaneous drainage.

DISCUSSION

In the context of abdominal aortic surgery, injury to the lymphatic trunk with a subsequent lymphatic leak usually follows extensive retroperitoneal space dissection, such as during repair of ruptured or inflammatory aneurysms [1–3]. Although not an uncommon complication, it rarely leads to symptomatic chyloperitoneum or chylous ascites, with fewer than 50 cases reported in the last 50 years [4].

Presentation varies based on the severity of the chyle leak, from progressive abdominal distension, pressure-related dyspnea, to widespread edema and paralytic ileus [1, 4]. However, in the majority of cases, the diagnosis is not suspected until diagnostic paracentesis is performed [5], yielding milky-white peritoneal fluid rich in triglycerides (>200 mg/dL) [6].

There is no agreed protocol for the treatment of chylous ascites following AAA surgery. Conservative management, combining a low-fat diet, medium-chain triglycerides (MCTs) regime and parenteral nutrition (TPN), is frequently advocated following initial diagnosis [1, 3, 5, 7], and is believed to promote healing by minimizing the lymphatic flow from the leaking duct [8]. Up to 80% of chylous ascites, reportedly, dry out with such approach [1, 4], and some feel that surgical intervention is only warranted after 4–6 weeks of persistent ascites [1, 9].

Insertion of a peritoneovenous shunt and suture ligation of the fistulae are two available surgical options [10]. Both carry a significant complications rate, however peritoneovenous shunt insertion is the less invasive procedure and more appropriate in patients who are unfit to undergo re-laparotomy with ligation of the leaking lymphatic vessel [4].

Favorable outcome depends on timely diagnosis and identification of the underlying pathology. The treatment of chylous ascites should therefore be selective and

tailored to the severity of patient's condition [11]. While an adequate trial of conservative measures should precede any surgical intervention, our case report shows that early consideration of peritoneovenous shunt insertion for refractory chyloperitoneum provides excellent and sustained results.

CONCLUSION

Chylous ascites is rare after aortic surgery and manifests itself about two weeks after operation, at times after discharge from hospital. It has an indolent course, but may resolve spontaneously up to two months after operation. Its course appears not to be foreshortened by diet, including omission of fat, but can be successfully treated surgically with a peritoneovenous shunt. If done early, a protracted hospital course may be avoided.

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Author Contributions

Moutaz Alkhusheh – Substantial contribution to conception and design, Revising the article critically for important intellectual content, Final approval to the version be published
Olga Blach – Substantial contribution to conception and design, Acquisition of data, Drafting the article, Final approval to the version be published
Matthew Button – Substantial contribution to conception and design, Revising the article critically for important intellectual content, Final approval to the version 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 PEER REVIEWED | OPEN ACCESS

Amiodarone-induced pulmonary toxicity (APT): A low dose fatal adverse event

Muhammad Imran Butt, Muhammad Asif Shahzad

ABSTRACT

Introduction: Amiodarone pulmonary toxicity (APT) can be a diagnostic challenge to clinicians as it has no pathognomonic clinical, laboratory, radiological or histological features. It can potentially be fatal particularly in high risk patients. Amiodarone pulmonary toxicity is dose dependent, however, low dosages have also been reported to cause severe pulmonary disease. Therefore, it should be considered in every patient with respiratory distress and on current or recent amiodarone therapy. Case Report: We report a case of APT with fatal outcome in a 49-year-old female taking the recommended doses of amiodarone with history of atrial fibrillation, rheumatic heart disease and pulmonary hypertension. Our patient was taking amiodarone for three years. She presented with severe respiratory distress necessitating endotracheal intubation. Despite treatment with systemic corticosteroids and broad spectrum antimicrobials, patient died in intensive care unit (ICU) after one month of admission. Amiodarone pulmonary toxicity is usually dose-dependent, however, our patient was taking safe doses which make this case unique. Conclusion: The knowledge of different safe dosage patterns is important for every working physician due to widely usage of the drug. The lowest effective dose of amiodarone should be determined for every patient requiring long-term treatment and needs a close and regular follow-up for early diagnosis of lung injury.

Keywords: Amiodarone, Fatal, Pulmonary, Toxicity

How to cite this article

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INTRODUCTION

Amiodarone is an antiarrhythmic drug widely used to treat various arrhythmias. Despite various adverse effects, it is considered the most potent antiarrhythmic drug with safety proven in many clinical trials. Of major side effects, Amiodarone-induced pulmonary toxicity (APT) is the most serious adverse event that can lead to death. It occurs dose dependently, however can occur with any dose. Therefore, it is important for physicians to be aware of the safe dosage patterns of the drug to minimize the incidence and fatality.

CASE REPORT

A 49-year-old female presented with progressive dyspnea over two weeks along with generalized weakness, dry cough and reduced exercise tolerance over preceding four weeks. On presentation, patient's respiratory rate was 35 per min, heart rate 75 bpm, blood pressure 95/48 mmHg and oxygen saturation 90% with FiO2 45% on continuous positive airway pressure (cPAP) . On chest auscultation there were diffuse crackles bilaterally. Jugular venous pressure was not elevated. Patient's respiratory condition did not improve on cPAP and few hours later patient was intubated due to type 2 respiratory failure (Arterial blood gas: pH 7.05, PCO_2 88, PaO_2 115, HCO_3 25, sat 95%).

The past medical history of patient included atrial fibrillation (AF), mitral valve replacement due to rheumatic heart disease, pulmonary hypertension, hypothyroidism and hypertension. Her medications included warfarin, thyroxine, perindopril and amiodarone. Amiodarone was started three years ago with initial dose of 600 milligram per day and tapered down to maintenance dose of 100 mg per day in three weeks. Patient's chest X-ray done overseas was reported normal one year ago.

Initial laboratory tests revealed slight leukocytosis ($11.6x10^9$/L) with rise in C-reactive protein (CRP) to 105 mg/L and normal procalcitonin level. Serial troponins were negative and ECG did not show any acute changes.

Chest X-ray (Figure 1) and computed tomography (CT) scan of the chest (Figure 2) showed diffuse bipulmonary interstitial infiltration. Serologic tests were negative for *Mycoplasma pneumoniae*, *Chlamydia* species and *Legionella*. The polymerase chain reaction of sputum and pharyngeal swabs were negative for influenza A, B and parainfluenza virus species. Extensive investigations ruled out any infective, autoimmune or neoplastic disorder. Coronary angiogram was normal and echocardiogram revealed takotsubo cardiomyopathy with ejection fraction of 30% . Pulmonary artery pressure was 45 mmHg. The patient underwent fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) which revealed interstitial fibrosis and foamy macrophages. Lung biopsy was not performed due to the risk involved in the procedure

Patient was started on broad-spectrum antibiotics for possible lower respiratory tract infection and amiodarone was immediately ceased. Patient was also given intravenous frusemide with no improvement in symptoms. Leukocytosis and CRP did not improve despite giving broad spectrum antibiotics. Computed tomography scan of chest was repeated which showed progressive pulmonary infiltrates in both lungs. Amiodarone toxicity was assumed the likely explanation and corticosteroid treatment was initiated two days after admission. Patient initially showed a quick response to steroids and came off ventilator (Figure 3). Steroids were stopped however the next day patient again developed severe dyspnea requiring re-intubation. Systemic steroids were reinstituted on top of antibiotics but no further improvement was noted. A percutaneous tracheostomy was performed on 25th day of admission.

The patient also developed acute kidney injury requiring continuous veno-venous hemodialysis (CVVD) with improvement in renal functions.

Despite the above treatment patient did not improve. Extensive discussion was made with family regarding the lung biopsy and transplant. Biopsy was deferred due the risk of clinical deterioration. The patient died after 30 days of ICU admission due respiratory failure.

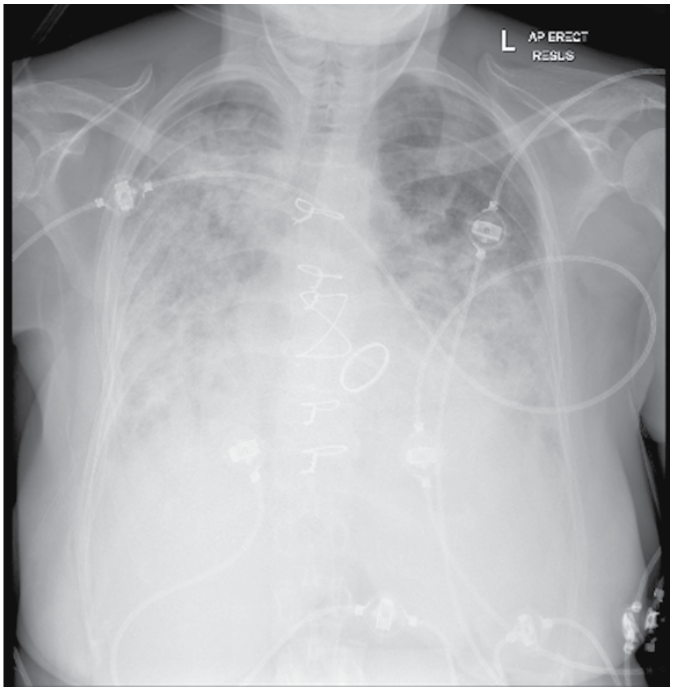

Figure 1: Chest X-ray on presentation with bilateral interstitial infiltrates.

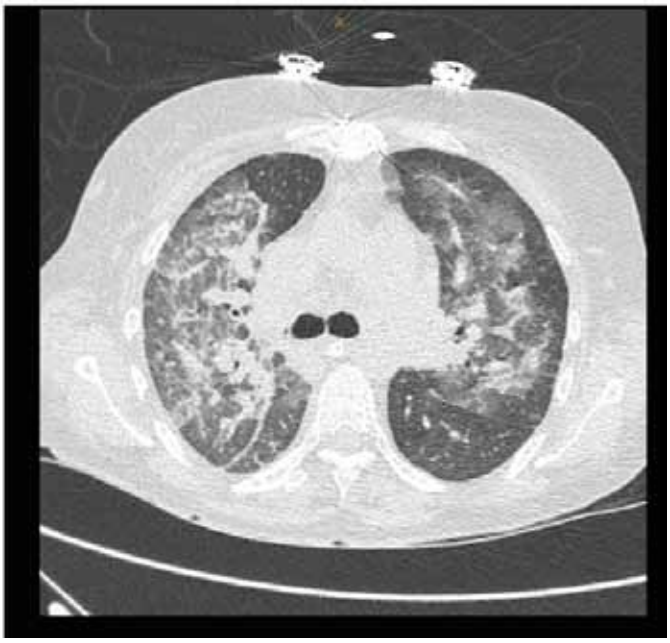

Figure 2: Computed tomography scan of chest showing ground glass interstitial infiltrates.

DISCUSSION

Amiodarone is an amphiphilic compound and contains iodine in its formulation. It is globally used antiarrhythmic drug and tends to accumulate in some organs including lungs.

Amongst several side effects (thyroid dysfunction, liver dysfunction, skin photosensitivity, corneal deposits, coagulopathy, neuropathy and disturbances in the intraventricular conduction) pulmonary toxicity is the most serious adverse effect [1]. Amiodarone pulmonary toxicity can present as adult respiratory distress syndrome (ARDS) which has high mortality rate of 50% [2] and can progress to severe pulmonary fibrosis [3].

Incidence and mortality of APT have been described in several studies. In patients on long-term treatment the incidence of APT ranges from 0.5–17% [2, 4]. It was seen less frequent in some recent reports ranging between 1.6% [5] and 2.9% [6] likely due to lowest effective doses.

In recent studies, the mortality of APT was seen in 9% [7] and 7% [5] of patients, however, in previous studies it was described as 5% [8]. The time of onset ranges from several months to years after initiation of treatment and varies among cases.

Amiodarone appears to accumulate in adipose tissue and in highly perfused organs and usually has a higher absorption rate in lungs than heart [9]. Its half-life is long and with chronic oral dosing it can be 30–108 days but is subject to interpatient variation. The apparent volume distribution is about 5, 000 liters [10]. Its active metabolite is desethylamiodarone which tends to accumulate in lung tissues five times more than the original drug and provides a continuous release with variable serum levels [9]. Among the risk factors, age and duration of treatment are considered the most important risk factors of APT [11]. The patients taking doses of 400 mg daily for more than two months or 200 mg daily for two years are at much higher risk of developing APT [4]. Other risk factors include male gender, history of cardiothoracic surgery, previous airways disease, exposure to high levels of supplemental oxygen and iodinated contrast [3, 4]. Previous cardiac surgery, pulmonary hypertension and relatively longer duration of treatment put our patient in high risk category.

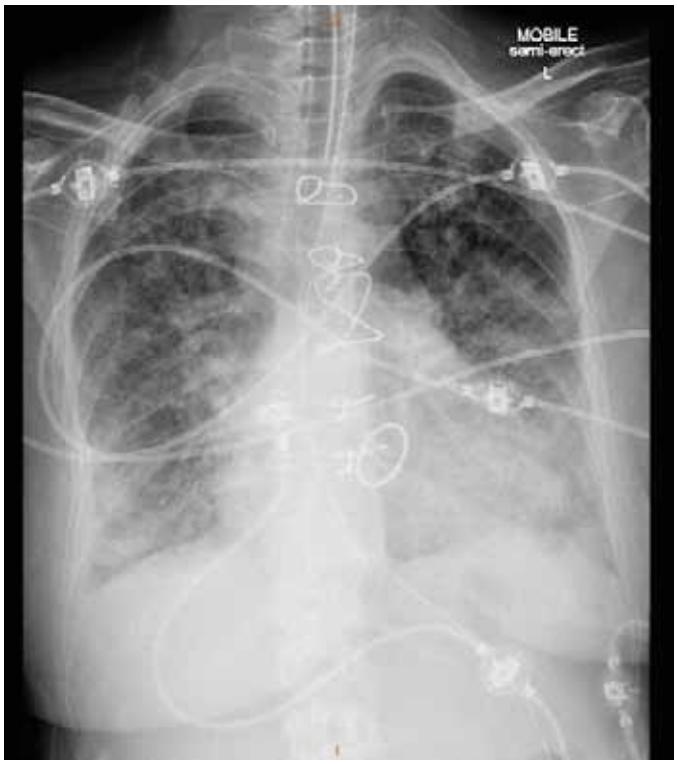

Figure 3: Chest X- ray after brief response to steroids therapy.

The mechanism of APT involves the direct toxic effects to lung tissues and immunologic reactions [12] leading to non-specific diffuse interstitial pneumonitis. Direct toxic effects include the accumulation of phospholipids due to less degradation and the generation of drug-mediated oxidants. The immunological reaction was found to be mediated by CD8 positive T-lymphocytes. These mechanisms lead to severe pulmonary fibrosis and explain the sudden onset and rapid progression of the disease after relatively smaller doses of amiodarone [12].

Patients may initially present with progressive and nonspecific symptoms such as generalized weakness, fever, cough, breathlessness, weight loss, pleuritic chest pain, and pleural effusion. However, these symptoms can be obscured by pre-existent heart failure or lungs disease [3]. Severe cases can present as ARDS.

As there are no confirmatory tests available [13], the diagnosis of APT is often of exclusion. It is based on history, clinical examination, radiographic features and exclusion of alternative causes of respiratory distress. Early radiographic features include localized or diffuse interstitial infiltrates or alveolar ground-glass appearances [2, 4]. Despite having ability to assess increased lung density, CT scan cannot exclude the normal drug accumulation in lung parenchyma [14]. Pulmonary function tests typically show a restrictive pattern with a decreased diffusion lung capacity of 15-20% but a mixed pattern can also be seen [15]. A decrease in the diffusion capacity for carbon monoxide is seen at the early stage of the disease [3]. Lung scintigraphy can help to distinguish any associated heart failure [13]. BAL may reveal a rise in polymorphonuclear leukocytes and CD8+ T cells indicating an inflammatory or immune reaction. The presence of foamy macrophages is in favor with the diagnosis but it is not a pathognomonic sign as these cells can also be seen in up to fifty percent of nontoxic patients [16]. If the diagnosis is uncertain, an open lung biopsy may be required. However, this should be avoided due to the risk of clinical deterioration after thoracic surgery.

In a study on 46 patients, it was found that severity of APT is proportional to the degree and rapidity of onset of lung injury. Those who survived improved slowly but with persistent progression [17].

The mainstay treatment is the discontinuation of amiodarone immediately. Due to its accumulation in fatty

tissues and long elimination half-life, pulmonary toxicity may initially progress despite drug discontinuation. Although systemic corticosteroids are also recommended for treatment, more well-controlled studies are required to demonstrate its efficacy. Prednisone should be initiated at 40 mg to 60 mg daily and tapered slowly over four to twelve months as early steroid withdrawal can cause relapse [18]. Obese patients with excess adipose tissue are more susceptible to recurrences with steroid tapering due to high lipophilicity of the drug [18].

No preventive measures have been described so far to prevent APT. However, identifying the smallest dose possible is considered an effective strategy. In an animal study, it was seen that vitamin E reduced the extent of lung injury after amiodarone administration [19]. However, more work needs to be done to find its role in prevention of APT.

There are several safe dosage regimens described. The recommended maintenance doses of amiodarone are 100–400 mg/day after initial doses of 600 mg/day over one month or 1000 mg/day for 1 week [20]. Other recommendations include 800–1200 mg/day for 1–3 weeks, reducing to 400 mg/day for further 2–3 months and maintaining therapy with up to 300 mg/day [21]. Maintenance doses are limited to 200–400 mg/d [22].

CONCLUSION

The incidence of amiodarone pulmonary toxicity (APT) has decreased in recent days with the use of lowest effective doses. However, due to increase usage of amiodarone and its fatal outcome, a strong clinical suspicion should be emphasized particularly in high risk groups. Amiodarone pulmonary toxicity occurs dose dependently, but low dosages have also been reported with severe lung injury after initiation of therapy. Clinical manifestations of pulmonary toxicity may be subtle, severe or life-threatening. Conscientious follow-up is required to identify the development of APT earlier and reduce its severity. The prognosis is favorable when diagnosed at early stage. Before starting amiodarone, patients should be educated about the potential adverse effects of the drug and asked to present early if they develop any new respiratory symptoms.

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Author Contributions

Muhammad Imran Butt – Substantial contributions to conception and study design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Muhammad Asif Shahzad – Acquisition of data, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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