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Patient chest computed tomography showing collapsed left lung apex with hydropneumothorax, entirely consolidated left lung with an anterior cavity. Right and left posterior lower lobes show fibrotic interstitial changes along with honeycombing.

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A novel approach of human embryonic stem cells therapy in treatment of Friedreich’s ataxia

Geeta Shroff

ABSTRACT

Introduction: Friedreich’s ataxia (FRDA) is an autosomal recessive inherited disease that damages nervous system and impairs muscle coordination. FRDA usually begins in childhood and is caused by expanded GAA triplet repeat within the first intron of the frataxin (FXN) gene leading to reduced level of mitochondrial protein frataxin. There is no effective treatment for FRDA. If stem cells are transplanted near the affected cells under oxidative stress in FRDA patients, they can produce tropic factors, thereby increasing the survival of the cells. In FRDA, the mechanism to remove the reactive oxygen species (ROS) is impaired leading to oxidative stress and cell death. Stem cells may have ability to protect cells susceptible to oxidative stress that occurs in FRDA. In our previous studies we have shown the improvement in the patients’ condition who were suffering from cerebral palsy and cortical visual impairment after human embryonic stem cells (hESCs) therapy. Case Series: Herein, I report three cases of FRDA patients who were treated with hESCs therapy. All the patients were suffering from problems like difficulty in walking, standing or climbing stairs and muscle weakness. After undergoing hESCs therapy, improvement in condition of all the patients was observed.

Conclusion: The hESCs therapy was effective in treating patients with FRDA. Further research is required to understand the mechanism of action of hESCs.

Keywords: Friedreich’s ataxia, GAA triplet repeat human embryonic stem cells, Neurodegenerative diseases

INTRODUCTION

An autosomal recessive inherited disease Friedreich’s ataxia (FRDA) is the most common form of hereditary ataxia that damages nervous system and impairs muscle coordination (ataxia). FRDA usually begins in childhood and is characterized by movement problems such as gait ataxia, or walking difficulty that worsens over time. FRDA is a rare disorder [1] caused by expanded GAA triplet repeat within the first intron of the frataxin (FXN) gene leading to reduced level of frataxin, a mitochondrial protein. [2, 3] FXN protein is involved in regulation of iron homeostasis, biosynthesis of iron-sulfur clusters, energy conversion and stimulation of oxidative phosphorylation. FXN prevents highly redox-reactive metal from generating oxidative stress [4–6]. Lack of FXN causes iron overloading and increase free-radical production [7] that triggers a series of metabolic derangements [4]. The underlying molecular mechanisms for instability in GAA repeat are currently unknown [8].
There is no effective treatment for FRDA [1]. Only few treatments with free-radical scavengers or antioxidants are available that counteract oxidative stress in FRDA. But there is no proof of the positive results in the neurological aspects of the disorder. Thus, alternative approaches must be developed to treat FRDA [9]. Human embryonic stem cells (hESCs) have unlimited proliferative capacity and potential to differentiate into all types of somatic cells [10, 11]. According to Jones et al., if stem cells are transplanted near the affected cells that are under oxidative stress, they can produce trophic factors, thereby increasing the survival of the cells in FRDA patients [9].

In our previous studies we have shown the improvement in patient’s condition who were suffering from cerebral palsy and cortical visual impairment after hESCs therapy [12, 13]. Herein, I report three cases of FRDA patients who were treated with hESCs therapy. Two of these patients (Case I and II) were siblings.

In this study, animal free and chromosomally stable hESCs (NTECH 2000n/n) were used. The cell lines are cultured and maintained as per our proprietary in-house patented technology in a GMP (Good manufacturing practices), GLP (Good Laboratory Practice) and GTP (Good Tissue Practices) certified Nutech Mediworld laboratory (Patent-WO 2007/141657A PCT/1B 2007 Published 13 December 2007). The evidence for the use of hESCs at Nutech Mediworld has been submitted and accepted at House of Lords, Regenerative Medicine, Science and Technology Committee [8].

Prior to start of the treatment all three patients provided a written informed consent. A thorough examination of the patients was done by the doctors and the rehabilitation team during the treatment. Video recordings were also made. The treatment consisted of three phases in which 0.25 mL hESCs were administered through intramuscular route twice daily and 1 mL of hESCs were administered through intravenous route twice every 7th day for 12 weeks initially and then four times over a period of 18 months (including gap phases). After the treatment, overall stamina, strength in upper limbs was increased and could do static cycling more effectively. The exercise endurance during physiotherapy improved. She could stand and walk more confidently without the fear of falling down. She could perceive fullness of urinary bladder and her bladder control was improved. She could stand and walk more confidently without the fear of falling down. She could perceive fullness of urinary bladder and her bladder control was improved. Her exercise endurance during physiotherapy increased and could do static cycling more effectively.

The details of the treatment have been elaborated elsewhere [12].

CASE SERIES

Case 1 and Case 2: A 25-year-old female (Case 1) and a 28-year-old male (Case 2) were admitted at Nutech Mediworld on July 2011 with chief complaints of difficulty in walking, standing, and climbing stairs, weakness in lower limbs and slowness of speech. They both were siblings. There was a history of five siblings death. They were born of a consanguineous marriage and father was diabetic. Both patients were born normal with a normal birth weight.

Case 1: Patient was well till 16 years of age, when she developed weakness of lower limbs which gradually increased with time. Her central nervous system (CNS) coordination was affected. The flaccidity in the upper limb was absent. She was wheelchair bound and needed help for her daily activities.

Case 2: Patient was apparently well until 12 years of age when he developed progressive weakness in all limbs and trunk with frequent falls. The weakness in lower limbs, difficulty in walking and climbing stairs deteriorated gradually with time followed by generalized weakness of body. He was bound to wheelchair for last eight years. There was atrophy of upper limb and weakness of hand muscles. The speech was affected from last two years. He also had complaints of edema in right foot.

At our facility, both were given hESCs therapy as a primary treatment.

In Case 1, after the first treatment, overall stamina, lower limb strength and knee flexion was improved. She could stand without support for 20 seconds and stand and walk with the help of a stick.

After a gap of 45 days, patient was admitted second time with the complaints of weakness in lower limbs and sustained burns in legs while taking shower. On examination, difficulty in initiating knee flexion in prone position was observed, but she could stand without support or with help of stick for few seconds. Again treatment was given. After the treatment balance was improved and she was able to walk faster.

A gap of three months was given. She was again admitted for third time with complaints of tiredness after walking 5–10 steps, decrease control of urination especially in morning with no bladder filling sensation and generalized weakness. She could not walk or stand without support. Human embryonic stem cells treatment was given again. After the treatment, she could walk 10–20 steps without support, strength in lower limbs was increased and bladder filled sensation was improved.

At fourth visit, the patient presented with complaints of generalized weakness of whole body, balancing issues while walking, and difficulty in bending both knees. After the treatment, the patient reported further improvement in her condition. Her lower limb muscle strength was improved. She could stand and walk more confidently without the fear of falling down. She could perceive fullness of urinary bladder and her bladder control was improved. Her exercise endurance during physiotherapy increased and could do static cycling more effectively.

The status of the patient before and after hESC therapy at visit 2, 3 and 4 is given in Table 1.

In Case 2, electrophysiology studies showed that lower limb was suggestive of severe motor sensory asymmetric peripheral neuropathy. After clinical examination, a brisk knee jerk, absence of ankle reflexes, pitting pedal edema, fasciculation in tongue, bilateral hypothenar wasting and dyssidiadochokinesia was reported. Examination details of CNS and motor system is given in Table 2.

The patient was given hESC therapy as a primary treatment four times over a period of 18 months (including gap phases). After the treatment, overall stamina and endurance was better, strength in upper limbs was
increased, he could flex his knees, and toes, walk in walkers with calipers, spasticity in legs was reduced and sitting balance was also improved. After 45 days, on visit 1, he was admitted with chief complains of weakness of limbs. hESC therapy was given again to this patient. The status of the patient before and after hESC therapy at visit 2, 3 is given in Table 1. At the end of the treatment, overall stamina and coordination was improved. The strength in limbs, trunk control, waking gait with walker, sitting, standing and walking with support was improved.

**Case 3:** A 35-year-old male was admitted at Nutech Mediworld on February 2006 with chief complaints of

<table>
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<th>After treatment</th>
<th>Case 2</th>
<th>Before treatment</th>
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<tr>
<td>Visit 2 (After 45 days)</td>
<td></td>
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<tr>
<td>Walking with help of crutches</td>
<td>Walk better and faster</td>
<td>Weakness of limbs (LL&gt;UL), coordination difficulties in upper limb</td>
<td>Improved strength in limbs</td>
<td></td>
<td></td>
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<tr>
<td>Weakness in lower limbs (left&gt;right)</td>
<td>Balance was improved</td>
<td>Difficulty in standing, walking and climbing stairs</td>
<td>Better trunk control and coordination, abdominal muscle strength increased</td>
<td></td>
<td></td>
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<tr>
<td>Visit 3 (After 3 months)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Tiredness after walking 5-10 steps</td>
<td>Can walk 10-20 steps</td>
<td>Cannot walk</td>
<td>Standing up from sitting position and walking with support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannot walk without support</td>
<td>Walk without support</td>
<td>In coordinative upper limbs</td>
<td>Coordination of upper limbs improved</td>
<td></td>
<td></td>
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<tr>
<td>Decrease control of urination, no bladder filling sensation</td>
<td>Achieved bladder control and felt bladder filling</td>
<td>Speech slurred</td>
<td>Dysarthria reduced</td>
<td></td>
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<tr>
<td>Generalized weakness</td>
<td>Lower limb strength increased</td>
<td></td>
<td></td>
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<td>Visit 4 (After 8 months)</td>
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<td></td>
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<tr>
<td>Weakness in both lower limbs</td>
<td>Lower limb strength improved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walked with stick and had balancing issues</td>
<td>Stand and walked more confidently</td>
<td></td>
<td></td>
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**Table 2: Examination of Motor system**

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<th>Lower limb</th>
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<tr>
<td>Tone</td>
<td>I</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Average</td>
<td>Decreased</td>
</tr>
<tr>
<td>Power</td>
<td>I</td>
<td>4/5</td>
<td>2/5</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>Spasticity</td>
<td>I</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Absent</td>
<td>Present</td>
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progressive weakness of the body over the last 20 years. The patient had a history of choking sensation with liquids and cardiomyopathy (left ventricular ejection fraction, LVEF- 15–20%) for which he was taking medicines. His elder sister had same disorder and she died due to heart failure in 2004. The patient was not able to stand, walk or sit. He used wheelchair and was unable to do his day to day activities. He managed to have food and dress by himself. His coordination and balance was lost and had slurred speech and hearing loss. A mild difficulty in swallowing with aspiration of liquids infrequently was also reported. The patient was given hESCs therapy as a primary treatment. The examination details of patient’s central nervous system and motor system is given in Table 2. After the treatment, spine curvature was improved, neck was more erect, leg movement was significantly increased, lower limbs spasticity was reduced and endurance was better. The patient was able to walk 5–7 steps forward and backward with full calipers.

DISCUSSION

In this study I observed that hESCs therapy was effective in treating patients with FRDA. Insufficiency of the protein frataxin in FRDA patients leads to spinocerebellar neurodegeneration along with associated movement disorders. FRDA patient also have increased risk of diabetes and cardiomyopathy, which are the leading cause of death [14]. In this cases, I observed that the patients were suffering from various problems like difficulty in walking, standing or climbing stairs and muscle weakness. After undergoing hESCs therapy, a marked improvement in the condition of all patients was noticed. At the end of the treatment, endurance of all patients was increased. They were able to stand and walk confidently. Other changes includes improved urinary bladder control in Case I, improved overall stamina and coordination in Case II and improved spine curvature in Case III. Our finding that the hESCs are capable of treating FRDA is supported by our previous studies, where hESCs have successfully treated the patients with cerebral palsy [12]. Human embryonic stem cells might have the potential to treat patients with neurodegenerative diseases such as cerebral palsy, Friedreich’s ataxia, etc.

Currently, there is no cure for FRDA. However, associated symptoms and complications can be treated [1]. Neurons and cardiomyocytes are the two affected cell types in FRDA [8]. As human stem cells have ability to migrate and home to the injury site [15], we could assume that hESCs might have also migrated to the affected brain and differentiated into neurons and cardiomyocytes. The size of the hESCs used in our study was < 1 µm, so it can be assumed that hESCs have permeated through the parenchyma via blood brain barrier. Though neurodegenerative diseases like Parkinson’s disease, multiple sclerosis, multiple system atrophy, Alzheimer disease, FRDA and Huntington’s disease have different etiology, but all these disease share a common trait involving mitochondrial dysfunction that lead to iron accumulation and ultimately cell death [2, 16, 17]. Several studies have shown the clinical benefits of hESCs in treating neurodegenerative diseases such as Parkinson’s disease and multiple sclerosis [18–20]. In current cases, I expect that hESCs have similar clinical benefits in reducing the clinical symptoms associated with FRDA.

An efficient antioxidant system in our body removes the oxidative stress. In FA, the mechanism to remove the reactive oxygen species (ROS) is impaired leading to oxidative stress and cell death [7, 9]. Stem cells may have ability to protect cells susceptible to oxidative stress that occurs in many neurodegenerative diseases like FRDA [9]. Jones et al. cultured FRDA cells undergoing oxidative stress in healthy human adipose stem cell conditioned medium. Increased cell survival and frataxin expression and, unregulated oxidative-stress-related genes were observed. This result was due the presence of trophic factors such brain-derived neurotrophic factor (BDNF) expressed by the adipose stem cells in the conditioned medium [21]. Jones et al. in their another study isolated mouse bone marrow mesenchymal stem cell-conditioned medium and cultured dorsal root ganglia neurons isolated from an FRDA mouse model. The results showed that the conditioned medium increased the neurons cell survival, decreased apoptosis when exposed to oxidative stress. The transcription of certain oxidative stress-related genes was also activated. Thus, autologous stem cells transplantation in FRDA patients may protect the affected neurons [9]. Stem cells such as mesenchymal stem cell, ESCs, induced pluripotent stem cells are capable of producing trophic factors [22]. So it is possible to consider that hESCs might have produced trophic factors at the affected part, thereby increasing the frataxin expression and preventing the cells degeneration. However, studies supporting this assumption are lacking. We can infer from our study that hESCs can lead to mild to moderate and short term improvement of few weeks in the patients with FRDA. In this study, the three patients did not come back on time after the therapy. FRDA is a progressive disease that requires regular injections of hESCs every three months in first year, every 4–8 months in second year and every 6–8 months in third years and thereafter yearly.

CONCLUSION

This case series provides a novel direction in which human embryonic stem cells (hESCs) therapy may be used in treatment of Friedreich’s ataxia (FRDA). I can postulate that hESCs have ability to modulate disease frequency and severity. I would continue to monitor the condition of the patients before retreatment is required. Further research is required to shed further light on
understanding the mechanism of action of hESCs.

LIST OF ABBREVIATIONS

FRDA- Friedreich’s ataxia  
FXN – frataxin  
ROS - Reactive oxygen species  
hESCs - Human embryonic stem cells  
CNS - Central nervous system  
LVEF - Left ventricular ejection fraction  
BDNF - Brain-derived neurotrophic factor  
GMP - Good manufacturing practices  
GLP - Good Laboratory Practice  
GTP - Good Tissue Practices

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Acute scrotum: A rare presentation

Jayalaxmi S. Aihole, Narendrababu M., Deepak J., Vinay Jadhav, Ramesh S.

ABSTRACT

Introduction: Amyand’s hernia (AH) is an inguinal hernia containing the appendix, which is normal or inflamed. This condition is extremely rare in children, especially in infants. This phenomenon was described in 1735, when Claudius Amyand performed a successful appendectomy on an 11-year-old boy who presented with an appendix in hernia sac; so, in his honor, his name was given to this type of hernia. It is seldom diagnosed preoperatively due to its unusual and infrequent clinical presentation; management involves herniotomy and appendicectomy if indicated.

Case Series: We are reporting two cases of AH, one in a four-year-old presented with partially reducible hernia; and another in a neonate who presented with acute epididymo-orchitis like picture.

Conclusion: Preoperative diagnosis of AH is rare but not very difficult with the current radiological investigations. Choice of the operation is appendectomy if appendix is inflamed, and hernitomy.

Keywords: Amyand's hernia, Inguinoscrotal swelling, Congenital inguinal hernia

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INTRODUCTION

Amyand’s hernia (AH) is an inguinal hernia containing the appendix. This condition is rare in children, especially in infants. Claudius Amyand, in 1735, performed appendectomy while doing herniotomy in an 11-year-old male child; and hence his name. Preoperative diagnosis is rare and management involves herniotomy and appendicectomy if indicated.

We are reporting two cases of AH, one in a four-year-old presented with partially reducible hernia; and another in a neonate who presented with acute epididymo-orchitis like picture.

On opening the hernia sac, appendix was revealed. Herniotomy and appendectomy was done.

CASE SERIES

Case 1: A four-year-old boy presented with inguinoscrotal swelling since one year. Pain was felt on and off recently with increase in its size since one week. Both testes were palpable separately. The swelling was partially reducible. Systemic examination was normal. Patient was electively posted for right herniotomy and on opening the sac, long tubular minimally inflamed appendix with hydrocele fluid was noted. Patient underwent appendectomy, herniotomy and Jaboulay’s
eversion of distal sac. Patient is doing well with two and a half years of follow-up.

**Case 2:** A 20-day, weighing 3.0 kg male neonates was brought to us with history of right scrotal swelling, excessive crying and fever of one day duration. His antenatal scans were normal and he was delivered at term by vaginal route. Clinical examination revealed reddish tender swelling of right scrotum with left scrotum with testis was normal. Abdominal examination was normal. The scrotal Doppler ultrasound revealed features of acute epididymo-orchitis with normal testicular blood flow and associated secondary hydrocele (Figure 1A–B). Hence the baby was managed expectantly with antibiotics and analgesics; complete resolution of the acute scrotum was noticed during follow up visit.

Two weeks later in the follow-up period the baby was brought with small painless, reducible inguinal swelling; clinical diagnosis of hernia was made and herniotomy was done. Intra-operatively appendix was noted in the hernia sac, its tip reaching the scrotum and had tell-tale evidence of past appendicular inflammation. Baby underwent appendectomy with herniotomy (Figure 2A–B) had uneventful postoperative period and doing well at first month follow-up visit.

**DISCUSSION**

Amyand’s hernia is an extremely rare condition. The rate of incidence is 0.1% of hernotomies. AH in less than one year old represent 2% of the total cases of appendicitis [1]. The pathophysiology of AH and its relationship with appendicitis are unknown [2, 3]. AH, is as rule, occurs in the right inguinal region. If left sided, it may be due to mobile cecum, malrotation, or situs inversus. The presence of a non-inflamed appendix in the inguinal hernia is three times more common in the children than in adults. This is due to persistent patency of the processus vaginalis in infancy and adulthood [2].

A congenital band extending from the appendix into the scrotum and attached to the right testis, and the funnel shaped tapering of the cecum in the neonate are two more possible pathogenetic factors [2].

Clinical presentation of an AH may be that of a normal, obstructed, or strangulated inguinal hernia, irrespective of whether the appendix is inflamed or not. Acute scrotum and abdominal pain are possible clinical presentations. Testicular torsion, especially when there is an undescended testis; inguinal lymphadenitis; epididymo orchitis and hydrocele of the spermatic cord are conditions that an AH may mimic.

The confirmatory diagnosis of an AH is made during surgical exploration of the groin, although radiological investigations like ultrasound, computed tomography will be helpful in few cases [1].

Even though appendectomy can be performed through an inguinal incision or with laparoscopy, many authors prefer to save the appendix when it is not inflamed, because of the importance of the lymphoid tissue in it, risk of wound infection and for its possible later use in urinary diversion, biliary tract reconstruction, and for antegrade bowel enemas [1]. Both of our patients had features of appendicitis and in the neonate the Amyand’s hernia with acute appendicitis presented as acute scrotum masquerading as epididymo-orchitis. Hence appendicectomy was done in both the patients and they had an uneventful postoperative course.

Neonatal appendicitis is extremely rare (0.1% of appendicitis cases in infancy, which constitutes 2% of pediatric appendicitis). Premature neonates accounts 50% of these cases, and only in one third of these, inflamed appendix lies within a hernia. This low frequency rate and the fact that only 20 of neonatal cases of AH have been reported in English publications render the cases of perforated appendix in premature neonates extremely rare [2].

Classification of AHS, after Losanoff and Bason, modified by Rikki as Rikkki’s classification of Ahs described in Table 1. Both of our cases belong to type 2 [4].
Literature suggests that majority will present in neonate, as obstructed or strangulated inguinal hernia and even with perforation with generalized peritonitis, systemic signs and symptoms of appendicitis are rarely evident. Our case presented like epididymo-orchitis like picture i.e. acute appendicitis [1,3].

Antonios Panagidis reported neonatal perforated AH presenting as an enterocutaneous scrotal fistula [2]. Kumar et al. reported neonatal pyocrotum and perforated appendicitis in 26 day old male baby with undescended testis, who was initially diagnosed to have testicular torsion [5].Luchman et al. reported a case of scrotal abscess following perforated appendicitis in six day old male neonate [6].

**CONCLUSION**

Amyand’s hernia (AH) is very rare and appendicitis in AH in neonates is extremely rare. Preoperative diagnosis is difficult unless presenting with appendicitis or its related complications. Herniotomy and appendicectomy, when indicated are recommended.

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A preterm very low birth weight male neonate with refractory hypoglycemia and hyperinsulinemia and hyperammonemia: A rare case report

Jillalla Narsing Rao, Swathi Chacham, Uppin Narayan Reddy, Janampally Ravikiran, Mohd Ahmeedulla Khan, Jakkampudi Nagasravani

ABSTRACT

Introduction: Hypoglycemia is an important metabolic complication in neonates, more so in newborns with perinatal risk factors. Physiological immaturity of gluconeogenesis, lipolysis coupled with hyperinsulinemia contributes to hypoglycemia in small for gestational age (SGA) neonates. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), a hyperinsulinemic condition is an important differential diagnosis for intractable and refractory hypoglycemia. Hyperinsulinemic-hyperammonemia (HI/HA) syndrome, a rare autosomal dominantly inherited disorder, is the second most common cause for hyperinsulinemic-hypoglycemia in infancy. Both symptomatic as well as asymptomatic hypoglycemia involves the occipital cortex leading to cortical blindness, necessitating early etiological diagnosis and prompt intervention. We report a preterm male neonate with rare manifestations of refractory hypoglycemia, hyperinsulinemia and hyperammonemia.

Case Report: A 30 weeks, 1300 grams male neonate, born by C-section had respiratory distress, requiring mechanical ventilation (MV) for 10 days. On 11th day of life, neonate developed recurrent apneic episodes along with jitteriness and seizures. Initial evaluation revealed low blood sugar levels which persisted despite high glucose infusion rate (GIR 12 mg/kg/min). There was hyperammonemia (serum NH3 levels 273 µg/dL) along with hyperinsulinemia. However, the serum cortisol, thyroid, growth hormone levels and blood lactate were normal. Similarly, metabolic screening for inborn errors of metabolism (IEM) was normal. Abdominal imaging with ultrasound and contrast-enhanced computed tomography (CT) scan did not reveal pancreatic hyperplasia. Persistent hypoglycemia, hyperinsulinemia along with hyperammonemia could suggest hyperammonemic hyperinsulinemic syndrome in this neonate. The infant responded to oral diazoxide. Conclusion: We report a preterm, very low birth weight (VLBW) male neonate with refractory hypoglycemia and hyperinsulinemia and hyperammonemia, which responded to diazoxide.

Keywords: Hyperammonemia, Hyperinsulinemic, Hypoglycemia, Persistent hyperinsulinemic hypoglycemia of infancy, Prematurity
INTRODUCTION

Hypoglycemia is one of the most common metabolic complication in neonates. Healthy as well as sick neonates are predisposed to hypoglycemia during the first week of life [1, 2]. Factors that further lead to hypoglycemia are prematurity, perinatal asphyxia, small for gestational age (SGA) and infant of diabetic mother (IDM). Insulin secretion depends upon the activity of potassium channels in pancreatic beta cells, which are influenced by fluctuations in blood glucose levels. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), a disorder of glucose metabolism is an important cause for refractory hypoglycemia in infants. It is characterized by inappropriate hyperinsulinemia and persistent hypoglycemia. Unregulated hyperinsulinemia despite hypoglycemia is a hallmark of PHHI [3], which usually manifests within the first three months of life. PHHI has both autosomal recessive inheritance (1:40,000–50,000 live births) and sporadic occurrence [3, 4]. McQuarrie first described PHHI [5, 6]. Hyperinsulinemic-hypoglycemia (HI/HA) syndrome, a rare disorder of Glutamate dehydrogenase mutation, leads to recurrent hyperinsulinemic-hypoglycemia and this has autosomal dominant mode of inheritance [7]. Early recognition and prompt intervention is crucial, as uncorrected hypoglycemia in neonatal period can lead to occipital cortical damage and subsequent cortical blindness.

CASE REPORT

A 1300 grams, 30 weeks, male neonate born by C-section, had normal extra-uterine transition (APGAR score: 6 and 7 @ 5 and 10 minutes), but developed respiratory distress soon after birth requiring mechanical ventilation (MV) for 10 days. Chest X-ray showed congenital pneumonia. On 11th day of life, the neonate had recurrent apneic episodes, jitteriness and seizures. On initial evaluation, blood sugar levels were low (20 mg/dL) and remained low despite high glucose infusion rate (GIR 12 mg/kg/min).

Hypoglycemia was attributed to prematurity, the very low birth weight (VLBW) status and sepsis. There was no facial dysmorphism, ambiguous genitalia or micropenis. However, the hypoglycemia persisted despite adequate antimicrobial coverage and the neonate was investigated for refractory hypoglycemia.

Important clinical conditions that lead to persistent hypoglycemia are congenital adrenal hyperplasia (CAH), hyperinsulinemic conditions (PHHI), inborn errors of metabolism (IEM) and pituitary insufficiency (genetic, metabolic, endocrinial). Hence, the neonate was evaluated for refractory hypoglycemia and these conditions. There was no hyponatremia, no hyperkalemia and 17 OHP levels were normal, thus ruling out congenital adrenal hyperplasia. Further evaluation showed normal serum cortisol (12.7 µg/dL), growth hormone (29.3 ng/mL) and thyroid profile ruling out adrenal insufficiency, hypopituitarism and hypothyroidism. Similarly, metabolic screening for IEM was normal. Paper chromatography of the urine in butanol acetic acid and water, showed normal excretory pattern. Ferric chloride test, 2,4-dinitrophenyl hydrazine test and nitroprusside screening for homocysteine test were negative. There was no metabolic acidosis in arterial blood gas analysis. There was hyperammononemia (serum NH levels 273 µg/dL (normal ammonia levels 40–80 µg/dL)) along with hyperinsulinemia. However, blood lactate levels were normal (lactate 14.4 mg/dL). Serum insulin levels during hypoglycemic episode were 0.7 milli units/L. Detectable insulin levels during hypoglycemic episode is an inappropriate insulin response, often seen in PHHI. Hence, abdominal imaging with ultrasound and contrast-enhanced CT scan was done to look for pancreatic hyperplasia and insulinomas. However, the imaging did not reveal pancreatic hyperplasia. However, micro insulinomas could not be ruled out in this case. Persistent hypoglycemia, hyperinsulinemia along with hyperammononemia could suggest hyperammononemic hyperinsulinemic syndrome in this neonate. Cranial ultrasound was done to screen for any intracranial pathology which was normal. The child was started on oral diazoxide, 10 mg/kg/day in three divided doses, in view of hyperinsulinemic hypoglycemia and the infant showed response within a week of initiating the therapy. Blood sugar levels were maintained well above 60 mg/dL. At sixth month, the infant was maintaining blood glucose levels on oral diazoxide. The infant required laser photocoagulation for retinopathy of prematurity at one month of life, but the brain stem evoked auditory potentials were normal at sixth month, indicating intact hearing mechanism. The patient was continuously followed-up for sixth months and had no major developmental abnormalities.

DISCUSSION

Hypoglycemia is one of the common neonatal complication in the first few days of life and is associated with long-term neuromorbidity [1, 2]. Small for gestation

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GLUD1 often results from glutamate dehydrogenase (GDH)
of PHHI (HI/HA) was considered. This HI/HA syndrome
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these were ruled out, the infant was further evaluated
and endocrinal causes like pituitary insufficiency. As
hyperplasia (CAH), inborn errors of metabolism (IEM)
birth weight status and sepsis were considered. Hence,
hyperplasia. This is often associated with absent ketone
production. As the index case had refractory, symptomatic
hyperammonemia syndrome (HI/HA), an IEM, described by Zammarchi et al. in 1996
is a form of PHHI [11]. PHHI can also be associated
with diffuse or focal adenomatoid pancreatic beta cell
hyperplasia. This is often associated with absent ketone
production. As the index case had refractory, symptomatic
hypoglycemia, causes other than prematurity, very low
birth weight status and sepsis were considered. Hence,
the neonate was investigated for congenital adrenal
hyperplasia (CAH), inborn errors of metabolism (IEM)
and endocrinal causes like pituitary insufficienty. As
these were ruled out, the infant was further evaluated
for PHHI, which revealed hyperinsulinemia along with
hyperammonemia. Hence, autosomal dominant variant
of PHHI (HI/HA) was considered. This HI/HA syndrome
often results from glutamate dehydrogenase (GDH)-
GLUD1 gene mutation [7, 12] and is associated with
persistently elevated serum ammonia levels (2–5 times
over normal limit). However, the hyperammonemia is not
associated with lethargy, irritability or altered sensorium,
as in the index neonate. The infant was treated with
oral diazoxide (10 mg/kg/day), as this is the treatment
choice for HI/HA syndrome. However, GLUD 1 gene
mutations could not be done due to financial constraints.
Though the effectiveness of diazoxide in neonatal period
is not optimum [13], the index infant showed response to
oral diazoxide and the glucose levels attained normally
within few days of therapy. As PHHI can also be
associated with diffuse or focal adenomatoid pancreatic
beta cell hyperplasia, the index neonate was subjected to
abdominal imaging with ultrasound and CT scan, which
did not reveal any pancreatic hyperplasia. Octreotide
scan, the definitive diagnostic tool was not feasible
due to financial limitations. Hypoglycemia, whether
symptomatic or asymptomatic leads to permanent brain
damage. Hence the aim of treatment is to maintain blood
sugar levels (above 60 mg/dL), irrespective of its etiology.
Therefore, the index infant was treated accordingly and
did not have major developmental abnormalities at sixth
month.

CONCLUSION
A preterm, 30 weeks, VLBW male neonate manifesting
with refractory hypoglycemia and inappropriately elevated
insulin levels, suggestive of persistent hyperinsulinemic
hypoglycemia of infancy (PHHI). Presence of
hyperammonemia along with hyperinsulinemia with
response to oral diazoxide therapy, could suggest a rare
entity of hyperinsulinemic-hyperammonemia (HI/HA).

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(SGA) premature neonates, infants born to diabetic
mothers and those with perinatal asphyxia are at further
risk for neonatal hypoglycemia. Index case had these
known risk factors like prematurity, SGA status although
there was no maternal diabetes. Glucose diffusion through
the placenta takes place along the concentration gradient,
resulting in 70–80% of glucose concentration in the fetus
when compared to the mother [8]. As insulin cannot cross
the placenta, the fetus secretes insulin independently [9].
When the umbilical cord is clamped, the glucose supply
to the neonate is stopped, but the insulin production
continues, leading to transient hyperinsulinemia coupled
with lower plasma glucose levels. This response results
in secretion of counter regulatory hormones (glucagon
and cortisol), which enhance glucose production by
glycogenolysis and gluconeogenesis [9]. As an adaptation
to persistent hypoglycemia, the brain utilizes alternate
substance like ketones.

Persistent hyperinsulinism, also known as persistent
hyperinsulinemic hypoglycemia of infancy (PHHI),
often manifests during first three months of life and is
associated with inappropriately high insulin levels for the
degree of hypoglycemia. It results from genetic defects in
insulin production and pancreatic beta cell dysfunction
[7, 10]. Plasma membrane sulfonylurea receptor
(SUR1) and potassium channel (Kir6.2) mutations are
autosomal recessively inherited [3] while glucokinase
gene mutations have autosomal dominant inheritance.

The hyperinsulinism hyperammonemia syndrome (HI/HA),
a genetic disorder described by Zammarchi et al. in 1996
is a form of PHHI [11]. PHHI can also be associated
with diffuse or focal adenomatoid pancreatic beta cell
hyperplasia. This is often associated with absent ketone
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Symptomatic late onset hypocalcemia in a full term female neonate with vitamin D deficiency due to maternal hypovitaminosis D: A rare case report

Swathi Chacham, Janampally Ravikiran, Uppin Narayan Reddy, Jillalla Narsing Rao, Mahender Reddy, Imeduddin

ABSTRACT

Introduction: Neonatal hypocalcemia (NH) is a common metabolic complication in neonates, more so in premature and high risk neonates. It is classified as early and late neonatal hypocalcemia. Early NH occurs in the first 24–48 hours of life while the late NH is observed at the end of the first week. Vitamin D deficiency is an important cause for hypocalcemic seizures in neonates, in developing countries. High rate of skeletal growth coupled with low vitamin D stores and maternal vitamin D deficiency makes them vulnerable to vitamin D deficiency. Case Report: A 2600 grams, term female neonate was born to a gravid 3 mother by C-section and had normal extra-uterine transition (APGAR score: 8&9 at 5 and 10 minutes of life). On eighth day of life, the neonate had multifocal clonic seizures with normal sensorium in between. No maternal risk factors were identified. There was no fever, lethargy, poor feeding, and clinical findings were unremarkable in the neonate. There was family history of neonatal seizures. Initial blood sugar and magnesium were normal. However, serum calcium levels were low (total 5.9 mg/dL, ionized 0.9 mg/dL) along with low phosphorous levels (1.7 mg/dL). Sepsis screen was negative, blood culture was sterile and cerebro spinal fluid analysis was normal. Similarly, neurosonogram, electroencephalogram, serum ammonia and lactate were normal, suggesting late onset hypocalcemic seizures. Both the neonatal and maternal vitamin D1 and 25-OH vitamin D were low, confirming maternal vitamin D deficiency causing neonatal vitamin D deficiency. The neonate responded to calcium and vitamin D supplementation with normal serum calcium levels in follow-up. Conclusion: We report a term, female neonate with late onset hypocalcemic seizures and vitamin D deficiency, due to maternal vitamin D deficiency.

Keywords: Neonatal hypocalcemia, Vitamin D deficiency, Seizures, Neonate

How to cite this article

INTRODUCTION

Neonatal hypocalcemia (NH), a commonly reported metabolic abnormality. Ionized calcium is vital for various metabolic pathways like blood. Coagulation, neuronal depolarization, integrity of cell membrane and plays a crucial role in enzyme catalysis. Major part of the body calcium exists in bones and muscles (99%) and the rest of the calcium is present in extracellular fluid (1%). Around 40% of the calcium in the extracellular fluid is bound to albumin, 10% is bound to citrate, phosphorus, lactate and sulfate and the rest (50%) exists as free ionized form, aiding in metabolic functions [1, 2]. Hypocalcemia is defined as total serum calcium of <8 mg/dL (2 mmol/L) or ionized calcium of <1.2 mmol/L in term neonates and <7 mg/dL (1.75 mmol/L) of total calcium or <4 mg/dL (1 mmol/L) of ionized calcium in preterm infants [3]. Neonatal hypocalcemia is classified into early and late based on the time of presentation [1]. The early NH usually manifests within 72 h, requiring short term calcium supplementation. While, the late NH occurs after 1st week of life and requires long-term calcium therapy [4–6]. There is a physiological nadir in serum calcium levels at 24–48 hours of life in healthy term neonates, which can reach hypocalcemic levels in neonates with perinatal risk factors like maternal diabetes, prematurity and perinatal asphyxia [1, 4–7], leading to early NH. Late NH usually results from either increased phosphate load (due to cow milk or renal insufficiency), hypomagnesemia, maternal vitamin D deficiency leading to neonatal vitamin D deficiency and hypoparathyroidism [1]. Breastfed infants born to and nursed by vitamin D deficient mothers usually have low serum 25(OH) D levels.

CASE REPORT

A 2600 grams full term female neonate presented with multifocal clonic seizures on eighth day of life. The neonate had normal sensorium in between. Seizures were not associated with fever, lethargy or feeding abnormalities and the clinical examination did not reveal any dysmorphic facies. Also, other clinical findings were unremarkable. This was born of a non-consanguineous marriage, to a gravid 3 mother by C-section and had normal extra uterine transition. There is no history of maternal diabetes, pregnancy induced hypertension, epilepsy and drug intake. Maternal hypothyroidism was present, which was controlled with thyroid replacement therapy. Family history of neonatal seizures, developmental delay and renal malformation was present in the elder male sibling, who died in infancy. Hence, in this neonate seizures were attributed to metabolic causes and the neonate was investigated. Initial blood sugar and magnesium were normal. However, the serum calcium levels were low (total 5.9 mg/dL, ionized 0.9 mg/dL) along with low phosphorous levels (1.7 mg/dL). Sepsis screen was negative, blood culture was sterile and the cerebrospinal fluid (CSF) analysis was normal, ruling out meningitis as the cause for seizures. Similarly, the neurosonogram, electroencephalogram (EEG), serum ammonia and lactate levels were normal, ruling out inborn errors of metabolism. There was no metabolic acidosis in the arterial blood gas analysis and the abdominal ultrasonography showed normal kidneys. Hence the seizures in this case were attributed to late onset hypocalcemia and the neonate was further investigated for hypoparathyroidism and vitamin D deficiency. Chest X-ray showed normal thymic shadow, ruling out the possibility of congenital hypoplasia of parathyroid glands. Serum parathyroid hormone and thyroid profile was normal. However, vitamin D levels were low (7.9 ng/mL) and 25 OH vitamin D levels were also low 23.30 ng/mL (normal range 30 to 74 ng/mL). The neonate’s thyroid profile was normal. The cause for vitamin D deficiency was attributed to maternal vitamin D deficiency and the level of mother’s vitamin D were done, which were found to be low. Thus, the diagnosis of maternal vitamin D deficiency, resulting in neonatal hypovitaminosis D and symptomatic late onset neonatal hypocalcemia was confirmed. The neonate was treated symptomatically and responded to calcium supplementation (100 mg/kg/day) along with vitamin D supplementation (1000 IU/ day) with normalization of serum calcium and vitamin D levels in follow-up at four weeks. The supplements were continued till six months of age and the infant was, neurodevelopmentally, normal at sixth month.

DISCUSSION

Neonatal hypocalcemia (NH) is a common metabolic event in the neonatal period, while early onset NH is a frequent manifestations in high risk neonates, late onset NH is rare. Incidence of late onset hypocalcemia in breastfed neonates is 1/10000 while, that in formula fed infants is 30/10000 [8]. Resistant or prolonged hypocalcemia is defined as symptomatic hypocalcemia not responding to appropriate doses of calcium supplementation, calcium requirement beyond 72 h of age in neonates and hypocalcemia manifesting beyond 1st week of life [1]. As the index infant had hypocalcemia beyond first week of life, it qualifies for resistant or prolonged hypocalcemia. Mostly prevalent causes of late onset NH include phosphate overload, hypoparathyroidism (transient or permanent), hypomagnesemia and vitamin D deficiency [1, 2]. Late onset NH is usually symptomatic and presents with tetany or seizures. The index neonate had severe hypocalcemia (total 5.9 mg/dL, ionized 0.9 mg/dL) manifesting with
seizures after first week of life and was investigated for neonatal seizures including the causes for late onset NH like hypomagnesemia, hypoparathyroidism and vitamin D deficiency. Evaluation for seizure zures revealed normal blood sugar levels, negative sepsis screen, sterile blood culture along with normal CSF analysis, ruling out hypoglycemia and meningitis. Normal neurosonogram, electrolyte panel (EEG), serum ammonia (39 µg/dL) and lactate (4.5 mg/dL) were normal, ruling out structural malformations and inborn errors of metabolism respectively. Further evaluation for late onset NH showed normal serum magnesium and parathormone (PTH) levels, ruling out the possibility of hypomagnesemia and hypoparathyroidism. Then the neonate was evaluated for vitamin D deficiency and both the serum vitamin D1 (7.9 ng/mL) and 25 OH vitamin D (23.30 ng/mL) were normal, confirming hypovitaminosis D. The most important causes of neonatal vitamin D deficiency include maternal vitamin D deficiency, renal insufficiency, malabsorption, and hepatobiliary disease. As the index neonate had normal renal function, liver function tests along with normal renal architecture and hepatobiliary tree in abdominal ultra sound, renal and hepatobiliary causes for hypovitaminosis D were ruled out. There were no features of malabsorption in the neonate. As mother’s vitamin D levels were low, maternal vitamin D deficiency was attributed to the neonatal hypovitaminosis D and symptomatic late onset neonatal hypocalcemia.

CONCLUSION

We report a term female neonate with symptomatic late onset neonatal hypocalcemia due to vitamin D deficiency and maternal hypovitaminosis D. There was clinical and biochemical response to calcium and vitamin D supplementation.

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Author Contributions

Swathi Chacham – 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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REFERENCES

Osteosarcoma of mandible: A case report

Gopal Chandra Halder, Santanu Patsa, Riteshkumar Baldevbhai Jadav, Jay Gopal Ray

ABSTRACT

Introduction: Osteosarcoma is common primary malignancy of bone that arises from the mesenchymal cells. It is commonly seen in younger patients having average age of 15 years. Generally, it involves long bones with fastest growth rate. The exact etiology for this tumor remains to be unknown but in some cases it runs in families. Osteosarcoma involving the jaw bones is relatively less frequently seen. Generally, osteosarcomas have diverse radiological and histopathological appearances. Case Report: A 31-year-old male presented with a small asymptomatic gingival growth in the lower right posterior region for a period of 20 days. The lesion extended both on the buccal and lingual aspect of 46 and 47 regions.

Conclusion: The subtle and asymptomatic clinical and radiological features of this type of lesion as seen in the present case may delay early diagnosis and poor treatment outcome. The purpose of this study was to report an osteosarcoma involving the lower jaw which presented as a soft tissue mass, mimicking an inflammatory gingival lesion.

Keywords: Asymptomatic osteosarcoma, Mandible, Orthopantomogram (OPG), Soft tissue

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INTRODUCTION

Osteosarcoma is the second most common primary bone tumor after multiple myeloma. The tumor usually arises from the metaphyseal growth plate of the long bones of the extremities of which 50% occur from the knee [1]. Osteosarcoma can be primary or secondary. Primary osteosarcoma can be classified into three subtypes: intramedullary, surface and extraskeletal [2]. Some histopathologists classified the tumor into the following types: osteoblastic, chondroblastic and fibroblastic depending on the amounts of osteoid, cartilage and collagen fibers presenting in the examined tissue section [3]. Occurrence of the tumor in the jaws is about 6–9% of the all osteosarcomas [4]. The incidence is slightly higher in blacks than in whites (Huvos et al. 1983). Male to female ratio is 1.5:1 and taller patients are more commonly affected in compared to normal of same age group [5]. Osteosarcoma is very rare in young children (<5 years). Primary osteosarcoma typically occurs in young patients (10–20 years) among which 75% occurs before the age of 20 years. The reason behind is that the growth centres of the bone are more active in puberty to adolescence time period [1]. Secondary osteosarcoma occurs in elderly patient, usually secondary to Paget's disease or post radiotherapy period. The mean age of mandibular osteosarcoma is 34–36 years and it is often considered as a distinct entity because of its predilection to older patients [1].
Jaw osteosarcoma is a rare and aggressive type of malignant tumor which is usually found in the third and fourth decades of life. Both jaws are involved with equal frequency without any gender predilection but in case of long bones, it has slightly higher frequency in male than in female [6]. It is frequently found at the posterior part of body and ramus of mandible. The maxillary tumours develop from the alveolar ridge, the sinus floor and palate. Pain and swelling are most common sign and symptom associated with looseness of teeth, lack of healing at the extracted site, hypoesthesia or paraesthesia in case of mandibular tumor [7, 8]. The biological behavior of the osteosarcoma in the long bones differ with the jaws osteosarcoma. There have been few reports of metastasis from jaw Osteosarcoma (1% of all malignancy) to a distant parts of body as compared to osteosarcoma of long bones which makes jaw osteosarcomas prognostically better [7, 9]. This case report emphasizes on the fact that asymptomatic lesions may occur in the jaws which can create diagnostic dilemma and delay early diagnosis.

Treatment of the jaws osteosarcoma is not well understood but in the case of long bones, it is well established. Disease free survival rate has been increased (from 20% in 1960s to 70% in 1980s) in the long bones osteosarcoma with the adjuvant of chemotherapy but it is not established in jaws osteosarcoma. Local recurrence is still a major cause of death in jaws osteosarcoma [8].

CASE REPORT

A 31-year-old male reported with a soft tissue swelling at right posterior lower molar regions for 20 days. Patient’s chief complaint was only swelling without any pain or discomfort, looseness of teeth, bleeding from the lesion or paresthesia of lips. Patient gave a history of extraction of the lower right second molar about 6–7 years back due to caries. The past medical history was not-significant. Extraoral examination did not reveal any facial asymmetry or palpable lymph nodes on either right or left submandibular and sublingual regions at the first reporting time in the outpatient department of Dr. R. Ahmed Dental College and Hospital. Intraoral examination revealed a diffuse erythematous soft 1.2x0.8 cm swelling in the 46 and 47 regions which appeared like a localized gingival granulation tissue mass. Surface epithelium was ulcerated occlusally and covered with slough. The presumptive diagnosis was an inflammatory gingival lesion on the basis of clinical findings. Orthopantomogram showed a well circumscribed approximately 0.5x0.5 cm diameter radiolucent area at the distal root apex of 46 without any root resorption (Figure 1). Distal root surface of 46 and mesial root surface of 48 showed widening of periodontal ligament space (Figure 1). A routine hemogram was advised. After obtaining written consent from the patient and his relative, incisional biopsy procedure was performed from the site of lesion under local anesthesia in the department of oral pathology. The tissue was preserved in 10% neutral buffered formalin and sent to the histopathology laboratory of Dr. R. Ahmed Dental College and Hospital, Kolkata for further processing. The tissue was embedded in paraffin wax after fixation and processing to prepare the wax block. Three serial sections from the wax block were made with the hand operated microtome (Leica Model No.RM2125RTS) in 4 µm thickness. The lesion kept on growing very fast in size (Figure 2).

Histopathological examination of the H&E stained sections revealed a parakeratinized stratified squamous epithelium with elongated rete ridges along with the fibrocellular connective tissue. The deeper part of sections showed round to spindle-shaped pleomorphic cells with hyperchromatic and bizarre nuclei which were arranged in an irregular pattern (Figure 3). Some parts of the sections revealed atypical eosinophilic osteoid cells (Figure 3). In addition to osteoid, the tumor cells produced chondroid material and fibrous connective tissue (Figure 4 and Figure 5). Histopathological features were suggestive of osteoblastic osteosarcoma. After final diagnosis, the patient was referred to the Chittaranjan Cancer Hospital, Kolkata, West Bengal. Patient was advised for computed tomography (CT) scan of the head and neck, chest and abdomen to exclude secondary metastasis. Image analysis revealed no secondary metastatic lesions. However, images and other reports of these investigations were not shared with us due to hospital rules. The lesion kept on growing very fast in size (Figure 2). Radical hemimandibulectomy followed by chemotherapy was done (Figure 6). In the regimen of chemotherapy patient was given doxorubicin (25 mg/m²) by intravenous route on first, second and third days with Cisplatin only on first day (100 mg/m²). Cycle was repeated after 21 days interval and six such cycles were given.

DISCUSSION

Primary osteosarcoma in jaws is a rare lesion. Early metastasis of osteosarcoma in lung is common but metastasis to jaw bones is extremely rare, accounting

Figure 1: Orthopantomogram showing 0.5x0.5 cm radiolucent area at root apex of mandibular right first molar.
for 1% of all malignancy [3]. Histopathologically, osteosarcoma is categorized into three subtypes—osteoblastic, chondroblastic and fibroblastic among which osteoblastic subtype is found in 60% of cases [4]. The classification was made depending on the relative amount of osteoid, cartilage, or collagen fibers production by the tumor cells. Sometimes, histopathological differentiation of osteosarcoma from malignant histiocytomas may be difficult [10]. Osteosarcoma predominantly occurs in rapidly growing bones [1]. Some chemical agents such as methylcholonthrene and chromium salt are linked to osteosarcoma [11]. The p53 and retinoblastoma (Rb) genes are well known as a tumor suppressor genes. This genes may become mutated, resulting in loss of normal protective function of body against a developing tumor. Mutations in both p53 and Rb genes have been found in the pathogenesis of osteosarcoma [12]. The p53 gene is mutated in 50% of all cancers and 22% of osteosarcoma [13]. Microscopic spreading of osteosarcoma is facilitated through narrow space. An intra-osseous lesion can spread to the adjacent tissue through periodontal ligaments, inferior alveolar canal, mental canal or through recently extracted tooth socket. It is often difficult to diagnose the lesion early due to its variable clinical and radiological features. Histopathological examination is the gold standard for final diagnosis. Immunohistochemical analysis was not done in this case. Literatures revealed that tumor cells showed positive staining for CD99, MIB-1 and S-100 and negative for AE1, AE3 and SMA [6]. Asymptomatic nature as seen in this case may delay histopathological examination. This case report can help to throw light on such lesions.

Osteosarcoma of jaw is an aggressive neoplasm with high rate of mortality despite a relatively low risk of distant metastases [14]. Early diagnosis and radical surgery followed by radiotherapy and/or chemotherapy have been found to result in good prognosis. Local recurrence after surgery is a major problem. Uncontrolled growth of
Jaw osteosarcoma is a major cause of death for patients than are the effect of distant metastases. Most common sites of metastases are lungs and brain. Metastases is not frequent from mandibular lesion with respect to maxilla but local recurrence is more frequent in maxillary region due to its anatomical closeness to other bones. In this case, distant metastasis was not found prior to surgery. Patient also withstood the complete course of chemotherapy and is still in good health.

CONCLUSION

A dental surgeon is in a unique position to diagnose very early oral mucosal changes associated with such aggressive lesions since intraoral examination is a consistent part of dental treatment procedures. Early diagnosis of an asymptomatic lesion is quite difficult due to the consciousness of patients. Such asymptomatic early lesions must be kept in mind during intraoral examination. This article may help to the dental professionals during the intra oral examination which may guide them to diagnose the lesion at an early stage, result in better prognosis.

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Author Contributions

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Atypical presentation of Rocky Mountain spotted fever in a young adult: A case report

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ABSTRACT

Introduction: Rocky Mountain spotted fever (RMSF) is a tick-borne disease that can be potentially lethal if left untreated. Its causative agent Rickettsia rickettsii is a gram negative intracellular bacterium that is known to have a tropism for vascular endothelial cells. Classic symptoms of RMSF include fever; which is almost always present, headaches and rash. However, all of these diagnostic clues may not be present which can lead to delay in diagnosis and appropriate antibiotic therapy leading to poor outcomes in certain cases. RMSF rarely may involve the myocardium but solely presenting with cardiac signs and symptoms without any of the typical features-fever, rash or headaches at any point is even rarer and may pose a diagnostic challenge. Case Report: We report a case of an atypical presentation of Rocky Mountain spotted fever in a healthy 20-year-old male. This report describes a case of a serologically proven RMSF infection in a patient who presented with chest pain, electrocardiographic changes and elevation of cardiac enzymes without any fever, rash or headaches. Conclusion: Rocky Mountain spotted fever can present solely with cardiac manifestations such as chest pain, electrocardiographic changes and elevation of cardiac markers without any of the typical features of Rocky Mountain spotted fever including fever.

Keywords: Chest pain, Myocarditis, Rickettsia rickettsii, Rocky mountain spotted fever

INTRODUCTION

Rocky Mountain spotted fever (RMSF) is a Rickettsial infection that has the potential of affecting any organ system in the human body. The center for disease control reports that there are five states in the United States including Missouri, Tennessee, Oklahoma, Arkansas and North Carolina that are notorious for having RMSF although it has been reported in other states [1]. When it comes to seasonality, RMSF is known to occur mostly during the summer but can also occur during any month of the year. The gram negative organism infects endothelial cells giving it the ability to affect any organ in the body and this can lead to multisystem failure. Myocarditis secondary to RMSF is an uncommon complication of the disease. The most common symptom of RMSF include headaches, rash and fever which is almost always present at some point during the course of the infection [2].
Although there have been few number of reported cases of Myocarditis secondary to RMSF, the frequency of occurrence is yet to be determined.

CASE REPORT

A 20-year-old male was admitted to the hospital with complaints of severe retrosternal chest pain that woke him up on the day of admission. A day prior to the day of admission the patient had retrosternal chest pain that lasted two hours and subsided without any intervention. On the day of admission, he was awakened by similar chest pain that prompted him to go to the hospital. The chest pain was associated with diaphoresis, five episodes of vomiting but no shortness of breath, abdominal pain, fever or headaches. He has no past medical history and no family history of premature coronary artery disease. He denied any history of smoking, drinking alcohol or use of illicit drugs. He is a college student who was born and lives in New Jersey.

On admission his vital signs showed a blood pressure 128/69 mmHg, heart rate 63 beats per minute, respiratory rate of 16 breaths per minute, temperature of 37.6°C and oxygen saturation of 99% on room air. Head and neck examinations were unremarkable. Lungs were clear to auscultation bilaterally.

Cardiovascular examination revealed a regular heart rate and rhythm. No pericardial rub, gallop or murmurs was noted. Carotid upstrokes were brisk and bilaterally equal and peripheral pulses were palpable in all four extremities. The rest of the examinations were unremarkable. Complete blood count level was within normal limits. Serum electrolytes were normal. His cardiac enzymes showed a creatine kinase level of 939 IU/L (normal 40–300 IU/L), creatine kinase-MB 58.62 ng/mL (normal 1.0–5.0ng/mL). Initial troponin I was 17.50 ng/mL (normal <0.30 ng/mL) and 20 hours later was 54.33 ng/mL. His renal function test was normal and his liver function test showed mild elevations in aspartate aminotransferase at 111 U/L (normal 15–40 U/L) and alanine aminotransferase at 54U/L (normal 5–40U/L). Urine drug screen was negative for cocaine. An electrocardiogram showed a 2 mm ST elevation in inferior leads and V6 (Figure 1). It also showed mild ST depression in leads V1–V3. The patient was given aspirin, clopidogrel and heparin. A left heart cardiac catheterization was done, result of which revealed normal coronaries (Figure 2) and normal left ventricular ejection. At this point further history was obtained from the patient who revealed that he had gone camping in the woods a month earlier in April 2014 but does not recall having any tick bite or any rash. At this point, presumptive diagnosis of myocarditis was made and Lyme serology was done. Lyme serology was found negative. Further diagnostic testing was pursued and result of RMSF IgG titre was elevated at 1:128 (normal <1:64) indicating recent infection with *Rickettsia rickettsii* which is the etiologic agent of RMSF. A diagnosis of myocarditis secondary to RMSF was made and patient was subsequently treated with doxycycline 100 mg twice a day for 21 days. At follow-up visit two weeks later, patient was symptom free.

DISCUSSION

RMSF is a *Rickettsia* infection that can cause severe systemic infection if not identified and properly treated. The incidence of RMSF has significantly increased from less than two cases per million persons in 2000 to more than six cases per million persons in 2010. However, the case fatality during this time frame decreased to less than 0.5% [1]. This could be attributed to early detection and treatment.

Clinical presentation of RMSF can be highly variable ranging from non-specific symptoms to the classic triad of fever, rash and headaches. In a clinical review study done by Kirk et al. [2] on 48 cases of RMSF seen between 1943 and 1986 only 62% of cases demonstrated the complete triad. Fever occurs in virtually all cases of
of 94 patients with RMSF showed that patients in whom mortality. Kirkland et al. [9] in their retrospective study can be associated with adverse outcome and even delay in treatment as studies have shown that delay in treatment due to RMSF. In this case report, the patient did not have any of the typical symptoms of the triad-fever, rash or headaches making diagnosis even more challenging at presentation.

Myocardial involvement is an uncommon complication associated with RMSF. Wolbach did the original studies in 1919 and since then, there have been several studies done to further illustrate cardiac involvement in RMSF. In a study by Marin-Garcia J et al., several pathologic findings were described including pericarditis, endocarditis, subendocardial myocardial necrosis and biventricular dilatation [5]. Several other pathogenic mechanisms have been proposed and reported in the myocardial involvement in RMSF including toxin effect as described by Belle et al. [6] to direct cytotoxic effect [5, 6].

Clinically, cardiac involvement in RMSF can be seen presenting with symptoms such as chest pain, dyspnea orthopnea. Elevations in cardiac makers such creatine kinase, troponin I and creatine kinase-myocardial band is also well documented. Electrocardiographic abnormalities seen ranges from sinus tachycardia to T-wave depression to ST-elevation. Atria fibrillation has also been reported. Echocardiography have been use to demonstrate left ventricular function during infection with RMSF and several months later and there have been variations in reported findings. Some people experience left ventricular dysfunction while some do not. Feltes [7] in his study of nine children with a diagnosis of RMSF who underwent echocardiogram within 72 hours of admission showed that 7 out of 9 patients had some degree of left ventricular impairment. In a follow up echocardiographic study 4 out of the 7 patients who had abnormal left ventricular function showed a resolution of the dysfunction suggesting reversibility of myocardial dysfunction in RMSF [7]. In contrast to this, a similar study by Marin-Garcia and Barrett [8] of nine patients with a diagnosis of RMSF and similar initial echocardiographic findings, three of their patients showed persistent echocardiographic abnormality at 10th month follow-up suggesting chronicity of cardiomyopathy due to RMSF. In this case report, the patient did not have any left ventricular abnormality during admission and so a follow-up echocardiogram was not warranted.

Treatment of RMSF is advised to be initiated as early as possible as studies have shown that delay in treatment can be associated with adverse outcome and even mortality. Kirkland et al. [9] in their retrospective study of 94 patients with RMSF showed that patients in whom treatment was initiated within five days of symptoms onset were significantly less likely to die compared with those in whom treatment was initiated after five days of symptoms onset (6.5% versus 22.9%). In cases, where there is high clinical suspicion such as in patients residing in or have visited endemic areas presenting with fever or headache or myalgia during the spring or summer empiric treatment should be initiated pending the results of RMSF test. Doxycycline is the drug of choice for both adults and children.

CONCLUSION

A very important point to note here is physicians should consider infectious causes at the top of the differential diagnosis of myocarditis in their young patients especially those with no personal or family history of premature coronary artery disease and this can go a long way to prevent unnecessary invasive cardiac procedures and limit health cost.

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Author Contributions
Nneka Iroka – 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
Mohammed Hossain – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
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A rare case of unilateral left side multicystic dysplastic kidney and contralateral Vesico-ureteric reflux in a male neonate

Naila Mazher, Swathi Chacham, Uppin Narayan Reddy, Jillalla Narsing Rao, Janampally Ravi Kiran, Jakkampudi Naga Sravani, Aslam

ABSTRACT

Introduction: Multicystic dysplastic kidney (MCDK) is a rare congenital disorder, resulting from malformation of the kidney during fetal development. It could be unilateral, bilateral or segmental and bilateral MCDK is incompatible with survival. Unilateral MCDK occurs in 1 in 4300 live births and combined incidence of unilateral and bilateral MCDK is 1 in 3600 live births. The malformed kidney is non-functional with multiple irregular cysts of varying size, separated by dysplastic parenchyma along with absent pelvicicaliceal system. Case Report: A 35-week, preterm, male neonate was born to a primigravid by C-Section. There was a history of second degree consanguinity. Antenatal ultrasonography at 17th week of gestation showed left side MCDK with oligohydramnios and without other malformations, which was confirmed by fetal magnetic resonance imaging (MRI). Postnatal ultrasonography also revealed left side MCDK with grade II vesico-ureteric reflux on the right side in micturating cystourethrogram and absent function in the affected kidney in dimercaptosuccinic acid (DMSA)scintigraphy. Conclusion: We report a preterm, male neonate with antenatally detected non-functional left side multicystic dysplastic kidney with postnatal confirmation and grade II vesico-ureteric reflux on the right side.

Keywords: Dimercaptosuccinic acid, Multicystic dysplastic kidney, Neonate, Oligohydramnios, Vesico-ureteric reflux

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INTRODUCTION

Multicystic dysplastic kidney (MCDK) is an infrequent congenital cystic malformation of the kidney. It is classified as unilateral, bilateral or segmental and bilateral MCDK is often lethal. The reported incidence of unilateral MCDK is 1 in 4300 live births [1] and that of combined incidence of unilateral and bilateral MCDK is 1 in 3600 live births. The dysplastic malformed kidney consists of non-functional, multiple non-communicating irregular cysts of varying size along with intervening dysplastic parenchyma and absent pelvicaliceal system. Although majority of the cases occur sporadically, autosomal dominant inheritance has also been reported [2]. MCDK results from an abnormal induction of the metanephric mesenchyme by the ureteral bud [3]. With the advances in antenatal screening by ultrasound, majority of these cases are diagnosed antenatally, which can be confirmed by postnatal ultrasound. MCDK can be complicated by hypertension, infection, renal failure and rarely malignant changes.

CASE REPORT

A 35-week, preterm, male neonate was born to a primigravid by C-section with normal APGAR score. There was a history of second degree consanguinity. Antenatal ultrasound at 17th week of gestation showed (Figure 1) left side multicystic dysplastic kidney with oligohydramnios (Amniotic fluid index-5). Fetal MRI confirmed left side MCDK and did not reveal other abnormalities. Fetal echo cardiography was also normal.

After birth, the neonate had respiratory distress requiring ventilatory support and baseline antimicrobials. Initially, pulmonary agenesis was suspected as it is an important accompaniment of renal malformations. However, the chest radiograph showed normal lung expansion and there were few in homogenous radio-opaque shadows, suggesting congenital pneumonia. The respiratory distress subsided after four days and the neonate was weaned from ventilator. Clinically, there were no potter's facies (Figure 2), there was no mass palpable per abdomen and the urine output was adequate with normal stream. His mean arterial pressure was normal (no evidence of hypertension) and the renal parameters were within normal range. Postnatal abdominal ultrasonography showed MCDK (Figure 3) with a normal right kidney and the postnatal echocardiography was normal. The neonate was started on uroprophylaxis with amoxicillin, in view of MCDK. The micturating cystourethrogram (MCUG) at 40th day of life revealed grade II vesicoureteric reflux (VUR) on the contra-lateral side (Figure 4). Further evaluation with DMSA scintigraphy at second month of life showed absent function in the left kidney (Figure 5). The infant received supportive and symptomatic treatment along with uroprophylaxis and was thriving well in periodic follow-up.

DISCUSSION

The MCDK consists of multiple cysts of various size with small intervening islands of immature glomeruli, primitive tubules, cysts derived from tubular and
glomerular structures. The left kidney is involved more often (55%) than the right kidney (45%). Similarly, the index neonate had MCDK on the left side. As per literature, males are affected more frequently than females (male: female ratio-1.48:1) [5]. Likewise, the index case was also male. Bilateral MCDK is often incompatible with life and it contributes to 20% of prenatally diagnosed cases. It is frequently associated with oligohydramnios, amnion nodosum, pulmonary hypoplasia, and Potter sequence.

The pathogenesis results from abnormal metanephros differentiation resulting from interrupted union of ureteric bud [3] with renal blastema and abnormal division at the stage of metanephros. This might be due to a disruption in the formation of the mesonephric duct, the malformation of the ureteric bud or the degeneration of the ureteric bud at an early stage. The final structure of the dysplastic kidney depends on the timing and degree of the injury to the ureteric bud. Mutations in genes responsible for ureteric bud development have been identified in syndromes with renal dysplasia, including MCDK. Specifically, mutations in EYA1 or SIX1 genes that lead to branchio-oto-renal (BOR) syndrome are associated with renal malformations, including MCDK [6, 7]. Exposure to viral infections and teratogens in utero has been associated with MCDK.

Dysplastic kidney may persist without any change, increase in size, or might undergo spontaneous involution. Calcification usually occurs when it persists till adulthood, but can be seen as early as three months of age. Most cases of unilateral MCDK undergo spontaneous involution. Index infant had no resolution of MCDK in follow-up and needs close monitoring for its complications. In prenatally diagnosed cases, the

Figure 3: Postnatal abdominal ultrasonography: Revealing multiple cysts of variable size in left kidney, separated by little or no echogenic parenchyma and unidentifiable renal pelvis.

Figure 4: Micturating cystourethrogram (MCUG) revealing right side grade II VUR.

Figure 5: Dimercaptosuccinic acid (DMSA) scintigraphy showing absent function in the MCDK (left kidney).
abnormal kidney is palpable in only 13–22% of patients. The mass is usually mobile, ballotable, irregular in shape and non-tender with occasional transillumination. It is usually asymptomatic and can remain undetected into adulthood, if not detected antenatally. However, in the index case, there was no palpable mass. MCDK has been reported in association with Alagille syndrome, Beckwith-Wiedemann syndrome, Branchio-oto-renal (BOR) syndrome, Joubert syndrome, Trisomy 18, Waardenburg syndrome type 1, and Renal coloboma syndrome. It is also associated with multiple non-renal and renal malformations including gastrointestinal, central nervous system, cardiovascular, and musculoskeletal system. In approximately 17–43%, there are also abnormalities of the contralateral kidney [8, 9], of which VUR is reported in 4–19% of patients [10,11]. Similarly, the index infant also had grade II VUR on the contra lateral side, though the exact cause of it is unknown. Ipsilateral VUR might also be present in segmental MCDK [12]. Ureteropelvic junction obstruction (UPJO) on the contralateral side has been reported in 7–12% of patients, which was not seen in the index case.

Most cases are detected during fetal ultrasonography and can be identified as early as 15 weeks of gestation. Urine for dipstick, microscopic analysis and culture should be obtained in patients with MCDK. Blood tests for creatinine, urea, and electrolytes should be performed. Renal ultrasonography is the recommended preliminary diagnostic imaging study [13] and all these investigations were done in the index infant.

Ultrasonography reveals randomly arranged multiple cysts of variable size, alienated by little or no echogenic parenchyma. Renal pelvis is usually not identified. Voiding cystourethrography (VCUG) should be performed to look for VUR. No difference in the incidence of urinary tract infections (UTIs) or renal scarring was observed between children with or without VUR in the contralateral kidney [10]. However this case did not have UTI, although there was grade II VUR on the contra lateral side. DMSA scintigraphy is indicated when, ultrasonography fails to reveal the classic features of MCDK and also to quantify the function of the affected kidney. In the current case, the DMSA scan showed absent function in the affected kidney. In the rare situation, where severe UPJO cannot be differentiated from MCDK by ultrasonography and DTPA renal scanning, a diagnostic puncture of a cyst with instillation of radiographic contrast material might help to distinguish these two disorders. The presence of cysts connected by tubular structures and the absence of a collecting system is diagnostic of MCDK. However, this was not required in our case.

Treatment is supportive and symptomatic. The role of nephrectomy is controversial and is indicated to treat or prevent complications like abdominal or flank pain, UTI, hypertension, or renal malignancy. Children with MCDK should undergo renal ultrasonography every 6–12 months until the age of five years or until involution is noted. Also, they should receive antibiotic prophylaxis during infancy and early childhood, as this age group is at highest risk of scarring due to pyelonephritis. Similarly, the index case was started on uroprophylaxis. Blood pressure monitoring is indicated once each year and if hypertension is evident, it should be treated. The index case had normal blood pressure in the follow-up, but requires close monitoring into childhood for detection of hypertension and its complications[14], which is required in this case. Prognosis depends on unilateral or bilateral occurrence of MCDK and the severity of associated anomalies. Most children with isolated unilateral MCDK are less prone for complications as in the index infant with a better prognosis.

**CONCLUSION**

We report a preterm, male neonate with antenatally detected multicystic dysplastic kidney (MCDK) on the left side with postnatal confirmation. The affected kidney was non functional on dimercaptosuccinic acid (DMSA) scintigraphy and was complicated by grade II vesico-ureteric reflex on the contra-lateral side.

**ABBREVIATIONS**

- Branchio-oto-renal (BOR) syndrome
- Dimercaptosuccinic acid (DMSA)
- Diethylenetriaminepentaacetic acid (DTPA)
- Intravenous pyelography (IVP)
- Magnetic resonance imaging (MRI)
- Multicystic dysplastic kidney (MCDK)
- Micturatingcystourethrogram (MCUG)
- Mercaptoacetyltyrlyglycine (MAG-3)
- Urinary tract infection (UTI)
- Ureteropelvic junction obstruction (UPJO)
- Voiding cystourethography (VCUG)
- Vesico-ureteric reflux (VUR)

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**Author Contributions**

Naila Mazher – 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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Guarantor
The corresponding author is the guarantor of submission.

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REFERENCES

ABSTRACT

Introduction: Agenesis of gallbladder is a rare (13–65 cases/100,000) anomaly, in which about 23% patient presents with symptoms of biliary disease. In these patients, ultrasonography (USG) abdomen frequently falsely reveals shrunken or contracted gallbladder and sometimes non-visualization of gallbladder (GB) in GB fossa. Basis of these misinterpreted reports these patients undergone unnecessary surgery and may encounter iatrogenic biliary tract injuries and portal injuries because of excessive dissection to find out the absent gallbladder and ectopic gallbladder. Case Report: A 40-year-old female attended surgical outdoor with complaint of pain right hypochondrium and dyspepsia since last four years patient followed-up with USG abdomen which was suggestive of chronic cholecystitis with choledolithiasis, and common bile duct (CBD) was normal in diameter on the basis of clinical symptoms and USG findings patient admitted and planned for laparoscopic cholecystectomy. On laparoscopy after removing the adhesions, exploration done up to the porta but gallbladder could not be visualized. On postoperative day-1 patient was sent for MRCP with MRI abdomen. On MRCP gallbladder and cystic duct were not visualized. CBD was normal in caliber. Liver and pancreas were normal. Hence the diagnosis of agenesis was made. Conclusion: Agenesis of gallbladder is an unusual anomaly in which about 23% presents as biliary disease. These patient frequently undergone surgery because of misinterpreted reports of USG abdomen, ERCP and CT abdomen. So, in cases with ultrasonographic diagnosis of scleroatrophic or non-visualization or suspicious of ectopic gallbladder and absence of wall echo shadow (WES) triad or double arc shadow, when non-visualization of gallbladder is present during laparoscopy or open exploration intraoperative cholangiogram, intraoperative ultrasound and postoperative MRCP or Endoscopic ultrasound (EUS) can help in the diagnosis of agenesis or ectopic gallbladder.

Keywords: Agenesis of gallbladder, Congenital, Absent gallbladder

INTRODUCTION

Agenesis of gallbladder is a rare (13–65 cases/100,000) anomaly, about 23% patient presents with symptoms of...
biliary disease [1, 2]. In these patients, ultrasonography (USG) abdomen frequently falsely reveals shrunken or contracted gallbladder and sometimes non-visualization of gallbladder in GB fossa [3]. Due to these misinterpreted reports, patients undergone unnecessary surgery, and may encounter iatrogenic biliary tract injuries and portal injuries, due to excessive dissection to find out the absent gallbladder and ectopic gallbladder [4]. Sometimes conversion to open exploration needed when an injury to biliary tract is suspected which adds morbidity to the patient. Preoperative imaging like MRCP and EUS should be considered [5]. And when such condition is encountered during intraoperatively, intraoperative cholangiography and intraoperative ultrasound can be done to rule-out agenesis and ectopic gallbladder [5].

**CASE REPORT**

A 40-year-old female attended surgical outdoor with complains of pain right hypochondrium and dyspepsia since last four years. Patient evaluated with USG abdomen which was suggestive of chronic cholecystitis with cholelithiasis, and CBD was normal in diameter. LFT's were with in normal limit. On the basis of clinical symptoms and USG findings patient admitted and planned for laparoscopic cholecystectomy.

On laparoscopy findings were:

1. Omentum and colonic loops were densely adherent to the inferior surface of liver (Figures 1A–B).
2. After removing the adhesions, exploration done up to the porta but gallbladder could not be visualized (Figure 2A–B).
3. Further exploration was done to rule out the ectopic gallbladder but gallbladder could not be visualized at those ectopic sites also.
4. CBD was normal in diameter.
5. Procedure terminated at this stage and decided to do postoperative MRCP in spite open conversion to prevent iatrogenic bile duct injuries.

On postoperative day-1 the patient was sent for MRCP with MRI abdomen. In MRCP findings, gallbladder and cystic duct were not visualized. CBD was normal in caliber. Liver and pancreas were normal (Figures 3A–B). Hence the diagnosis of agenesis was made.

In postoperative period patient sent for ERCP sphincterotomy. Patient followed-up for three months and she was comfortable without any episode of pain and dyspepsia. Followed up last month patient is doing well. final diagnosis was agenesis of gall bladder.

**DISCUSSION**

Agenesis of gallbladder was first reported by Lemery and Bergman in 1701 and 1702 respectively [2]. The incidence of agenesis in surgical cases is (0.007–0.027%) and in autopsy reports (0.04–0.13%) [6, 7]. Gallbladder develop late in first month of intrauterine life from distal part of hepatic diverticular bud of the foregut. Agenesis of gallbladder is explained by two developmental theories [8, 9]:

1. Failure of hepatic diverticula to develop into gallbladder.
2. Failure of recanalization of cystic duct and gallbladder.

Agenesis of gallbladder may present as [10]:

1. Neonates with multiple fetal anomalies (15–16%): In these patients, agenesis usually diagnosed on autopsy because of death in perinatal period due to associated GIT, GUT, CVS, anomalies.
2. Asymptomatic (35%): In these patients, agenesis recognized at autopsy and during laparotomy for other cause.
3. Symptomatic (40–60%): In these patient agenesis discovered on USG abdomen, MRCP, EUS and
during laparoscopy for evaluation of (colicky) pain right hypochondrium (90%), dyspepsia, vomiting.

Cause of pain in symptomatic patients includes biliary dyskinesia, adhesion in the GB fossa or periportal adhesions, remnant cystic duct stone and choledocholithiasis. ERCP sphincterotomy and adhesiolysis resolved the pain in these patients [11]. Agenesis of gall bladder is associated with congenital syndromes cerebrotendinous xanthomatosis, G-syndrome, Klippel–Feil syndrome, trisomy 18 and some cases reported after thalidomide therapy [12–15]. On laparoscopy if gallbladder is not visualize in GB fossa, dissection should be carried out up to the porta and usual sites for ectopic gallbladder, which are intrahepatic, retrohepatic, left sided, or within the falciform or lesser omentum, to prove the agenesis of gallbladder [8]. But sometimes this dissection is lead to major biliary tract injuries. So, excessive dissection and open exploration is avoided. On USG and CT abdomen diagnosis of agenesis is limited by bowel gas artifacts due to adhesions at liver bed which makes shadowy opacities, periportal tissue,

Figure 2: (A, B) CBD dissected up to the porta hepatis. Both right and left hepatic duct seen, but gallbladder and cystic duct are not visualized.

Figure 3: (A, B) MRCP films showing normal CBD and absence of cystic duct and gallbladder.
lipoma, liver hemangioma or migrated liver tissue [10, 16–18]. ERCP contributes little in diagnosis of agenesis because nonvisualization of gallbladder is interpreted as cystic duct obstruction [19].

MRCP is non-invasive and best method to delineate intrahepatic and extrahepatic biliary tract. Preoperative MRCP should be considered in cases of USG diagnosis of non-visualization of gallbladder [20]. Other diagnostic modality includes EUS, intra-op ultrasound and selective arteriography can be used for agenesis. But their availability is less [19]. There were some cases reported in which AGB was diagnosed preoperatively and the operation was avoided [16].

Agenesis of gallbladder is an unusual anomaly of which about 23% presents with biliary disease [2]. It is sometimes associated with anomalies of other system also and seems to be familiar inheritance [21]. These patient frequently undergo surgery because of misinterpreted reports of USG abdomen, ERCP and CT abdomen. So, in cases with ultrasonographic diagnosis of scleroatrophic or nonvisualization or suspicious of ectopic gallbladder and absence of WES triad or double arc shadow, Further preoperative investigation like MRCP and EUS should be done to rule out agenesis and ectopic gallbladder to avoid unnecessary surgery and iatrogenic biliary injuries.

CONCLUSION

When nonvisualization of gallbladder is present during laparoscopy or open exploration intra-operative cholangiogram, intraoperative ultrasound and postoperative MRCP or endoscopic ultrasonography (EUS) can help in the diagnosis of agenesis or ectopic gallbladder.

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Atul Kumar Mittal – Substantial contributions to conception and design, 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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Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

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REFERENCES

Managing clozapine-induced neutropenic fever: A case report

Regis G. Rosa, Maria D. Rosa, Alcina J. S. Barros

ABSTRACT

Introduction: Clozapine is an atypical antipsychotic, which is associated with an increased risk of neutropenia. Given that the signs and symptoms of infection in neutropenic patients are often subtle or absent because of the lack of an appropriate inflammatory response, fever may constitute the sole indicator of a serious underlying infection. Unfortunately, data about management of patients with neutropenic fever secondary to clozapine are scarce. Consequently, the entire management of this syndrome is based on extrapolation of data from the experience with cancer patients with neutropenia secondary to cytotoxic chemotherapy. Case Report: Herein, we describe the management of a neutropenic fever case complicated with septic shock and acute respiratory failure in an 57-year-old Caucasian female with the diagnosis of schizophrenia and type-2 diabetes mellitus, who was being treated with clozapine. The patient rapidly developed cardiorespiratory collapse requiring mechanical ventilation and vasoactive drugs few minutes after arrival at hospital. Profound neutropenia (absolute neutrophil count 60 cells/mm³) and lobar pneumonia were diagnosed. Broad-spectrum antimicrobial therapy with piperacillin-tazobactam plus vancomycin and supportive intensive care were promptly implemented. The clozapine-induced neutropenia was managed with filgrastim. Pseudomonas aeruginosa was isolated from the tracheal aspirate and blood cultures. After a total length of hospital stay of 44 days, the patient was discharged home. Conclusion: Neutropenic fever is a serious complication of clozapine treatment. Prompt administration of empiric broad-spectrum antibiotics and supportive care are required to avoid the high levels of mortality associated with this syndrome. Keywords: Clozapine, Critical care, Febrile neutropenia, Neutropenic fever, Septic, Shock

How to cite this article


INTRODUCTION

Neutropenia is the most feared adverse effect of clozapine, an antipsychotic dibenzodiazepine, primarily because its occurrence is known to predispose patients to severe infections [1]. The estimated incidence of clozapine-induced neutropenia ranges from 0.5–2.0% of patients treated with this medication, with the majority of cases occurring within the first three months after the start of treatment [2]. Although the exact mechanism of neutrophil toxicity is unknown, some evidence suggests immunologically mediated reactions may play a role [3].
Neutropenic fever (NF) is a syndrome characterized by fever in the presence of neutropenia (absolute neutrophil count < 500 cells/mm$^3$) [4]. NF constitutes a medical emergency that requires the prompt administration of empirical broad-spectrum antimicrobials to prevent the characteristically high probability of mortality, which may reach values of approximately 10% in specialized centers [5,6]. The classical signs and symptoms of infection are often subtle or absent because an appropriate inflammatory response is missing due to granulocytopenia [7], underscoring the importance of early assessment and appropriate management of patients with NF. Among factors related to NF treatment, microbiologically effective initial antibiotics, time to antibiotic administration, and restoration of tissue perfusion play important roles in reducing mortality [8–10]. Herein, we describe the management of a NF episode complicated with septic shock in a 57-year-old Caucasian female with refractory schizophrenia after four weeks of treatment with clozapine.

**CASE REPORT**

A 57-year-old Caucasian female who had been diagnosed with paranoid schizophrenia since the age of 20 and type 2 diabetes mellitus since the age of 45 was admitted to a tertiary referral hospital due to fever (axillary temperature 38.9°C), sinusoidal tachycardia (heart rate 110 bpm), malaise, and dehydration. She had a history of recent hospitalization due to refractory psychosis in which her antipsychotic treatment was switched from risperidone to clozapine. Clozapine treatment had been started 3 months earlier due to side effects of risperidone. Upon discharge, the patient was using quetiapine for the treatment of schizophrenia with good control of psychotic symptoms. For the current hospitalization due to refractory psychosis, the antipsychotic treatment was switched from risperidone to clozapine. Clozapine treatment had been titrated up to a dosage of 400 mg orally per day starting four weeks before the hospitalization recounted here, and the routine white blood cell counts had been normal at the second and third weeks of treatment.

At the current hospitalization, the patient rapidly developed cardiorespiratory collapse requiring mechanical ventilation and continuous infusion of norepinephrine despite initial oxygen administration and fluid challenge with 1 L of crystalloid. She also presented oliguria (urine output < 0.5 mL/kg/h) and capillary refill time > 2 s. The complete blood cell count demonstrated leukopenia (total leukocyte count 410 cells/mm$^3$) and profound neutropenia (absolute neutrophil count 60 cells/mm$^3$) with no abnormalities in serum electrolytes or liver function tests. The initial C-reactive protein was elevated (96 mg/L) as was serum creatinine and BUN (3.5 mg/dL and 62 mg/dL, respectively). There were no abnormalities in serum electrolytes or liver function tests. The initial chest X-ray showed a lobar consolidation in the upper-right pulmonary lobe. After obtaining two samples of blood cultures and quantitative tracheal aspirate, the patient was treated according to current guidelines for the management of NF with 4.5 g piperacillin-tazobactam administered intravenously over a 4 h period every 8 h, plus 1.0 g vancomycin administered intravenously every 12 h [4, 11–13]. The time between emergency arrival and antibiotic administration was 50 min. Acute respiratory failure was managed through a lung-protective mechanical ventilation strategy with low tidal volumes (6 ml per kilogram of ideal body weight) [14]. Restoration of tissue perfusion was performed with vasopressors, inotropes, and intravenous fluids according to established early goal-directed therapy for septic shock [15]. The clozapine-induced neutropenia was treated by subcutaneously administering 5 mg/kg/day of Filgrastim, a granulocyte colony-stimulating factor. After implementing these measures, septic shock progressively improved and the vasopressor dose was gradually reduced. Peripheral perfusion and diuresis substantially improved without the need for hemodialysis. *Pseudomonas aeruginosa* was isolated from the tracheal aspirate and blood cultures. The isolated bacteria was sensitive to piperacillin-tazobactam and carbapenens, and resistant to cefepime, fluoroquinolones, and aminoglycosides. After results of the antimicrobial susceptibility tests, vancomycin treatment was suspended given that there was no evidence of infection by gram-positive bacteria. After the fifth day of treatment, neutrophil counts began to increase, and reached values above 500 cells/mm$^3$ after the eighth day. The antimicrobial treatment with piperacillin-tazobactam was maintained for 14 days, and the patient was extubated on the tenth day. The patient stayed 13 days in the ICU and 44 days in the hospital. Upon discharge, the patient was using quetiapine for the treatment of schizophrenia with good control of psychotic symptoms.

**DISCUSSION**

The present case report describes the successful management of a severe case of NF complicated with septic shock. Probably, the profound neutropenia caused by clozapine followed by a high virulent bacterial infection (*Pseudomonas aeruginosa*) contributed to the complicated course of NF. Successful management in this situation is noteworthy as the expected mortality rate for neutropenic patients with septic shock has been reported to be quite high at 35–50% [16,17].

According to current guidelines, patients with NF should be treated initially with empiric intravenous therapy, comprising β-lactam antibiotic monotherapy with antipseudomonal activity (i.e. ceftazidime, cefepime, piperacillin/tazobactam, meropenem, or imipenem) within 1 hour from onset of neutropenic sepsis [4,18]. This recommended regimen reflects the principle of broad-spectrum initial therapy that focuses primarily on aerobic gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, Klebsiella spp., and Enterobacter spp., and aerobic gram-positive bacteria such as methicillin-susceptible staphylococci and viridans streptococci. The addition of vancomycin to the initial
regimen, which aims to combat resistant gram-positive bacteria (i.e. methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*), is indicated in cases of hemodynamic instability, suspected catheter-related infection, pneumonia, or infection of the skin and soft tissue. Our patient was treated initially with the combination of piperacillin-tazobactam and vancomycin due to the presence of hemodynamic instability and pneumonia. Glycopeptidase was discontinued as soon as the initial cultures ensured the absence of infection by gram-positive bacteria. Filgrastim, a colony-stimulating factor, was used in this case as means to decrease the duration of clozapine-induced neutropenia. Its presumed efficacy is based on case reports [19–20] and studies in cancer patients under cytotoxic chemotherapy [21]. Given that protective mechanical ventilation and appropriate restoration of tissue through fluid challenge and vasopressor are two measures associated with better outcomes in critically ill patients, they likely played important roles in the positive outcome reported here [18].

**CONCLUSION**

In summary, patients with clozapine-induced neutropenia are at risk for severe infections. The timely administration of appropriate antimicrobials as well as rapid tissue-perfusion restoration are of paramount importance to avoid unfavorable outcomes in this context.

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**Author Contributions**

Regis G. Rosa – 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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The corresponding author is the guarantor of submission.

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**REFERENCES**


Polycythemia vera and microvascular dysfunction in a 26-year-old male presenting with chest pain

Erika Jones, Nava Greenfield, Puja K. Mehta, Chrisandra Shufelt, Louise Thomson, C. Noel Bairey Merz

ABSTRACT

Introduction: Signs and symptoms of myocardial ischemia in the setting of no obstructive coronary artery disease (CAD) is often found in women. One of the mechanisms thought to contribute is coronary vascular dysfunction (CvAD). Coronary reactivity testing (CRT) is used to assess endothelial and non-endothelial dependent CvAD, but is not routinely performed. Case Report: We report a case of a healthy 26-year-old male with persistent chest pain after ST elevation myocardial infarction with normal coronary arteries. Stress cardiac magnetic resonance imaging showed normal rest and stress first pass perfusion, with an incidental finding of an enlarged spleen. He underwent CRT and was found to have slow flow and coronary endothelial dysfunction. Due to his enlarged spleen and an elevated hematocrit at 50% he was referred to a hematologist and diagnosed with polycythemia vera (PV). Although the risk of thrombosis and myocardial infarction is known in PV, the pathophysiology is not well understood. In our patient no thrombus was visualized on angiogram. Conclusion: The findings of his CRT in the setting of PV offer an interesting link between hematological disorders, endothelial dysfunction, and persistent chest pain with no obstructive CAD.

Keywords: Chest pain, Coronary endothelial dysfunction, Coronary reactivity testing, Microvascular dysfunction, Polycythemia vera

INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative disorder, associated with an increased risk of myocardial infarction (MI) and stroke. The mechanism for developing these adverse cardiovascular (CV) events has been attributed to the development of thrombosis, either in the micro or macro vasculature, however, recent reports have suggested that there may be more to the pathophysiology, especially for young patients with this disease who present with signs and symptoms of myocardial ischemia [1].

There is a growing body of evidence showing that one cause of myocardial ischemia and persistent chest pain in patients with no obstructive coronary artery disease (CAD) is coronary microvascular dysfunction (CMD) and endothelial dysfunction [2]. CMD refers to impaired hyperemic response of the myocardial resistant vessels in response to exercise or vasodilator stimuli. CMD can
be due to endothelial or non-endothelial dysfunction. Endothelial dysfunction is a proposed mechanism of chest pain, ischemia, and even infarction in at least some cases of patients with PV [3]. We present a case of an otherwise healthy 26-year-old male who developed a MI as his initial presentation of PV and was found to have endothelial dysfunction on invasive coronary reactivity testing (CRT).

CASE REPORT

A 26-year-old male with a past medical history significant for eosinophilic esophagitis and acid reflux presented to the emergency department with a three month history of atypical, progressively worsening substernal chest pain. The chest pain began suddenly and was not associated with exertion or emotion. Given his lack of cardiac risk factors and history of GERD, the chest pain was previously attributed to esophageal spasms for which he was prescribed sublingual nitroglycerin, omeprazole, dexlansoprazole, calcium channel blockers and amitriptyline, none of which relieved his pain. On the day of his emergency department visit his substernal chest pain worsened to 10/10. His EKG had ST elevations in leads I, II and avF, labs showed an elevated troponin level that peaked at 1.55, elevated hematocrit (50%), an elevated white blood cell count (15.37 K/uL) and no splenomegaly appreciated on exam. Echo showed normal left ventricular systolic function with no wall motion abnormalities. A cardiac catheterization demonstrated no obstructive CAD, no thrombus was visualized, but slow flow was evident in his left anterior descending artery (LAD). Given lack of evidence of any obstructive CAD his symptoms were thought to be secondary to pericarditis. His pain persisted and with no clear etiology of his chest pain, the patient sought further investigations.

The patient was referred to our facility for further workup where he received a regadenoson stress cardiac magnetic resonance imaging (CMRI) myocardial perfusion study which showed normal rest and stress first pass perfusion, normal biventricular systolic function, no evidence of scar by delayed enhancement. Incidental note was made of splenomegaly with liver length, 16 cm on scout images (Figure 1). Given persistent chest pain and a history of an ST elevation MI, he underwent CRT to clarify diagnosis and to assess endothelial and non-endothelial dependent micro and macro vascular function. CRT was performed by placing a Doppler FloWire (Volcano Inc., San Diego, USA) in the left anterior descending (LAD) artery. Vasoactive substances were infused through a guiding catheter placed in the left main, and changes in LAD diameter and blood flow velocity in response to adenosine, acetylcholine and nitroglycerin were measured. We confirmed slow flow with a thrombolysis in myocardial infarction (TIMI) 2 flow and a TIMI frame count of 42 with a corrected TIMI frame count of 25. His CRT findings are outlined in Table 1.

The patient was seen by a hematologist who confirmed a Jak2 mutation and an elevated hematocrit (Hct), consistent with a diagnosis of PV. He was started on aspirin, pegylated interferon, and phlebotomies to keep his Hct below 45%, which improved his symptoms. He continues to experience occasional chest pain, dizziness and fatigue although generally feels drastically improved from his initial presentation.

Figure 1: Coronal scout image done at the time of cardiac magnetic resonance imaging incidentally found increased craniocaudal dimension of the spleen (*) 16 cm.

Table 1: Coronary Reactivity Testing Results

<table>
<thead>
<tr>
<th>Patient Results</th>
<th>Normal Reference</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine-Coronary Flow Reserve (CFR)</td>
<td>5.5</td>
<td>≥ 2.32</td>
</tr>
<tr>
<td>Acetylcholine Coronary blood flow response</td>
<td>160% increase</td>
<td>≥130%</td>
</tr>
<tr>
<td>Acetylcholine LAD diameter response</td>
<td>4.4% constriction</td>
<td>Any dilation</td>
</tr>
<tr>
<td>Nitroglycerin LAD diameter response</td>
<td>3% dilation</td>
<td>≥15%</td>
</tr>
</tbody>
</table>
DISCUSSION

Chest pain is a common chief complaint with a wide differential diagnosis. Problems with diagnosis and treatments arise when patients present with atypical symptoms and/or have little to no risk factors for heart disease. We describe an unusual case of a previously healthy young man with no known cardiac risk factors, in whom an ST elevation MI with no obstructive CAD was the first presentation of PV. There is a growing body of evidence that one of the causes of ischemia with no obstructive CAD is coronary vascular dysfunction (CVaD) [2]. Endothelial and non-endothelial dependent vascular function can be abnormal in those with no obstructive CAD who have signs and symptoms of ischemia, and should be considered as an etiology in those with unexplained chest pain. If a coronary angiogram is performed and no thrombosis is visualized then perhaps CRT may add further diagnostic information. In this case the patient demonstrated slow flow which is considered a marker for increased microvascular resistance and endothelial dysfunction [4].

Patients with PV are predisposed to vascular complications such as venous and arterial thrombosis. Prior thrombotic event and age >65 are the two risk factors that increase risk of further CV events in patients with PV [5]. The pathogenesis of coronary thrombosis seen in PV is not fully understood, however it is likely that multiple factors play a part such as hyperviscosity with decreased blood flow, platelet activation and functional abnormalities, leukocyte and platelet aggregation [6]. Increased platelet activation through interaction between abnormal hematocrit, activated white cells, turbulent flow can provoke endothelial activation and injury [6]. Nuenteufl et al. [3] investigated endothelium-dependent flow mediated vasodilation (FMD) and endothelium-independent nitroglycerin-induced vasodilation (NMD) in patients with PV versus controls and found that FMD but not NMD was significantly impaired in patients with PV leading to the thought that endothelial dysfunction may play a role in thromboembolic complications.

Acute coronary syndrome (ACS) in patients with PV is thought to be due to coronary thrombosis in large coronary arteries which can be seen on coronary angiography but microthrombi in the coronary microcirculation are not visualized on catheterization. There are case reports of PV presenting as an ST elevation MI with visualized coronary lesions and distal thrombosis [7]; however there are other case reports where an angiogram was performed showing normal coronary arteries in both patient with PV and essential thrombocytosis (ET) [1]. Rossi et al. compared characteristics in patient with PV versus ET and found that ACS was more common in PV, 11.4% versus 9.4%, raising the question of whether ACS is indeed caused by platelet rich thrombi [8]. Studies have shown that thrombi are more common in PV versus ET and therefore thrombocytosis alone is not sufficient to explain coronary thrombi and other mechanisms such as slow flow, hyperviscosity, microvascular and endothelial dysfunction as a cause of ACS may need to be further investigated. Leukocytosis, which was present in our patient, has been shown to be a risk factor for developing thrombosis [9]. Falanga et al. [10] showed that activated leukocyte markers were simultaneously elevated with markers of endothelial damage including thrombomodulin and von Willebrand factor antigen in both patients with PV and ET compared to controls.

CONCLUSION

We report a young male patient whose first presentation of polycythemia vera (PV) was an ST elevation MI, followed by persistent chest pain, who had an abnormal coronary vascular reactivity test. Coronary slow flow and endothelial dysfunction should be considered in patients with persistent chest pain and no obstructive coronary artery disease (CAD) as in this case. The findings of his abnormal coronary reactivity testing (CRT) in the setting of PV offer an interesting link between hematological disorders, endothelial dysfunction and persistent chest pain with no obstructive CAD.

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Author Contributions

Erika Jones – 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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The corresponding author is the guarantor of submission.

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Authors declare no conflict of interest.

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REFERENCES


CASE REPORT

Extraskeletal myxoid chondrosarcoma of the foot: A case report

Carlos Cano Gala, Germán Borobio León, Roberto González Alconada, Laura Alonso Guardo, Diego A. Rendón Díaz, Francisco J. García García, Juan F. Blanco Blanco

ABSTRACT

Introduction: Extraskeletal myxoid chondrosarcoma (EMC) is a rare neoplasm that affects soft tissue and is independent from normal cartilage, bone and periosteum. Due to its low frequency, there is no clear consensus on its treatment. Case Report: We present the case of a 39-year-old male with pain in plantar region of right foot of several months of evolution. After a Tru-Cut biopsy, the patient was diagnosed with EMC of the right foot and was performed an amputation below-knee. Conclusion: EMC located on the foot is an extremely infrequent condition that has rarely been published. This article reviews the published literature to reach a consensus on the best approach for its treatment.

Keywords: Chondrosarcoma, Extraskeletal, Extraskeletal myxoid chondrosarcoma (EMC), Foot

INTRODUCTION

In the year 1972, Enzinger and Shiraki [1] defined the myxoid variant of extraskeletal chondrosarcoma, based on the multinodular growth of primitive chondroblast-like cells in an abundant myxoid matrix. The age at presentation of this neoplasm ranges from 4 to 92 years, and it mainly affects middle-aged patients. There is no sexual or racial predilection.

Histogenesis of EMC is controversial. In any case, chondroblast differentiation is a proven fact in several histochemical and ultrastructural studies.

In spite of the fact that, according to the reviewed literature, most cases appear on the lower limbs, location on the foot is very rare. In this article, we present the case of EMC of the foot and we review the cases published over the last years.

CASE REPORT

We present a case of a 39-year-old male who is admitted in our department after being referred from Primary Care, with pain on the plantar region of the right foot of several months of evolution. In the physical examination, the patient presents a hard immobile tumor of approximately 3–4 cm on the base of the fourth metatarsal bone. The rest of the physical examination is normal. An MRI is performed, and it reveals a solid lesion of 3.4x3.5x3 cm
in size, with necrotic areas inside, located on the plantar region and infiltrating different musculotendinous and bone structures in the area (Figure 1).

Further bone scan, chest X-ray and blood tests are normal.

A Tru-Cut biopsy is performed on the safest and most accessible area (dorsum of the base of the fourth metatarsal bone). The histopathological report describes a chondral origin tissue, with low cellularity and atypia, surrounded by abundant myxoid matrix. The specimen was unencapsulated. After a review of literature and confirmation that there is no clear consensus on an optimum treatment, an amputation below-knee is performed because it is the most functional choice with non-affected borders. The patient was not undergone to chemotherapy.

Table 1: Summary of cases of chondrosarcoma of the foot published in literature

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Staging at diagnosis</th>
<th>Size (cm)</th>
<th>Cellularity</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>NO</td>
<td>5</td>
<td>High</td>
<td>Local resection + extended resection + amputation</td>
<td>Disease-free/4 years</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>41</td>
<td>Lung metastasis</td>
<td>7</td>
<td>Low</td>
<td>Chemotherapy</td>
<td>Lung metastasis/14 years</td>
</tr>
<tr>
<td>3</td>
<td>W</td>
<td>78</td>
<td>NO</td>
<td>5</td>
<td>Low</td>
<td>Amputation</td>
<td>Disease-free/5 years</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>48</td>
<td>NO</td>
<td>9</td>
<td>Low</td>
<td>Amputation</td>
<td>Disease-free/6 years</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>51</td>
<td>NO</td>
<td>6.5</td>
<td>Low</td>
<td>Amputation</td>
<td>Disease-free/2 years</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>49</td>
<td>NO</td>
<td>6</td>
<td>Low</td>
<td>Extended resection</td>
<td>Chest wall metastasis/ Alive after 14 years</td>
</tr>
<tr>
<td>7</td>
<td>W</td>
<td>76</td>
<td>NO</td>
<td>8</td>
<td>Low</td>
<td>Extended resection</td>
<td>Disease-free/7 months</td>
</tr>
<tr>
<td>8</td>
<td>W</td>
<td>61</td>
<td>NO</td>
<td>6</td>
<td>Low</td>
<td>Amputation</td>
<td>Disease-free/4 months</td>
</tr>
<tr>
<td>9</td>
<td>W</td>
<td>43</td>
<td>NO</td>
<td>3</td>
<td>Low</td>
<td>Extended resection</td>
<td>Disease-free/8 years</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>32</td>
<td>NO</td>
<td>4</td>
<td>Low</td>
<td>Amputation</td>
<td>Disease-free/4 years</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>39</td>
<td>NO</td>
<td>5</td>
<td>Low</td>
<td>Amputation</td>
<td>Disease-free/4 months</td>
</tr>
</tbody>
</table>

The postoperative evolution was favorable. Five months after surgery the patient clinical state is good and there is no evidence of distance metastasis in the monthly controls that are performed.

DISCUSSION

Extraskeletal myxoid chondrosarcoma is a rare entity that can be located both on the upper and the lower limbs, and is more commonly found on the thigh and the knee [2]. The foot is an extremely rare location for this pathology, and it receives different treatments depending on reviewed literature [3]. The age at presentation ranges from 4 to 92 years, and it is most common in midlife. There is no sexual or racial predilection.

Usually, patients present a clinical history of pain on the affected region and the appearance of a growing mass of months of evolution. The tumor grows very slowly and it is sometimes a casual finding, which can delay diagnosis significantly [4, 5].

Plain X-rays usually show a soft tissue mass that sometimes penetrates the underlying bone. The
diagnostic study is completed with MRI and an adequate staging study that includes a bone scan and an analysis with tumor markers. Diagnostic certainty is obtained with the anatomopathological study of a sample obtained either via biopsy or complete removal of the tumor.

There is no consensus in reviewed literature with regard to the optimum treatment. Table 1 gives an analysis of the cases of EMC of the foot found in the literature. As we can see, in most of them (63%), including our case, the patients underwent amputation (amputation level is not specified in the studies). In view of the data, both the patients who underwent amputation and those in whom the tumor was resected with free margins are alive and disease-free in the follow-up control studies that were carried out (with the exception of one case in which the patient maintains the lung metastasis of the initial diagnosis [6] and another case in which the patient developed a metastasis in the chest wall 36 months after diagnosis and who is still alive 14 years after the initial treatment [7].

The reviewed literature shows a relatively good prognosis of the tumor, with prolonged survival. This characteristic is not only applicable to cases of the foot; most studies report a good prognosis regardless of the location. Saleh et al., in a study from 1992 on 10 patients with EMC of different locations (one of them of the foot) question this good prognosis. The authors present a series in which, in spite of a long survival, 100% of the patients developed distant metastasis or local recurrence (many of them more than 10 years later). The only case of their series in which the location of the tumor was on the foot presented with lung metastasis at diagnosis, and the patient received chemotherapy as a single treatment (without response). Fourteen years later, the patient is still alive and the lung metastases are still present [6].

Our analysis reveals that most of the patients show long-term survival, even in the presence of metastasis. The low number of cases with location on the foot makes it difficult to discern clear prognostic factors. Oliveira et al. [8] refer to prognostic factors such as the size of the tumor, cellularity, mitotic activity, or the presence of different immunohistochemical markers, regardless of the location.

**CONCLUSION**

Extraskelatal myxoid chondrosarcoma (EMC) of the foot is an extremely rare condition with a relatively good prognosis even in the presence of distant metastasis, and which in most cases shows good results with amputation, which should be as functional as possible, as a treatment of choice. Larger case series are required to establish clear criteria with regard to prognostic factors.

**Author Contributions**

Carlos Cano Gala – 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

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

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**Guarantor**

The corresponding author is the guarantor of submission.

**Conflict of Interest**

Authors declare no conflict of interest.

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**REFERENCES**


CASE REPORT

A rare and catastrophic manifestation of mycobacterium Avium complex pulmonary disease: A case report

Enrique O. Ortiz-Diaz

ABSTRACT

Introduction: Non-tuberculous mycobacteria (NTM), most commonly Mycobacterium avium Complex (MAC), cause certain clinically known syndromes in immunocompetent and immunodeficient patients. Case Report: The patient’s clinical setting illustrates an unusual and fatal manifestation of NTM, a left lung necrotizing-cavitating pneumonia in an immunosuppressed host. Conclusion: Severe necrotizing pneumonia is a rare manifestation of NTM considered after exclusion of other cavitating lung diseases. Also, it adds to the current literature whether anti-neutrophil cytoplasmic antibodies are associated with mycobacterial infections.

Keywords: Cavitating Lung Disease, Immunosuppression, Non-tuberculous mycobacteria

INTRODUCTION

Non-tuberculosis mycobacterial (NTM) infections in the lung usually present as a chronic fibrocavitary disease, an allergic reaction, or as an extra-pulmonary dissemination in patients with T cell immunosuppression [1]. The case illustrates an uncommon presentation of NTM pulmonary disease in the form of severe necrotizing pneumonia and bronchopleural fistula.

CASE REPORT

A 65-year-old Mexican man with rheumatoid arthritis was admitted to the hospital with left-sided chest pain, productive cough and progressive dyspnea over a week. Progressive pleuritic chest pain, disabling dyspnea (New York Heart Association Class IV) and productive cough were reported 10 days prior to admission. His review of systems was affirmative for chills, rigors, and a 20-pound weight loss in an indeterminate amount of time. Patient had a baseline chronic non-productive cough, which changed in terms of brown phlegm production without blood.

Past medical history was remarkable for long standing rheumatoid arthritis for which he took dexamethasone (10 mg/day) and various over-the-counter non-steroidal anti-inflammatory agents on a daily basis without medical guidance. When the patient arrived to the emergency room, a left pneumothorax was diagnosed by chest radiograph and 28 Fr chest tube was surgically placed before being admitted to the general medical ward (Figure 1).

His physical examination was significant to find an elderly patient with chronic ill dishevelled appearance, using a nasal cannula at 6 L/min. The patient was afebrile with sinus tachycardia and a blood pressure of 140/65 mmHg. Chest tube was in the left lateral hemithorax. The chest drain had abundant yellow fluid with air bubbles noticeable on passive expiration without coughing. On auscultation of the chest, patient had bilateral mid-to-end inspiratory “velcro” crackles at the bases,
decreased breath sounds on the left anterior and lateral hemithorax along with dullness to percussion in the same area. Heart was found to have regular tachycardia without rub or murmurs. There was non-palpable cervical lymphadenopathy but there was poor dentition without visible jugular venous distention. Abdomen and extremities were unremarkable.

Hematological findings included thrombocytosis and leukocytosis with neutrophilia. Electrolytes were unexceptional. Chest radiographs before and after chest tube insertion are shown in Figure 1. Chest radiograph on the right showing a partially expanded but consolidated left lung, along with deep sulcus sign, a central cavity and a chest tube resting superiorly and medially. A computed tomography of the chest showed hydro-pneumothorax with upper lobe cavities and bibasilar fibrotic changes with honeycombing (Figure 2). Serology reported positive rheumatoid factor (941 units by nephelometry) and anti-myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) by ELISA. Mycobacterium tuberculosis polymerase chain reaction (PCR) probe returned negative. Bacterial and fungal cultures were finalized as negative. Sputum and pleural fluid acid-fast cultures recognized acid-fast positive organisms finalized as non-tuberculous mycobacteria (NTM), specifically MAC (Mycobacterium intracellulare).

Patient received broad-spectrum antibiotics targeting *S. aureus* and *Pseudomonas aeruginosa*. When, acid-fast stains returned positive results, patient was added 4-drug standard therapy for *Mycobacterium tuberculosis* on hospital day-2. When *M. tuberculosis* PCR was found negative. The patient was changed to clarithromycin 500 mg orally twice daily, ethambutol 15 mg/kg daily and rifampin 600 mg orally daily on the fourth hospital day. The patient progressed to severe hypoxemic respiratory failure undergoing orotracheal intubation on hospital day-5 and invasive mechanical ventilation. Patient’s introduction to positive pressure ventilation caused the patient to worsen bronchopleural fistula airflow and die of refractory hypoxemia in the intensive care unit at the sixth day of admission. An autopsy was not obtained.

**DISCUSSION**

The patient presented with an acute-subacute left upper lobe cavitating-necrotizing pneumonia in the setting of steroid-mediated immunosuppression and baseline fibrotic parenchymal abnormalities. The differential diagnosis encompasses bacterial (*Staphylococcus aureus*, *Klebsiella* species, *Pseudomonas aeruginosa*), fungal (endemic fungi, *Aspergillus*, etc). Other bacterial etiologies causing a more chronic, less clinically catastrophic complications include *Nocardia* and *Actinomyces* species. Parasites such as *Echinococcus* and *Paragonimus* species have been described to cause a similar setting. Since, the patient was born and frequently travelled to Mexico, *Mycobacterium tuberculosis* should be considered as well. This would be an unusual presentation for NTM as explained in the discussion below. Less likely in this case, pulmonary infarction, Caplan’s syndrome (rheumatoid arthritis), vasculitis, (e.g., Wegener’s granulomatosis), and cavitating neoplasms (squamous cell cancer) [2].

**NTM Pulmonary Infections Presentation**

The patient illustrates an unusual manifestation of NTM in the immunosuppressed host. NTM group encompasses over 150 species excluding *Mycobacterium leprae* and *M. tuberculosis* [3]. NTM clinical manifestations depend on the host’s immune competency and geographical location. Over 115 species of NTM have been reported to cause disease in humans [3]. MAC is the most common pathogenic NTM in North America [4]. The estimated NTM associated pulmonary disease prevalence is increasing compared to three decades ago [4]. Classically, NTM clinical presentation ranges from chronic fibrocavitary-nodular disease (most commonly in patients with pulmonary structural abnormalities
such as chronic obstructive pulmonary disease and bronchiectasis) to allergic disease (hypersensitivity pneumonitis). Both entities are described in patients with non-specific systemic symptoms, dyspnea, cough, specific high resolution computed tomography abnormalities and sputum, bronchoalveolar or pleural culture results (or histological diagnosis) [1, 5]. Considering immunocompromised hosts, specifically with CD4+ T cell deficiency (prototypically acquired immune deficiency syndrome), disseminated or extra-thoracic NTM infection is well described. This subgroup variably presents with fever of unknown origin, gastrointestinal symptoms, generalized lymphadenopathy, cytopenias and less commonly diffuse skin nodules, pustules, and ulcers [1]. Since NTM could be considered a contaminant, specific context and exclusion of other diseases must exist to ascertain the diagnosis [1, 5].

Necrotizing pneumonia is an infrequent presentation of NTM even in immunocompromised hosts. The patient described in the scenario above represents the first reported to have such a severe cavitary-necrotizing pneumonia, bronchopleural fistula causing refractory hypoxemia. Other case reports exist for milder acute presentations [6, 7]. Waller et al. reported an immunocompetent southeastern American woman with microbiological and surgical pathological diagnosis of multi-lobar MAC pneumonia with hypoxic respiratory failure [7]. Asnis et. al. described an immunocompetent gentleman with right upper lobe pneumonia and eccentrically large mediastinal adenopathy. A right paratracheal node biopsy yielded the diagnosis during the patient’s hospital course [6].

The described patient’s serological studies revealed a positive ANCA-MPO antibody. There is an overlap in symptoms, radiological and pathological findings due to MAC infection and pulmonary vasculitis as they occupy the same differential diagnosis for this presentation. Others have found co-occurrence of ANCA antibodies in chronic suppurative infections such as *Mycobacterium tuberculosis* and NTM infections [8–12]. Chaimnuay et al. described an elderly lady with positive ANCA vasculitis and a lung lesion that recovered in culture MAC. Patient responded clinically to anti-mycobacterial treatment without initiating immunosuppressive therapy [8]. Nakayama et al. reported a case of an elderly lady with pulmonary artery vasculitis-stenosis and a right upper lobe cavitary lesion. Sputum culture recovered MAC. The patient was treated with immunosuppressive and antimycobacterial therapy with good clinical-radiological response [9]. There are unanswered questions whether there are associations between the two since it has been only described through case reports.

**CONCLUSION**

Non-tuberculous mycobacteria should be considered in the necrotizing-cavitating pneumonia differential diagnosis. It is the first report to describe such a severe manifestation of NTM disease. The case adds to the current literature whether anti-neutrophil cytoplasmic antibodies are associated with mycobacterial infections.

**********

**Author Contributions**

Enrique O. Ortiz-Diaz – 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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**REFERENCES**


TREATMENT OF RENAL FIBROMUSCULAR DYSPLASIA IN AN ADOLESCENT MALE: A CASE REPORT

Dennis M. Fry, Ojas A. Pradhan

ABSTRACT

Introduction: Fibromuscular dysplasia (FMD) is a rare vascular disease that causes stenosis in the major arteries such as the renal and carotid arteries. The exact prevalence of FMD in the general population is not known. It is often presented with symptoms of hypertension. Mainly reported in middle-aged females, the diagnosis of FMD is often delayed. There are very few case reports of FMD in males and children in literature. Case Report: We report the case of a 13-year-old asymptomatic boy found to have FMD in the right renal artery (RRA). An angiography revealed high grade stenosis that was corrected by surgery. A hepatorenal bypass using anastomosis of the gastroduodenal artery (GDA) to RRA was deemed appropriate. An angioplasty at the anastomosis six weeks after this procedure corrected an upward trend in postsurgical blood pressure readings and RRA blood velocities. Two years after the surgery, the patient has well-controlled blood pressure, managed with low dose of ACE-inhibitors. Conclusion: Hepatorenal bypass of RRA through anastomosis of GDA was a viable surgical option in this case. The monitoring of blood pressure readings allowed for early detection and correction of any postsurgical stenosis.

Keywords: Adolescent male, Fibromuscular dysplasia (FMD), Hepatorenal bypass, Renal hypertension,

INTRODUCTION

Fibromuscular dysplasia (FMD) is a rare noninflammatory and non-atherosclerotic disease that most commonly causes stenosis of the renal and carotid arteries. It is characterized by a “string of beads” appearance due to post-stenotic aneurysms [1]. FMD is most commonly reported in young to middle-aged females. Few comprehensive reports of FMD in adolescent males exist [2, 3]. FMD is routinely diagnosed and corrected through angiogram and subsequent percutaneous transluminal angioplasty (PTA) [1–3].

Here, we report a case of FMD in a 13-year-old boy who underwent a hepatorenal bypass within one month of the initial discovery, and a detailed surveillance report over a period of two years.

CASE REPORT

A 13-year-old boy during a routine visit to the pediatrician, was found to have blood pressure readings of approximately 190/120 mmHg. The patient had no significant medical history and showed no symptoms associated with hypertension. He was rushed to the hospital and subjected to multiple investigative procedures including a physical examination, urinalysis,
blood test for renal panel and CBC, duplex ultrasound of abdominal organs and vessels, and echocardiography. With the exception of elevated right renal artery (RRA) blood velocities and elevated blood aldosterone level, no other results occurred outside the normal ranges. The patient was administered increasing dosages of various anti-hypertensive medications including beta-blockers, ACE-inhibitors, calcium-channel blockers and central alpha agonists (CAA) over next three weeks. These medications poorly controlled the blood pressure.

High velocities in the RRA suggested stenosis in excess of 60%. An abdominal aortic angiography followed, which indicated high-grade 95% stenosis just beyond the origin of the RRA and significant poststenotic dilation with two small aneurysms in the dilated segment. The high stenosis and beaded aneurysms led to the diagnosis of FMD (Figure 1). A large peri-ureteric collateral flow extending into right renal hilum was detected. The left renal artery showed no signs of stenosis. The superior mesenteric, celiac, and gastroduodenal arteries (GDA) were widely patent. Due to more than 95% stenosis of RRA, the case was deemed unsuitable for balloon angioplasty and was referred for surgery.

Within two weeks, a hepatorenal bypass of the RRA was completed using anastomosis of the GDA to the RRA. Postsurgical Doppler readings showed adequate blood flow in the hepatorenal artery bypass (Figure 2). The patient was discharged after three days, advised to continue beta-blockers to control blood pressure, and record daily blood pressure measurements.

Blood pressure readings initially declined following the bypass surgery, but gradually increased over a period of six weeks (Figure 3). Relatively higher renal velocities from a duplex ultrasound in this period supported the possibility of re-stenosis at the site of anastomosis (Table 1). A second angiography suggested 50% stenosis at the anastomosis and concurrently a PTA was performed using a 4 mm balloon. Within a week, the blood pressure readings decreased noticeably and the patient was put on ACE-inhibitors to control the blood pressure (Figure 3). Subsequent, continued monitoring over the next two years showed a steady decrease in the blood pressure readings and renovascular duplex velocities (Figure 4, Table 1). The patient continues to be monitored through regular check-ups while on a decreasing dose of ACE-inhibitors.

DISCUSSION

The prevalence of FMD in the general population is not known [4]. However, Plouin et al. report that the prevalence of symptomatic renal FMD is about 4 in 1000. Renal FMD accounts for nearly 58% of all reported FMD cases [5]. FMD is thought to be more prevalent in females than in males; representing 91% of patients in the US FMD registry. Patients in this registry had a mean age of 51.9 years with averages of 4 to 9 years separating the initial symptoms of FMD and its diagnosis [1]. Literature review also indicates limited studies of FMD in males or in pediatric cases [1, 5]. The most common symptom of FMD is hypertension with a prevalence of 63.8% in the U.S. FMD registry [1]. Secondary symptoms of hypertension include headaches, dizziness, pulsatile tinnitus, neck pain, and chest pain. In this case, the patient was completely asymptomatic for hypertension. Elevated blood pressure was the only indication of any problem.

As such, this study is unique for the presentation of FMD in an adolescent male that was diagnosed and treated in relatively short period of time.

Although angioplasty remains the gold standard for correcting FMD, Trinquart et al. reported that salutary

![Image 1](https://example.com/image1)

**Figure 1:** Preoperative computed tomography angiogram image showing stenosis of RRA adjacent to the abdominal aorta with post-stenotic dilation and contained aneurysms- characteristic of FMD, a large peri-ureteric flow to the right kidney, and a normally perfused left kidney.

![Image 2](https://example.com/image2)

**Figure 2:** Postoperative computed tomography angiogram image showing anastomosis of the GDA to the RRA.
blood pressure responses were more likely among younger patients after surgical revascularization for renal FMD [2, 6]. Contemporary surgical treatments of pediatric renovascular hypertension suggest aortic implantation of normal renal artery beyond the stenosis [7]. This case, however, demonstrates that GDA could be used for revascularization of RRA in an adolescent with FMD. Previously, Moncure et al. had shown that GDA was successful in the revascularization of atherosclerotic patients [8]. The patient’s age allowed for the remodeling of the diameter of the arterial lumen at the point of anastomosis to accommodate larger blood flow demand. A large peri-ureteric collateral blood flow supported the kidney allowing for gradual remodeling of anastomosis.

As recommended by Olin et al., regular monitoring of blood pressure post-surgery also proved to be beneficial in detecting reduction in blood flow at anastomosis, which was later corrected by balloon angioplasty [1]. Though surveillance by measurement of blood pressure and periodic doppler ultrasound imaging continues after 2 years, hypertension is well controlled and patient is waning off of anti-hypertensive medication (Table 1).

**CONCLUSION**

This case shows that gastroduodenal arteries (GDA) can be used for revascularization of right renal artery in adolescent patients of fibromuscular dysplasia (FMD). The remodeling of arterial lumen, possibly due to natural growth and increased blood flow demand by the kidney, allowed for the viability of this revascularization. Regular postsurgical blood pressure monitoring aided in early detection of postsurgical stenosis.

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**Author Contributions**

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

Ojas A. Pradhan – 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.

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Large spigelian hernia: A case report

Linus Eze, Kenneth Agu, Stephen Edino

ABSTRACT

Introduction: Spigelian hernia is a rare variety of ventral abdominal hernia accounting for less than 2% of all abdominal hernias. Preoperative diagnosis is usually difficult and patients may present with intestinal obstruction. Treatment involves patient optimization and repair of the hernia. The latter is achieved either by open or laparoscopic technique with or without mesh. Outcome is usually excellent. Case Report: We report an unusually large spigelian hernia (20x30 cm) with an obvious ventral swelling in a 79-year-old female with malnutrition and uncontrolled diabetes mellitus. There was no associated intestinal obstruction. At operation, contents of the sac included viable small bowel, omentum, part of transverse colon, lower stomach, cecum and vermiform appendix. She was stabilized, had an open repair without mesh and was followed-up for eight months without signs of recurrence or other complications. Conclusion: Spigelian hernia is rare and preoperative diagnosis difficult in the majority of cases. Occasionally, like in this case, an obvious ventral swelling was present making diagnosis easier. Repair of the hernia was done by open technique without use of mesh due to the narrow defect on the abdominal wall.

Keywords: Abdomen, Hernia, Large, Spigelian

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INTRODUCTION

Spigelian hernia is the protrusion of pre-peritoneal fat, a sac of peritoneum or an organ through a defect or weakness in the spigelian fascia [1]. This hernia derives its name from Josef Klinkosch who was the first to describe it and named it after the Belgian anatomist Adriaan Van der Spiegel who was the first to describe the semi-lunar line as reported by Mittal et al. [2].

Most spigelian hernias protrude from the linea semilunaris where it meets the arcuate line, the point from which the posterior rectus sheath is deficient downwards. This area is also known as spigelian hernia belt and is located in a transverse band lying 0 cm to 6 cm, below the umbilicus but cranial to a line running between both anterior superior iliac spines where the spigelian fascia is widest [3]. However, spigelian hernia has been reported to occur above the umbilicus [4].

The incidence of spigelian hernia is about 0.12% of all abdominal hernias occurring between 4th and 7th decades of life [5]. Most patients are over 50 years of age with a male: female ratio of 1.1:1.8 giving a slight female preponderance. Because the hernia, especially when small, is located between tissue planes, it has been described as interparietal, interstitial, or intermuscular hernia.

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The defect or weakness in the spigelian fascia can be congenital or acquired. The acquired variety may arise from factors that lead to an increase in intra-abdominal pressure such as weight lifting, pregnancy and parturition, chronic cough, constipation and abdominal obesity. Also, operations with insertion of drain or laparoscopic ports within spigelian fascia may predispose to herniation.

The hernias are usually small and lie between different muscle planes making them inconspicuous and difficult to diagnose preoperatively. The hernia sac may contain omentum, small intestine, part of the colon, inflamed appendix or incarcerated Meckel’s diverticulum [6].

CASE REPORT

A 79-year-old female presented with a five year history of right ventral abdominal swelling with occasional abdominal discomfort. Initially, the swelling was small, mildly painful and disappeared on lying down. It gradually increased to approximately 20 cm by 30 cm at presentation. There was no associated change in bowel habit or other gastrointestinal symptoms. There was no history of cough, fever or past abdominal surgery. She had eight pregnancies but with only two surviving daughters both of whom were married. Due to poverty, she had no means of seeking and obtaining medical assistance and presented at a free rural medical program at her village from where she was referred for management under the sponsorship of a humanitarian organization. On physical examination, she was elderly, malnourished, pale, depressed and with poor general health. She had a blood pressure of 200/110 mmHg with a pulse rate of 80 beats/minute.

The chest was clinically clear. The abdomen revealed a large protruding irreducible swelling on the right side measuring approximately 20 cm by 30 cm in the widest dimensions (Figure 1). There were visible peristalsis and exaggerated bowel sounds. A wide defect was felt below the umbilicus and lateral to the right rectus abdominis muscle and measured 8 cm in diameter. A diagnosis of large irreducible spigelian hernia was made.

Laboratory investigation results showed a packed cell volume of 40%, normal electrolytes, urea and creatinine, glycosuria (3+), fasting blood glucose 380 mg/dl. Plain chest radiograph showed aortic unfolding but clear lung fields and abdominal ultrasonography noted bowel gas and peristalsis in the sac.

The patient was admitted and treatment for her diabetes mellitus and hypertension commenced. She was commenced on subcutaneous insulin which was converted to intravenous insulin added to 5% glucose infusion and potassium chloride intraoperatively. She was given oral nifedipine for the hypertension which was administered on the morning of operation and immediate postoperative period with little quantity of water.

The patient was counseled and consent obtained for operation. In the theatre, her diabetes control was continued with glucose/insulin/potassium infusion. Under general anesthesia with cuffed tracheal intubation and good muscle relaxation a transverse incision was made over the mass.

The fibres of external oblique muscles were split to get to the hernia sac with a narrow neck (Figure 2). This was opened revealing viable small bowel, omentum, part of transverse colon, lower stomach, cecum and vermiform appendix held by minimal adhesions which were released by sharp/blunt dissection. The contents of the sac were returned to the peritoneal cavity and the former was trimmed down to the neck and closed using continuous Vicryl 2/0 suture. The aponeurotic tissue around the remarkably narrow spigelian fascial defect was approximated over the closed sac with non-absorbable (nylon 0) suture. Subsequently, the wound was closed in layers without drainage.

Postoperatively, patient had a rapid and uneventful recovery and was discharged on the 10th postoperative day. She has been followed-up for eight months and has remained well with no hernia recurrence.

Figure 1: Physical examination of the abdominal swelling.

Figure 2: Exposed sac of the hernia.
DISCUSSION

The case been reported was a female which is in keeping with an earlier report that gave a female to male ratio of 1.8:1.1. Also the patient was aged 74 years when she first noticed the hernia putting her in the upper limit of most reported cases that occurred between the 4th and 7th decade.

Most spigelian hernias are small and the symptoms are usually non-specific. The first presentation may be from intestinal obstruction owing to the narrow and rigid borders of the fascial defect. In this case, it was a relatively large protuberant hernia and the diagnosis was obvious with the defect palpated at the lateral border of the right rectus abdominis muscle. Most of the reported hernias occurred on the right side.

Diagnosis of spigelian hernia is difficult due to its rarity and paucity of specific symptoms. Only about 50% of cases are diagnosed preoperatively. Diagnosis can be facilitated by use of ultrasonography or CT scan [7]. However, CT scan provides greater sensitivity and specificity. This uncommon hernia with its diagnostic difficulty may mimic other lesions around the affected site in the abdominal wall including rectus sheath hematoma, seroma, peritoneal abscess, lipoma, or peritoneal tumor implants.

The most common content of the sac is omentum, but intestine, appendix, gallbladder, or ovary has been reported in literature [6, 8]. In our patient presumably due to the large size, it contained viable small bowel, omentum, part of transverse colon, distal stomach, cecum and vermiform appendix.

Urgent repair of spigelian hernia is recommended because of high risk of intestinal obstruction and strangulation. In most cases, it is possible to directly approximate the fascia to close the defect but cases with large defect will require use of prosthetic mesh. This repair can be accomplished by open technique which we utilized or laparoscopically [9]. In our case, though the hernia was unusually large, the neck of the sac and the fascial defect was quite narrow making it easy to co-apt the firm edges of the aponeurosis adequately without tension using nylon 0.

CONCLUSION

Spigelian hernias are rare, commonly small and carry a high risk of complication because of difficulty with preoperative diagnosis. However, when large like in the index case, diagnosis is relatively easy and repair by open technique can effect a cure.

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Author Contributions

Linus Eze – 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
Kenneth Agu – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Stephen Edino – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

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Pediatric omental infarction: Value of the laparoscope

Ian Robertson, Domhnall O’Connor, Waqar Khan, Kevin Barry

CASE REPORT

An eight-year-old boy presented to the emergency department with a one-day history of progressive right iliac fossa pain, associated with anorexia but no nausea or vomiting. He was considered obese and weighed 48.6 kg. His vital signs were within normal limits. Clinical examination revealed marked abdominal tenderness in the right iliac fossa and suprapubic area. The patient had an elevated C-reactive protein (CRP) level at 6.1 mg/L. All other hematological and biochemical markers were within normal limits. A clinical diagnosis of acute appendicitis was therefore made and early surgical intervention was planned in the form of open appendicectomy.

At surgery, the appendix was not located in the right iliac fossa or right paracolic region. In order to discern the exact anatomical location of the appendix, conversion to laparoscopy was employed. A grossly normal appendix was subsequently visualized in the subhepatic space. An incidental finding of a portion of infarcted omentum was noted in the left upper quadrant (Figure 1). The portion of infarcted omentum was then excised laparoscopically. In addition, laparoscopic appendicectomy was performed in order to avoid future confusion regarding the presence of an open appendicectomy incision in the right iliac fossa.

The patient made an uneventful postoperative recovery and was discharged three days later. Final histology reports confirmed a diagnosis of primary omental infarction and a normal appendix.

DISCUSSION

Omental infarction is a rare cause of right-sided abdominal pain, especially in the pediatric population. 0.1% of pediatric patients, undergoing surgery for suspected appendicitis, will prove to have omental infarction [1]. Omental infarction may be classified as primary or secondary. Primary infarction is considered idiopathic, such as in our patient, whereas secondary infarction is due to an underlying pathology, either local or systemic. Further associations have been reported between pediatric omental infarction and vasculitis [2]. Anatomical variations to the omentum may predispose pediatric patients to omental infarction in the post-prandial state [3]. Obesity has been implicated as a risk factor for primary omental infarction in children and the...
inflammatory effects of adipose tissue may also contribute to the pathogenesis of this condition [4]. Weights in excess of the 90th percentile have been reported in many such cases [2, 5]. In our case, the patient's weight was above the 97th percentile for his age (48.6 kg). Age and sex have both been studied and shown to have a causative association with omental infarction. Eighty percent of all reported cases of omental infarction occur in adults, with a predominance in the 4th and 5th decades of life [3, 6]. Males have a 2:1 predominance over females and this may be due to an increased amount of fat in the male omentum [1, 5].

Omental infarction usually presents acutely with abdominal pain. It may mimic acute appendicitis. Prodromal symptoms such as nausea, vomiting or altered bowel habit are usually absent [7]. Preoperative imaging is required in order to definitively diagnose omental infarction in children. However, this may not be available in all centers. The two most effective imaging modalities are abdominal ultrasound and computed tomography. Omental infarction classically presents as a wedge/triangular shaped, non-compressible hyperechoic mass deep to the anterior abdominal wall on ultrasound. Recognition of omental infarction on ultrasound however is operator-dependent [2]. The sensitivity of ultrasound has been reported as 64% in the pediatric population [8]. While computed tomography is considered a more sensitive technique (up to 90%), issues regarding availability and concern for exposure to ionizing radiation in children may preclude its use. Should computed tomography be employed, the classical appearance of omental infarction consists of an area of hyperattenuation deep to the anterior abdominal wall. In children, the diagnosis of acute appendicitis is almost always clinically based and as such, imaging studies are rarely requested. For this reason, the diagnosis of omental infarction may prove elusive, as happened in this case.

If diagnosed preoperatively, omental infarction may be managed conservatively with appropriate analgesia. The condition is generally self-limiting and will resolve spontaneously with time. Van Kerkhove et al. note the rates of complications after omental infarction in children are clinically insignificant, describing them as “academic” [1]. Potential complications of omental infarction include adhesion formation and bowel obstruction. When diagnosed at the time of surgery, the infarcted omental segment can be removed. This is facilitated by the laparoscopic approach, as in our patient [6].

CONCLUSION

There have been relatively few cases of pediatric omental infarction published in the literature. Each newly reported case provides a unique learning opportunity. Omental infarction should be considered as part of the differential diagnosis for acute, right sided abdominal pain in children. While a conservative approach is the preferred management option, preoperative imaging studies are not generally employed, particularly in circumstances where a clinical diagnosis of acute appendicitis has been made.

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