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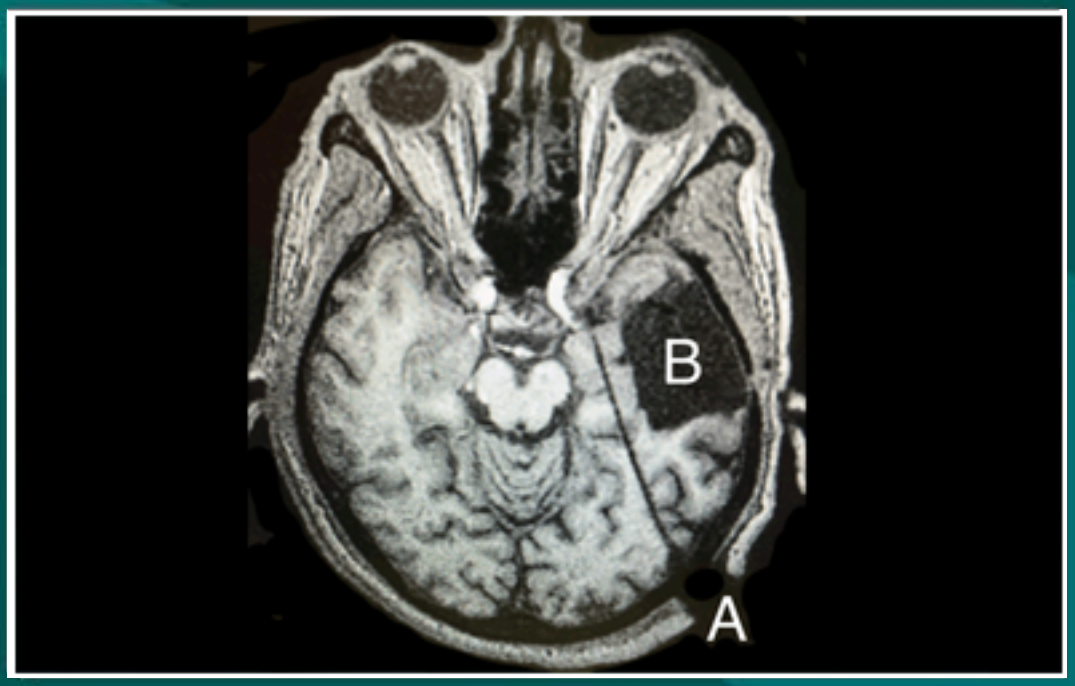

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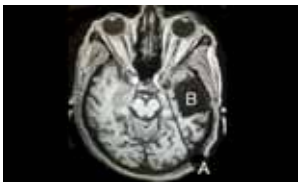

All Articles:

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Contents

Vol. 7, No. 8 (August 2016)

Cover Image

Case Series

Case Report

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CASE SERIES

PEER REVIEWED | OPEN ACCESS

Atypical femoral fractures: Possible association with long-term bisphosphonate usage

Prakash Selvam, Sivamurugan Soundarapandian, Ravisubramaniam Soundarapandian, Cheralathan Senguttuvan

ABSTRACT

Introduction: Atypical femoral fractures are being identified as a specific type of femoral fracture with regards to the anatomical location, fracture pattern, low energy trauma and possible association with long-term usage of bisphosphonates. Though there is no conclusive evidence to suggest a causal association of bisphosphonates with this type of femur fracture, the recent increase in reporting of such fractures in patients under long-term usage of bisphosphonates justifies the need for research into the association between the two. Case Series: We intend to report two such cases that presented to our institution. Both patients presented with the characteristics of atypical femoral fractures which included low energy trauma, anatomical location, transverse or short oblique configuration with a medial spike, no comminution and lateral cortical thickening. Both patients underwent surgical fixation and were followed-up till union of the fracture. Conclusion: Identifying this specific fracture and treating it with caution is necessary as they tend to take more time to heal in comparison with high energy trauma femoral fracture. Educating physicians and surgeons regarding this type of fracture is of prime importance both in prevention as well as treatment of this type of fracture, which contributes to significant reduction of morbidity and mortality to the patient. Careful prescription of bisphosphonates for patients with definite indications and proper monitoring during follow-up would be another justifiable preventive measure.

Keywords: Atypical femoral fracture, Bisphosphonates, Stress fracture

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INTRODUCTION

Atypical femoral fractures are being identified as a specific type of femoral fracture with regards to the anatomical location extending from subtrochanteric to supracondylar region of femur, fracture pattern showing transverse or short oblique configuration with medial spike, low energy trauma, female preponderance and possible association with long-term usage of bisphosphonates [1–4]. Bisphosphonates form a very important class of drugs used in day to day practice for multiple indications. It becomes essential to continue therapy in certain conditions but there have been incidences where the patient continues therapy beyond the necessary duration of therapy [1]. Though there is no conclusive evidence to suggest a causal association of bisphosphonates with this type of femur fracture, the recent increase in reporting of such fractures in patients under long-term usage of bisphosphonates justifies the need for research into the association between the two [1]. The clinical challenge posed by this type of fracture is identifying and treating it accordingly as this has a major bearing in post-injury functionality status and on quality of life [4].

CASE SERIES

We intend to report two such cases that presented to our institution. Informed consent was obtained from the patients to use their clinical data for academic purposes alone. Patient demographics are summarized in Table 1. Both patients presented with the characteristics of atypical femoral fractures which included low energy trauma, characteristic anatomical location, transverse or short oblique configuration with a medial spike, no comminution and lateral cortical thickening.

Case 1

A 62-year-old male pensioner without any pre-existing co-morbid conditions reported to our institution during September 2013 with alleged history of fall from standing position and sustained Sub-trochanteric fracture of left femur. The patient underwent fixation with Angled blade plate and was under follow-up. The fracture showed delayed union, therefore the patient was kept under toe touch weight bearing but unfortunately patient suffered a second trivial fall one year after the first fracture and developed sub-trochanteric fracture on the opposite side. This made us ponder about the unusual presentation and made us to do a detailed retrospective analysis of the patient characteristics. On probing, the patient revealed history of taking bisphosphonates for three years on prescription by a primary care physician for Osteopenia, which was not elucidated on first presentation. The patient also admitted to have had thigh pain since two weeks prior to the second fracture. Relook at the first radiograph (Figure 1) showed stress reaction on the lateral cortex of contralateral femur. This made us do a detailed literature search regarding this type of fracture and confirm that this specific pattern matches the typical description of atypical femoral fractures reported in literature [1–3]. We stopped bisphosphonate medication and fixed both femurs with proximal femoral nail (Figure 2). Both fracture healed at about six months. At one year follow-up patient is doing full weight bearing without any difficulty (Figure 3).

Case 2

A 73-year-old female, a known case of hypertension and dyslipidemia, presented with proximal third femur fracture left side with lateral tibial plateau fracture right knee with alleged history of fall from standing position. The radiograph (Figure 4) showed features matching the description of atypical femoral fractures and on detailed elucidation of history the patient revealed that she was on bisphosphonate medication for last five years on prescription by her gynecologist. The patient too had been having vague thigh pain since two weeks prior to the injury. This patient had lateral cortical stress reaction on contralateral femur but did not have thigh pain on that side. We advised stopping the medication and patient underwent fixation with ante-grade femoral nail for femur fracture and percutaneous screw fixation for lateral tibial plateau fracture. We had advised prophylactic fixation for the contralateral femur but since the patient was not willing for it, she has been given a word of caution and advised to report immediately if she developed thigh pain on right side. Patient is presently under follow-up and radiograph (Figure 5) taken 12 weeks following surgery showing evidence of fracture union on operated side.

DISCUSSION

Bisphosphonates being a very important class of drugs in management of osteoporosis have been prescribed very commonly by primary care physicians and surgeons. There have been many publications reporting fractures in patients on long-term bisphosphonate medications [2–4]. Majority of these fractures have been reported in female patients [2]. The percentage of population who took bisphosphonate medication and developing fracture while on treatment is low [3]. There have been postulates indicating genetic polymorphism among general population that may contribute to increased risk of development of these fractures in certain individuals in comparison to general population [1]. The American Society of Bone and mineral research has devised a diagnostic criteria with major and minor features to classify a fracture as atypical femoral fracture [1]. The important features being low energy trauma, location

Table 1: Patient demographics

Patient characteristics		Case 1	Case 2
Age		62	73
Sex		Male	Female
Fracture Characteristics	Location of fracture	Right side: 1 cm distal to lesser trochanter	10 cm distal to lesser trochanter
		Left side: 3 cm distal to lesser trochanter	
	Fracture configuration	Transverse fracture with superior medial spike	Transverse fracture with inferior medial spike
		Transverse fracture with inferior medial spike	
	Nature of Trauma	Low energy (Fall from standing height)	Low energy (Fall from standing height)
	Comminution	No	No
	Thickening of cortex	Seen laterally	Seen laterally
Bisphosphonate exposure history	Name of drug	Alendronate	Ibandronic acid
	Dosage of drug	70 mg once a week	150 mg once a month
	Duration and patient adherence	3 years of continuous therapy started during 2012	5 years of continuous therapy started during 2010
	Condition for which therapy advised	Osteopenia	Osteopenia
History of prior low energy trauma fracture		Right Subtrochanteric fracture presented during September 2013 with Stress reaction on the left side	Lateral tibial plateau fracture of opposite knee
		Left side fracture occurred during September 2014	
Co-morbid conditions	Presence of Vitamin D deficiency	Insufficiency – 19.8 ng/ml	Insufficiency – 23.8 ng/ml (2012)
			Sufficiency – 31 ng/ml (2015)
	Other co-morbid conditions	Nil	Dyslipidemia
			Hypertension
			Hysterectomy (Indication not known)
		Calcium carbonate 500mg + Calcitriol 0.25 mg	Calcium carbonate 500mg + Calcitriol 0.25 mg
			Indapamide 1.5 mg for hypertension
			Atorvastatin 20 mg for dyslipidemia
Special Investigations	Bone densitometry	Not done	DEXA scan
			Right femur (2012) 0.757
			Left femur (2012) 0.759
			Right femur (2015) 0.757
			Left femur (2015) 0.816
	Bone turnover markers	Not done	Not done
	Bone histomorphometry	Not done	Not done

of fracture which should be distal to lesser trochanter and proximal to supracondylar region, transverse or short oblique configuration with a medial spike without comminution, presence of prodromal thigh pain.

The fracture may present bilateral in some cases or may show features of lateral cortical stress reaction [1, 5]. All the above features have been noted in our cases. It should be noted that stress fractures which occur in young and fit athletes usually starts from the medial cortex in contrast to atypical femoral fractures where the fracture

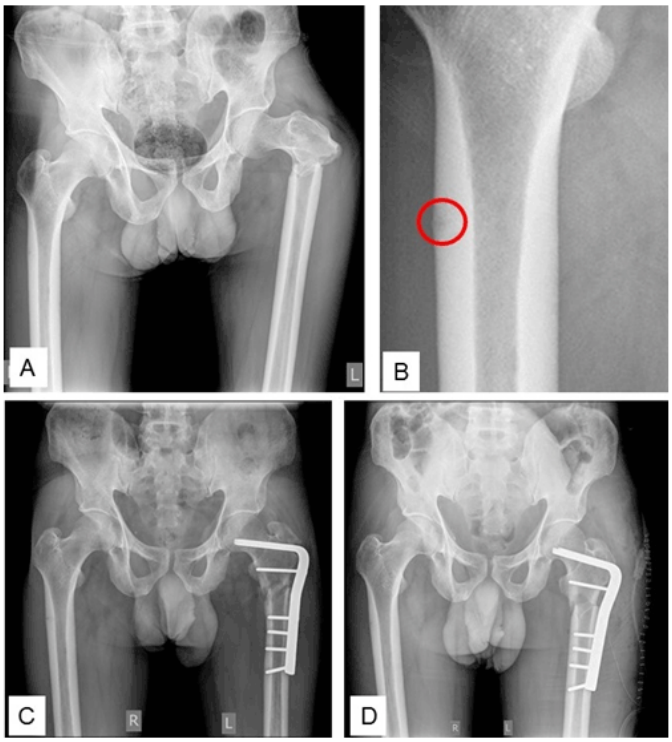

Figure 1: (A) Radiograph showing anteroposterior view of both proximal femurs at the time of presentation, (B) Magnified view of the lateral cortex of right femur showing cortical stress reaction (red circle), (C) Immediate postoperative radiograph, (D) Radiograph taken during ninth month follow-up showing no evidence of union.

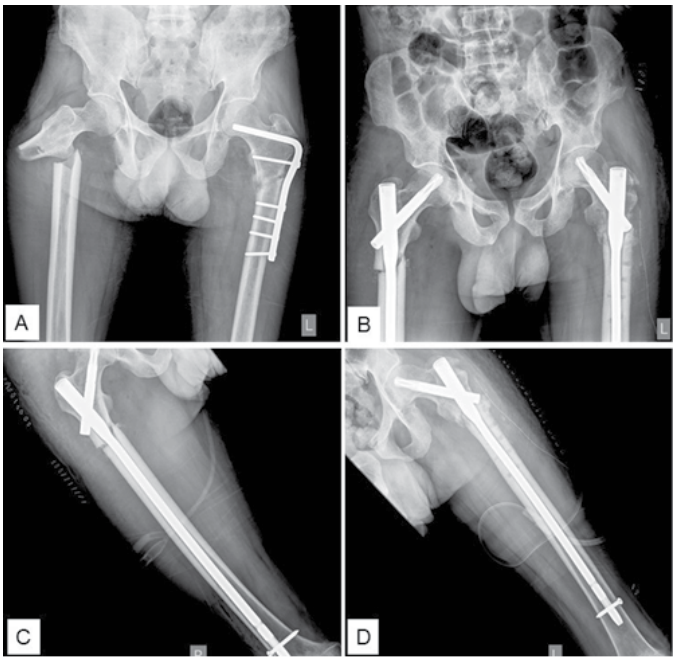

Figure 2: (A) Radiograph taken at the time of second fall corresponding to one year follow-up of first surgery; (B–D) Immediate postoperative radiograph after bilateral fixation with proximal femoral nail.

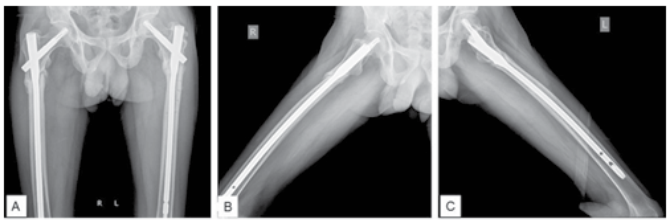

Figure 3: (A) Radiograph showing anteroposterior view of both proximal femurs, (B, C) Radiograph showing lateral view of proximal femurs at one year follow-up after second surgery

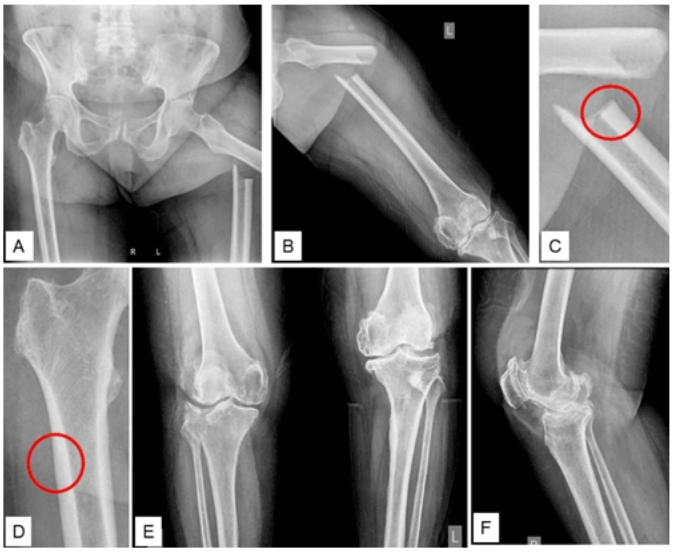

Figure 4: (A, B) Anteroposterior view of both proximal femurs, (C) Magnified view of left femur showing lateral cortical stress reaction (red circle), (D) Magnified view of right femur showing lateral cortical stress reaction (red circle), (E) Anteroposterior view of both knee showing lateral tibial plateau fracture on right side, and (F) Lateral view of right knee.

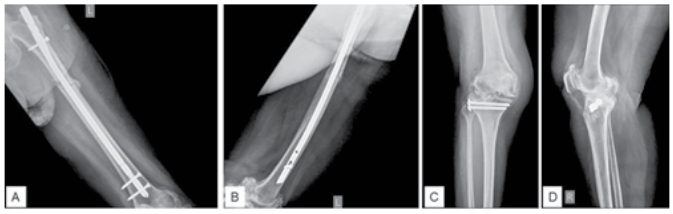

Figure 5: (A) Anteroposterior view, (B) Lateral view of left femur showing radiological signs of on-going union, (C) Anteroposterior view and (D) Lateral view of right knee. All radiographs taken at 12 weeks of follow-up.

line starts from the lateral cortex and progresses medially [1]. The possible mechanisms by which bisphosphonates could contribute to development of fractures include altering collagen integrity, homogeneity of bone mineral density distribution, decreased bone remodeling which is manifested as micro-architectural deterioration, crack initiation, crack progression, delayed healing of cracks [1, 2]. Though bisphosphonates do not interfere with callus formation they have been postulated to interfere with fracture healing during the phase of remodeling

from immature callus to mature bone [1]. This causes retention of callus which is seen as lateral cortical thickening in radiograph. They have also postulated that bisphosphonates could cause indirect inhibition of angiogenesis which is usually coupled with osteoclastic remodeling [1]. But majority of the above postulates are based on animal studies and there is no conclusive evidence yet to establish a causal association between bisphosphonates and atypical femoral fractures. In vitro studies to demonstrate that bisphosphonates do inhibit osteogenesis have also been published [6].

There have been reports of fractures occurring in other bones in patients on long-term bisphosphonate medications but majority seem to be case reports [7, 8]. There have been debates about the ideal duration of therapy for bisphosphonates but evidence from literature supports that there is no proven efficacy beyond five years of continuous therapy [1]. Literature review shows the duration of treatment in cases reported with atypical femoral fractures ranged from 2–8 years [2]. With regards to diagnosis, majority of the fractures are identified based on the typical radiograph findings. In case of patients who present with incomplete fractures or doubtful findings on routine radiographs, it is suggested to do CT scan or MRI scan to confirm the lateral cortical stress reactions [1, 2]. Some publications also include bone scan studies to detect stress reactions [1, 2]. Histomorphometric analysis with biopsy samples obtained from iliac crest or fracture site have been considered to be added valuable evidence for research purposes [1].

Recommendations regarding management of these fractures depend on the patient presentation, with all manifested fracture to be ideally fixed with intramedullary devices, since they did not interfere with fracture hematoma and are biomechanically in advantage when compared to extramedullary devices [1, 9]. Both of our cases were fixed with intramedullary device with first case requiring revision from angled blade plate. For patients who present with thigh pain and lateral cortical stress reaction, current literature suggest prophylactic fixation which significantly reduces morbidity to the patient [10]. For patients not willing for surgery, after explaining the risk of fracture the physician may advise partial weight bearing until radiological appearance of union [1], which was done in our second case. Literature evidence also supports use of teriparatide to hasten healing in this type of fracture [1], but we have not used it in both of our cases. Supplementation of vitamin D and calcium is justified for patients in whom investigations confirm deficiency [1].

CONCLUSION

Identifying this specific fracture and treating it with caution is necessary as they tend to take more time to heal in comparison with high energy trauma femoral fracture. Educating physicians and surgeons regarding this type of fracture is of prime importance both in prevention and treatment of this type of fracture, which contributes to significant reduction of morbidity and mortality to the patient. More research is needed to arrive at a risk benefit ratio which might justify administration of bisphosphonates in a patient and to decide on the appropriate duration of individualized therapy.

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Author Contributions

Prakash Selvam – 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
Sivamurugan Soundarapandian – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ravisubramaniam Soundarapandian – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Cheralathan Senguttuvan – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE SERIES

PEER REVIEWED | OPEN ACCESS

Complicated Meckel's diverticulum

Ahmad Solyman Ahmad, Yasser Abdel Razek Mohamed, Mazin Abdullah Arif, Albroumi Said Abdullah

ABSTRACT

Introduction: Meckel's diverticulum is rare among the general population. Symptoms are varied, the diagnosis is often difficult and the abnormality is usually an incidental finding in laparotomies. Undiagnosed Meckel's diverticulitis harbor a considerable probability of complications; including perforation and peritonitis. Case Series: Herein, we report two cases, first case was a 27-year-old male presented with non-specific lower abdominal pain and nausea. Meckel's diverticulitis was on top of the differential diagnosis by CECT scan of the abdomen. He underwent surgical resection of the Meckel's diverticulum and appendectomy. The second case was 47-year-old male presented with epigastric pain shifted to the right lower abdomen and one episode of vomiting. The erect abdominal radiograph revealed pneumoperitoneum, which necessitates urgent laparotomy and diverticulectomy. Conclusion: Meckel's diverticulum cases are the most common gastrointestinal congenital anomalies despite its relative rarity, but should be pursued in diagnosis and treated surgically because of the high rate of inflammation, intestinal obstruction and perforation.

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INTRODUCTION

Meckel's diverticulum is a remnant of omphalomesenteric duct. Small percentage of Meckel's diverticula become symptomatic when it bleeds, typically due to presence of ectopic gastric mucosa rarely, diverticulum contains rests of pancreatic tissue Incidence: 2% of general population, Found within 2 feet of ileocecal valve. Most have clinical symptoms before two years of age (Rule of 2s). Embryologically, it is a result of partial obliteration of the omphalomesenteric duct during the fifth week of gestation and contains the three layers of the small intestine, so that it is a true diverticulum. Usually, it measures about 1 and 10 cm in length [1].

Meckel's diverticulum is the most common one of omphalomesenteric duct anomalies, which also includes umbilicoileal fistula, umbilical sinus, umbilical cyst, and fibrous cord connecting ileum to umbilicus. This finding is clinically significant because this band can cause obstruction or volvulus [2]. Meckel's diverticulum

is equal is incidence among genders, despite the higher complication rate in males and has no association with other major congenital malformations. However it is more founded in patients with Crohn's disease than in the general population [2, 3].

CASE SERIES

Case 1

A 27-year-old male presented with a non-specific abdominal pain and nausea, mainly at the right iliac fossa, since three hours. There was no associated fever.

On examination the abdomen was soft, with mild tenderness at the lower abdomen without rigidity or guarding.

On investigation, white blood cell count was 5.77x10^3/uL and hemoglobin was 13.4 g/dl.

Initial ultrasonography examination was inconclusive as there was a slight prominence of gut loops with some localized fluid like collection in right iliac fossa. Contrast-enhanced computed tomography (CECT) of abdomen and pelvis was advised for further evaluation. The CECT scan of abdomen and pelvis showed a blind end bowel loop, containing air fluid level, emerging from the distal ileum; localized fluid collection with air fluid level as well as multiple regional mesenteric lymph nodes averaging 8.5 mm are seen adjacent to this loop; the appendix measures 8 mm in cross-sectional diameter. These findings were accompanied by dilated small bowel loop, measures 42 mm in diameter; likely ileus. Therefore, the possibility of Meckel's diverticulitis and or appendicitis, with possible perforation was considered (Figure 1A–B).

The surgical interference confirmed the diagnosis of a complicated Meckel's diverticulum by inflammation with a gangrenous portion. The Meckel's diverticulum was resected along with the secondarily inflamed appendix. Anatomical closure of the small bowel into two layers was implemented.

Case 2

The second case was 47-year-old male, presented with epigastric pain shifted to the right lower abdomen and one episode of vomiting.

On examination the abdomen was soft, with tenderness at the right iliac fossa. Yet, there was no rigidity or guarding.

On investigation white blood cell count was 9.79x10^3/uL and hemoglobin was 14.35 g/dl. The erect abdominal X-rays revealed pneumoperitoneum, which necessitated urgent laparotomy, perforated Meckel's diverticulum diagnosis was surgically confirmed and diverticulectomy had been done (Figure 2A–B).

Histopathological examination described a blind ended small bowel segment, 1.5 cm in diameter and 3 cm in length with a 1 cm perforation rent. Normal bowel wall layers were found, with no detected heterotopic gastric or pancreatic tissues.

DISCUSSION

Meckel's diverticulum is a remnant of omphalomesenteric duct found in 2–3% of autopsy series. Minority of Meckel's diverticula become symptomatic. This is attributed to presence of ectopic gastric mucosa. Rarely, diverticulum contains rests of pancreatic tissue. The omphalomesenteric duct was connection between yolk sac and primitive digestive tract in embryogenesis.

Meckel's diverticulum is the most common form of omphalomesenteric duct anomalies, which also includes umbilicoileal fistula, umbilical sinus, umbilical cyst, and fibrous cord connecting ileum to umbilicus.

There is a 4.2–6.4% lifetime risk of complications [3–5]. Common complications to MD are gastrointestinal bleeding, intussusception, obstruction and diverticulitis.

Meckel's diverticulum usually measures 5–6 cm in length, positioned within 2 feet proximal to ileocecal valve. Enteroliths are found in lumen in some cases. The "Rule of 2s" refers to its 2% prevalence, 2-feet distance from the ileocecal valve, 2 inches length, containing one

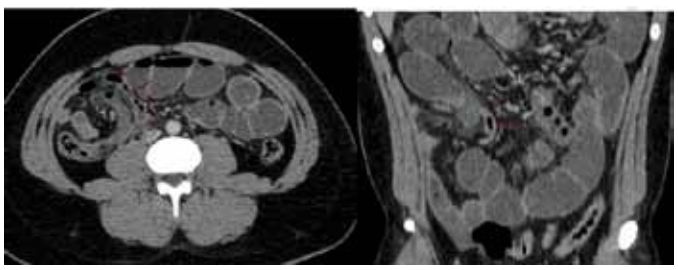

Figure 1: Contrast enhanced computed tomography scan of abdomen: (A) Axial, (B) coronal reformats showing Meckel's diverticulum as non-dilated air and fluid filled short loop in between the dilated fluid filled small bowel loops. There is crescent shaped localized fluid collection with air fluid level and no marginal enhancement adjacent to diverticulum denoting localized perforation.

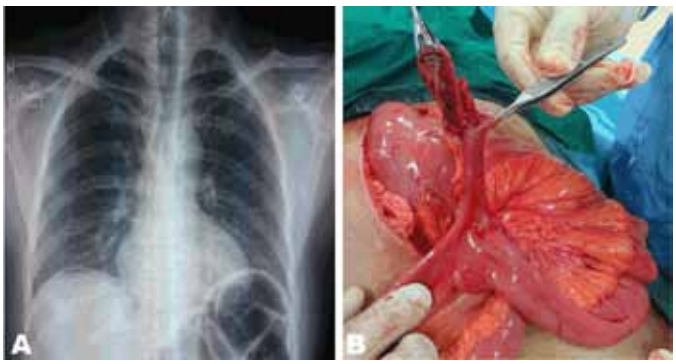

Figure 2: (A) Plain radiography of chest showed air under the right cupola of the diaphragm denoting hollow viscous perforation, (B) Intraoperative photography showing the Meckel's diverticulum with gangrenous perforated tip.

or two types of heterotopic gastric or pancreatic tissue and usually symptomatic by the age of two years.

Histologically, it composed of same layers as adjacent small bowel but with addition of heterotopic gastric or pancreatic rests.

Meckel's diverticulum frequently presented with gastrointestinal bleeding, ulceration, abdominal pain, or mass.

However, it may also presented as intermittent abdominal pain, occult fecal blood, hematochezia, small bowel obstruction and intussusception.

Perforation of Meckel's diverticulum with hemoperitoneum in children is rare and serious.

Meckel's diverticulum can be complicated with torsion, which may be present with nonspecific abdominal pain and mass Meckel's diverticulum often become symptomatic before two years of age 60% of patients come to medical attention before 10 years of age.

Males are equal to females in true incidence; however complications rate is higher in males.

Ectopic gastric mucosa is protruding into the lumen of the diverticulum and neoplasms show contrast enhancement [6]. The imaging of Meckel's diverticulum is important to avoid the considerable risk of perforation and gross peritonitis because of the non-specific findings of the Meckel's diverticulum and its clinical resemblance to appendicitis. Open or laparoscopic resection of the surrounding bowel and diverticulum are the proper surgical treatment.

CONCLUSION

Meckel's diverticulum is one of the most common gastrointestinal anomalies, and requires rapid surgical treatment due to its common complications. It should be kept in differential diagnosis during radiological evaluation of patients presented with acute abdomen.

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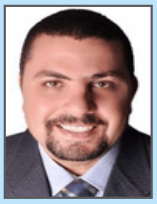

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Acute pancreatitis due to intragastric balloon

Orlando Jorge Martins Torres, Jose Maria Assunção Moraes-Junior, Camila Cristina S. Torres, Everardo de Almeida Nunes

ABSTRACT

Introduction: Intragastric balloon therapy is an option for treatment of obesity. Some complications have been reported but acute pancreatitis due to compression of the pancreas is a rare event. The aim of this study is report a case of acute pancreatitis due to intragastric balloon insertion. Case Report: In a 33-year-old male with BMI of 43.4 kg/m², intragastric balloon was inserted in the gastric fundus, the follow-up was uneventful. After four months, the patient had acute abdominal pain, nausea, vomiting and abdominal distension. Laboratory tests showed serum amylase 618 U/l and serum lipase 906 U/l. A CT scan showed that the tail of the pancreas was heterogeneous, minimal fluid and inflammation of peripancreatic fat. The intragastric balloon was observed causing compression at the transition from the body to the pancreatic tail. The intragastric balloon was removed and the patient underwent laparoscopic cholecystectomy. The inspection of the gallbladder was normal and the histology showed no signs of microlithiasis. The patient was discharged asymptomatic. Conclusion: Intragastric balloon is a common procedure in obese patients and pancreas compression due to the balloon should be included as cause of acute pancreatitis in these patients.

Keywords: Acute pancreatitis, Intragastric balloon, Obesity, Pancreatitis

How to cite this article

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INTRODUCTION

Obesity is considered an epidemic disease, a serious public health problem and associated with morbidity, mortality and quality of life. In addition, obesity is an independent risk factor for death. Obesity treatment options include medical treatment, endoscopic and surgery. Medication has been reported to be ineffective in the long-term treatment, and intragastric balloon and bariatric surgery have been shown to result in substantial weight reduction. Intragastric balloon therapy is indicated for temporary use and has been establish as a part of a multidisciplinary weight management program. The application is easy and has low morbidity and mortality

[1]. Some common complications included abdominal pain, nausea, vomiting and discomfort. There are also a few reported cases of esophagitis, gastritis, small bowel obstruction, antral impaction and gastric perforation. Compression of the pancreas by intra-gastric balloon leading to acute pancreatitis has been a rare event [2, 3]. The aim of this study is to present a rare complication of acute pancreatitis due to intragastric balloon used for treatment of obesity.

CASE REPORT

A 33-year-old male, clinical doctor, was referred from the Department of endocrinology to the Department of Gastroenterology and Digestive Endoscopy for management of obesity. His BMI was 43.4 kg/m² (weight 127 kg and height 171 cm). The intragastric balloon was inserted in the gastric fundus, uneventful and the procedure was tolerated very well. Within four months, he lost approximately 22 kg. From this date, the patient began to have abdominal pain, nausea and vomiting of moderate intensity. One week later, he presented sudden acute abdominal pain, nausea, vomiting and abdominal distension. The patient was taken to the emergency department and treated initially with symptomatic. The patient had no history of alcohol consumption. Laboratory tests showed leukocytosis and normal renal function. Serum amylase was 618 U/l, serum lipase was 906 U/l. Total bilirubin was 0.8 mg/dl, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT), were all normal. Transabdominal ultrasonography revealed a normal gallbladder without stones or biliary sludge and the bile duct diameter was 4 mm. A computed tomography scan of the abdomen was performed and showed that the tail of the pancreas was heterogeneously enhanced, with indistinct margins due to inflammation of peripancreatic fat. Some stranding and minimal fluid was also present. The intragastric balloon was also observed causing compression at the transition from the body to the pancreatic tail (Figures 1 and 2). A systematic investigation for other causes of acute pancreatitis was conducted. The diagnosis of acute pancreatitis due to compression by intragastric balloon was made.

An upper gastrointestinal endoscopy was performed, and the intragastric balloon was removed. A week later, the patient underwent laparoscopic cholecystectomy. The inspection of the mucosa of the gallbladder was normal and there was no gallstone or biliary sludge. The histopathologic study showed no signs of microlithiasis or cholecystitis. The postoperative course was uneventful, the amylase and lipase levels came back to normal and the patient was discharged asymptomatic.

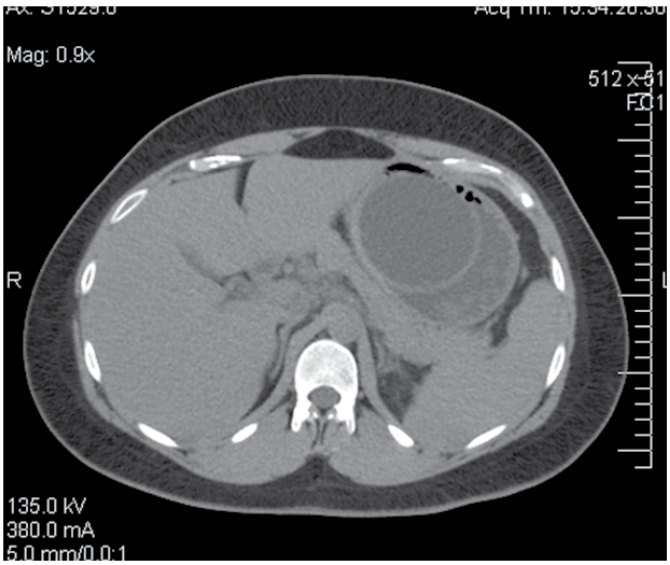

Figure 1: Computed tomography scan of the abdomen showing compression of the pancreas by the intragastric balloon.

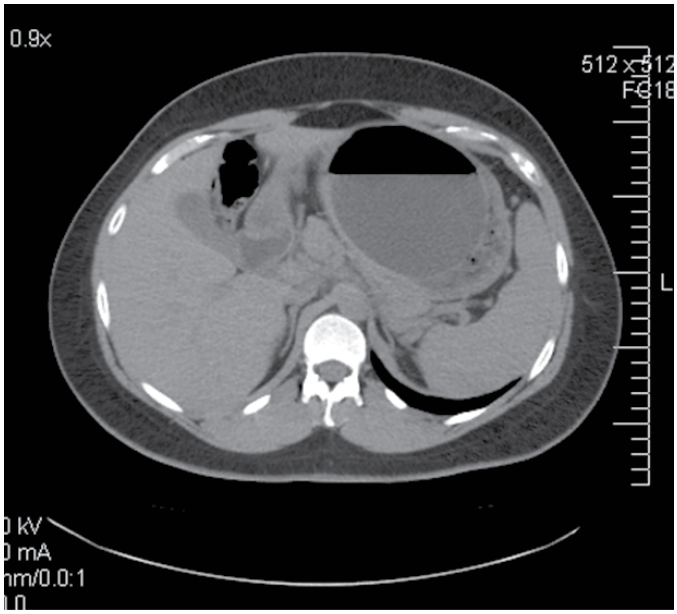

Figure 2: Computed tomography scan of the abdomen showing edema in the tail of the pancreas.

DISCUSSION

Acute pancreatitis is defined by Atlanta classification as abdominal pain that suggest pancreatitis, levels of serum amylase and lipase three or more times the normal value and imaging with characteristics findings. The process of acute pancreatitis can evolve the whole pancreas and cause reactions in many others organs. A variety of conditions can cause acute pancreatitis, but gallstones are implicated in the majority of cases. Others causes are alcohol abuse, hyperlipidemia, drugs

and endoscopic retrograde cholangiopancreatography. Mechanical causes of acute pancreatitis occur due to obstruction of the pancreatic duct or by direct trauma to the pancreas. Although the mechanism is not well defined, the nature and severity of the obstruction appear to influence the course of the disease. Acute pancreatitis with slow ductal obstruction due to pancreatic cancer is rare [2].

Pancreatic trauma may cause acute pancreatitis by a crash injury, transection of the pancreas or can result in injury of ductal structures. The diagnosis is suspected based on the clinical findings, although sometimes a blunt trauma may confuse the pancreas where it crosses the spine [2–4]. In this case, compression of the pancreas and its duct by the inflated balloon was responsible for acute pancreatitis, but we have to rule out others causes of acute pancreatitis like gallstones.

Normally, the balloon is located at the fundus of the stomach, without relation to the pancreas. In this case, on the contrary, the balloon was in contact with the pancreas leading to compression of the pancreatic duct and pancreatitis. Intragastric balloon is a common procedure in obese patients and pancreas compression due to the balloon should be included as cause of acute pancreatitis in these patients as observed by Mohammed et al. [3–6]. Others common complications of intragastric balloon are pain, nausea, vomiting and discomfort. Uncommon complications have been reported as esophagitis, gastritis and gastric perforation. After the diagnosis is confirmed, the intragastric balloon must be removed [3, 5, 6].

CONCLUSION

Intragastric balloon is a common procedure in obese patients and pancreas compression due to the balloon should be included as cause of acute pancreatitis in these patients.

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Author Contributions

Orlando Jorge Martins Torres – 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

Jose Maria Assunção Moraes-Junior – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Camila Cristina S. Torres – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Everardo de Almeida Nunes – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Adenocarcinoma of the transverse colon and gastrocolic fistula in a patient with situs inversus totalis: A case report

Nathalia Emanuelle Gasparini Magalhães Rodrigues

ABSTRACT

Introduction: Situs solitus is the normal position of thoracic and abdominal organs in the human body. Situs inversus is a mirror image of situs solitus. Situs ambiguus is an intermediate arrangement between both. Situs inversus is a rare condition, and usually does not cause any symptoms when isolated. There are a lot of case reports addressing situs inversus totalis (SIT) associated with cancer. However, the relation between both remains unclear. Gastrocolic fistula (GCF) is also a rare condition, and adenocarcinoma of the transverse colon is its most common cause in the Western world. Case Report: Herein, we report a case of a 61-year-old male with situs inversus totalis associated with adenocarcinoma of the transverse colon and gastrocolic fistula. Conclusion: The relation between SIT and cancer remains unclear. More studies are necessary to demonstrate it. In contrast, the relation between cancer and GCF is well defined, being the adenocarcinoma of the transverse colon the most common cause of GCF in the Western world.

Keywords: Adenocarcinoma of the transverse colon, Gastrocolic fistula, Situs inversus totalis, Situs solitus

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INTRODUCTION

The term situs means site, position. The normal position of thoracic and abdominal organs in the human body is referred to as situs solitus. Situs inversus is a mirror image of situs solitus. Situs ambiguus is an intermediate arrangement between both. Situs inversus is a rare condition, presented in 0.01% of the population [1, 2]. It can be classified as situs inversus with levocardia or dextrocardia. Levocardia refers to a cardiac apex pointed to the left, and dextrocardia a cardiac apex pointed to the right [2]. Situs inversus combined with dextrocardia is called situs inversus totalis (SIT).

Situs inversus totalis can be an isolated condition, or be associated with other diseases. Congenital heart defects occur in 3–5% of patients, being transposition of the great vessels the main condition [1, 2]. Primary ciliary dyskinesia occurs in about 25% of patients, being Kartagener syndrome the main diagnosis [1–3]. As an isolated condition, generally does not cause any symptoms.

Many cases of SIT associated with cancer have been reported in the literature; however, SIT is not itself a premalignant condition [4]. Herein, we report a case of

SIT associated with adenocarcinoma of the transverse colon and gastrocolic fistula.

CASE REPORT

A 61-year-old male arrived at our emergency department complaining of abdominal pain for the last 30 days. The pain was poorly localized and characterized. It worsened in the 24 hours prior to seeking medical care. Patient was also complaining of chronic bloody diarrhea, mostly melena. Had only one episode of bright red blood per rectum, and one episode of vomit (digested food with no blood), both occurring in the 24 hours prior to seeking medical care. Patient uses ethanol and tobacco chronically. He was admitted for investigation. On admission laboratory examinations showed hemoglobin 3.5 g/dl and hematocrit 11.2%. The patient was immediately submitted to blood transfusion. During hospitalization, abdominal computed tomography scan showed situs inversus with signs of dextrocardia, an expansive, concentric and mucosal lesion located in the gastric antrum, left urinary tract calculus and left hydronephrosis (Figure 1). The first upper endoscopy showed an infiltrative lesion in the gastric antrum. The patient presented hematemesis followed by hemodynamic decompensation eight days after upper endoscopy. He was resubmitted to an upper endoscopy, which revealed a gastrocolic fistula, and was maintained with a nasogastric tube draining fecaloid secretion. Gastric infiltrative lesion was biopsied in the first upper endoscopy; the results were released nine days later and showed an ulcerated and well differentiated adenocarcinoma of the gastric antrum, with tubular pattern. Colonoscopy revealed an infiltrative and circumferential lesion in the transverse colon, occupying 90% of its lumen (Figure 2). After diagnostic investigation, patient was submitted to resection of the gastric antrum, cecum, ascendant colon and transverse colon – 2/3 of its extension (Figure 3A–B). It was made an anastomosis between the terminal ileum and the distal transverse colon, and a Roux-en-Y anastomosis to connect stomach and intestine (Figure 4). The patient presented good recovery in the postoperative period. Histopathologic examination of the resected portion showed adenocarcinoma of the transverse colon penetrating the gastric wall, and gastritis. Two out of twelve examined lymph nodes from the surrounding fat tissue were affected. Postoperative histopathology did not show adenocarcinoma of the gastric antrum.

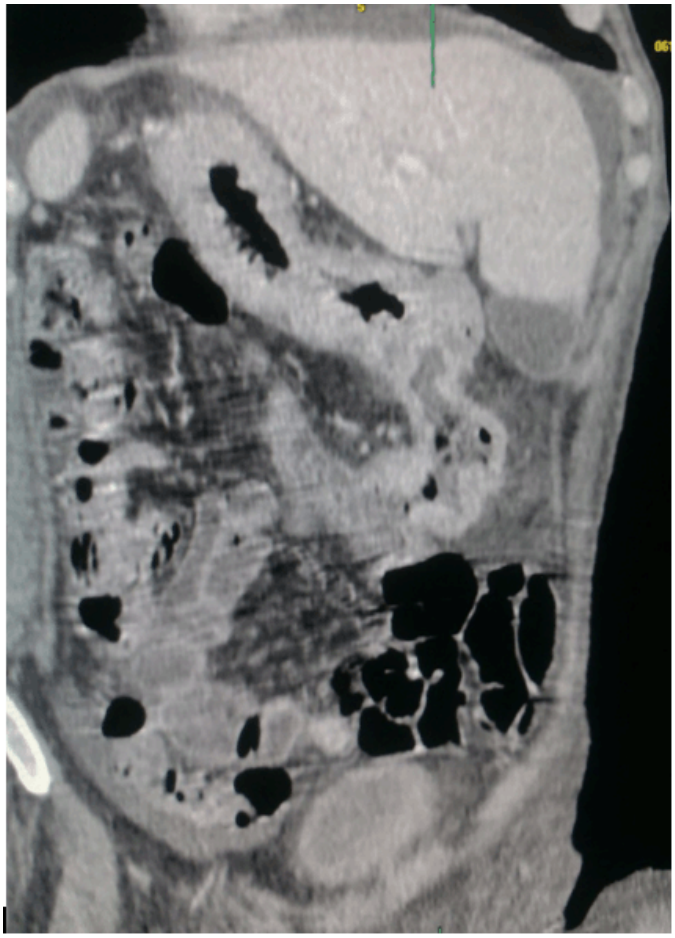

Figure 1: Abdominal computed tomography scan (coronal reconstruction) showing situs inversus with dextrocardia signs and a lesion at the gastric antrum.

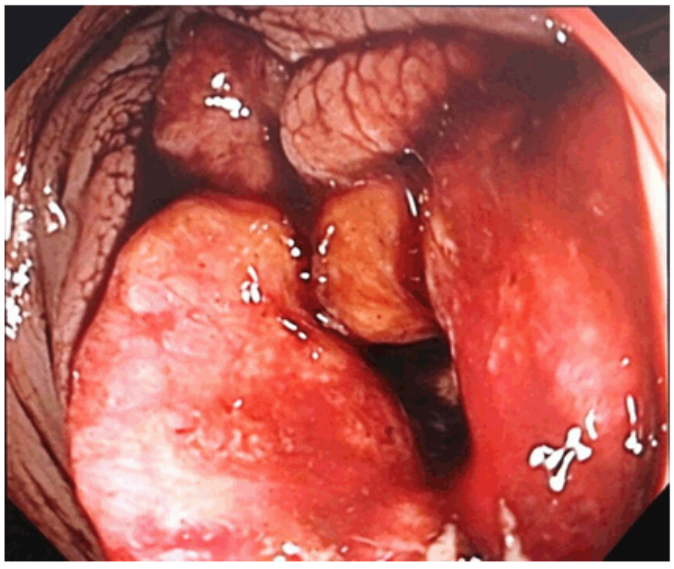

Figure 2: Colonoscopy showing a circumferential lesion at the transverse colon, occupying 90% of its lumen.

DISCUSSION

The genetic cause of SIT is unclear. There is evidence of microdeletion of chromosome sub-band 2q37.3 as a cause of it [5], as well as balanced reciprocal translocation t(5;11)(q32;q24.2) [6], UVRAG gene abnormalities [7],

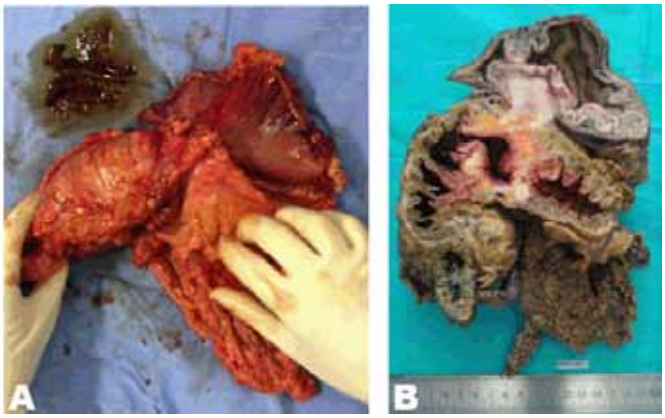

Figure 3: (A) Resected portion — gastric antrum, cecum, ascendant colon and transverse colon, (B) Resected portion after analysis by the pathology department.

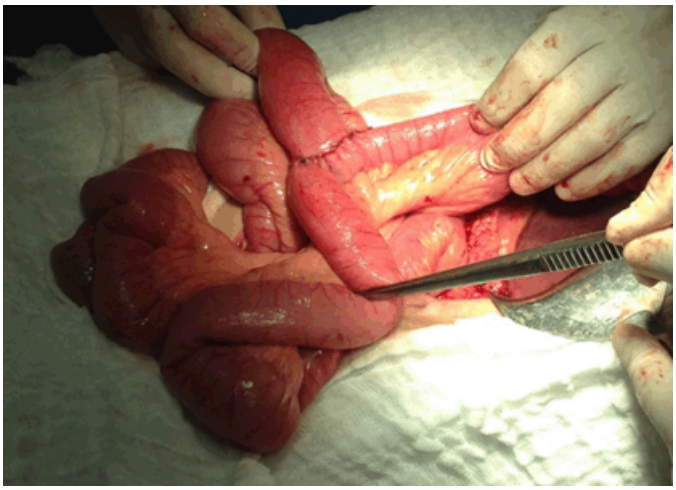

Figure 4: Roux-en-Y anastomosis.

and KIF3 complex motor protein deficiency [8]. The last two are also linked to the development of cancer. Deficiency of the KIF3 complex (an intracellular motor protein) prevents transportation of N-cadherin and β-catenin (cell-adhesion factors) to the cell surface. This process is linked both to SIT and the development and progression of cancer [8].

Our patient was diagnosed with SIT, adenocarcinoma of the transverse colon and gastrocolic fistula (GCF). He was not submitted to genetic testing. According to Galiatsatos et al. [9], 41 cases of malignancy in patients with situs abnormalities were reported in English literature from 1980–2005. Most cases (73%) were of single malignancies in patients with SIT. Nine cases (22%) were of cancer in patients with situs ambiguus, and only one, aside from the case reported by Galiatsatos et al. [9], was of multiple tumors in the same individual. Regarding the association between SIT and GCF, there are no previous reported cases when searching in the PubMed database.

Gastrocolic fistula is a rare complication of both benign and malignant conditions. The most common cause of GCF used to be benign peptic ulcer. However, with the advance of H2 antagonists and proton pump inhibitors, and the decreased necessity to use surgery to treat it, this scenario has changed. Nowadays, in the Western world, the most common cause of GCF is adenocarcinoma of the transverse colon, with an incidence of 0.3–0.4% in operated cases [10–12]. In the Eastern world, the most common cause is adenocarcinoma of the stomach.

There are two theories regarding the development of a fistula. The first one says the tumor invades the gastrocolic omentum directly from the originating organ. The second one says an ulcer provokes a surrounding inflammatory peritoneal reaction leading to the adherence and fistulation between the two organs [10–13].

Gastrocolic fistula was identified in our patient by means of an upper endoscopy. Most authors say barium enema is the most sensitive test for detecting GCF, because it is able to create a pressure in the lumen of the colon, which is essential for moving the barium through the fistula into the stomach [11, 13, 14]. The ability of barium enema in determining the primary malignant location is low. Immunohistochemical staining is important at this point, in determining the primary malignant lesion and formulating the postoperative chemotherapy scheme [14]. Upper endoscopy and colonoscopy are good for visualizing the fistula opening and taking biopsy samples for histopathology examination. The CT scan is useful in both delineating the fistula and identifying the underlying etiology.

Regarding the treatment of GCF, surgical approaches have changed over time, from second and third-stage surgeries to the current one-stage en bloc resection [13]. The previous approaches included colostomy to improve the patient's nutritional status and minimize mortality. The advance of enteral and parenteral nutritional support and intensive care medicine has made the one-stage procedure the favored approach in minimizing mortality [14]. Our patient had one-stage procedure with no intraoperative complications linked to the different surgical approach required for a patient with SIT.

Despite all improvement regarding the treatment, most patients have a poor prognosis and long-term survival has rarely been reported [14]. Our patient has now survived for one year and four months.

CONCLUSION

We decided to present this case because there are no previous reports in the literature connecting situs inversus totalis (SIT), adenocarcinoma of the transverse colon, and gastrocolic fistula (GCF). Furthermore, both SIT and GCF are rare conditions. The relation between SIT and cancer remains unclear. In contrast, the relation between cancer and GCF is well defined, being the adenocarcinoma of the transverse colon the most common cause of GCF in the Western world. Gastrocolic fistula usually needs

radical en bloc resection to be treated; nevertheless, most patients have a poor prognosis and long-term survival has rarely been reported.

****

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Author Contributions
Nathalia Emanuelle Gasparini Magalhães Rodrigues – 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.

Conflict of Interest
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CASE REPORT PEER REVIEWED | OPEN ACCESS

Heterotopic pregnancy and subsequent pregnancy outcome: A case report

Steve Kyende Mutiso, Abraham Mwaniki Mukaindo

ABSTRACT

Introduction: Heterotopic pregnancy resulting from spontaneous conception is a rare occurrence. Most will present with symptoms and signs similar to an ectopic pregnancy and surgical management with salpingectomy is often required. We present a case of heterotopic pregnancy that we managed in our facility and its subsequent live pregnancy outcome. Case Report: An African lady in her first pregnancy presented with abdominal pain with subsequent investigations revealing a heterotopic pregnancy composed of an intrauterine and tubal pregnancy. She underwent laparoscopic salpingectomy recovering well and carried the intrauterine pregnancy to term with a live birth being the outcome. Conclusion: The case presented is a case of heterotopic pregnancy resulting from spontaneous conception. Surgical management is the preferred method of management and this was required for the reported patient. The outcome of the intrauterine pregnancy is usually good after surgical removal of an ectopic pregnancy and the patient in this report had a relatively uncomplicated pregnancy with a good perinatal outcome. This case adds to the small body of evidence on heterotopic pregnancies, their management and subsequent outcome.

Keywords: Heterotopic, Outcome, Pregnancy

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INTRODUCTION

A heterotopic pregnancy is a pregnancy that has two simultaneous pregnancy at different implantation sites [1]. Heterotopic pregnancy is a rare occurrence occurring in about 1 in 30,000 pregnancies although the incidence is higher in pregnancies resulting from assisted reproductive techniques [2, 3]. Almost all of heterotopic pregnancies will require surgical management of the ectopic pregnancy to offer better outcomes to the intrauterine pregnancy [1, 4]. About two-thirds of the intrauterine pregnancies proceed to term with no associated major complications although some may need exogenous progesterone support [3]. We present a case of heterotopic pregnancy consisting of an intrauterine and right tubal pregnancy and the patient's subsequent follow-up and outcome of the pregnancy at term.

CASE REPORT

The patient was a 24-year-old African female in her first pregnancy. She was at seven weeks gestation by dates and had not started antenatal follow-up. She presented with a complaint of lower abdominal pain that had been present for the last three days. The pain was central in location, intermittent in nature and she described it as mild to moderate in severity. She had no per vaginal bleeding although reported a vaginal discharge that was white. She had no associated symptoms of nausea or vomiting and did not report any dizziness, palpitations or easy fatigability. She was a banker by profession and had been able to continue with her daily duties despite her pain. She had not been on any contraception and the pregnancy was a planned pregnancy.

Past medical history of the patient revealed that she had been treated for smear positive pulmonary tuberculosis three years back and had completed her treatment schedule of drugs. She also had a history of bronchial asthma and was on inhaler medication (salbutamol) when symptoms arose. This had been diagnosed in her childhood. Finally, she reported that she had spells of dyspepsia that was managed also with symptomatic medications. She had no prior occurrence of pelvic inflammatory disease or tubal surgery. She had no other prior surgeries and she did not smoke or take alcohol. She was married and had no family history of chronic medical conditions.

On examination, she was in good general condition, and had no systemic signs of dehydration or pallor. Her vitals were all normal with a pulse of 96 beats per minute and blood pressure of 138/78 mmHg. Her respiration rate was 16 breaths per minute and she was saturating at 98% on room air. She was afebrile with a temperature of 36.4°C. Abdominal examination revealed mild suprapubic tenderness with no abdominal masses.

Diagnostic assessment of the patient first involved a full hemogram. This was normal with a hemoglobin level of 12.4 g/dL, a white cell count of $6.53x10^9$/L and a platelet count of $269x10^9$ cells per liter. She had a beta-hCG (human chorionic gonadotropin) level done which was 48,219 mIU/ml. A transvaginal sonogram was requested which revealed a viable intrauterine pregnancy at six weeks and one day by crown rump length (CRL), a right adnexal ectopic pregnancy whose CRL dated it at six weeks and five days (Figure 1) with a recordable heartbeat (Figure 2), a right ovarian corpus luteal cyst that was 1.5 centimeters in diameter and free fluid in the Pouch of Douglas (POD) (Figure 3). The scans conclusion was a heterotopic pregnancy with a viable intrauterine and right adnexal ectopic that was possibly ruptured due to free fluid in the POD.

The diagnosis at this point was a heterotopic pregnancy and this was explained to the patient. Her subsequent plan was to involve her being admitted for emergency laparoscopy and possible right salpingectomy for the ectopic. She agreed to this and we proceeded to admit her. We further ordered a cross match of one unit of packed red blood cells to be kept in reserve for theatre in case it would be needed. The operation was booked to be done within an hour of her presenting to our hospital.

The laparoscopy was done under general anesthesia. Cohen's cannula was not inserted for uterine manipulation and instead we resorted to using a gauze rolled on an ovum forceps for uterine manipulation if required. She was positioned in the Lloyd–Davis position and primary trocar (10 mm) entry was done after veres insufflation. Entry pressures used were 18 mmHg while we operated at pressures of 15 mmHg. Two secondary ports (6 mm each) were inserted bilaterally at the iliac regions under direct vision. Intraoperatively we found an enlarged uterus which was hyperemic possible due to pregnancy with a ruptured right tubal (ampullary) pregnancy, there was also a hemoperitoneum of about 200 milliliters (Figure 4). Both ovaries and the left tube appeared normal. We subsequently did a right salpingectomy using endoloop then bipolar coagulation (Figure 5) and scissors to cut the tube off and suction of the hemoperitoneum with minimal peritoneal lavage (Figure 6). All instruments and ports were removed under vision and closure of the ports done.

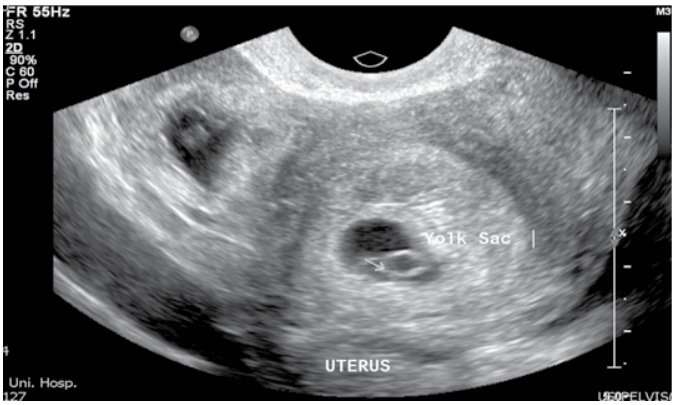

Figure 1: Sonogram showing the intrauterine pregnancy and concurrent adnexal pregnancy.

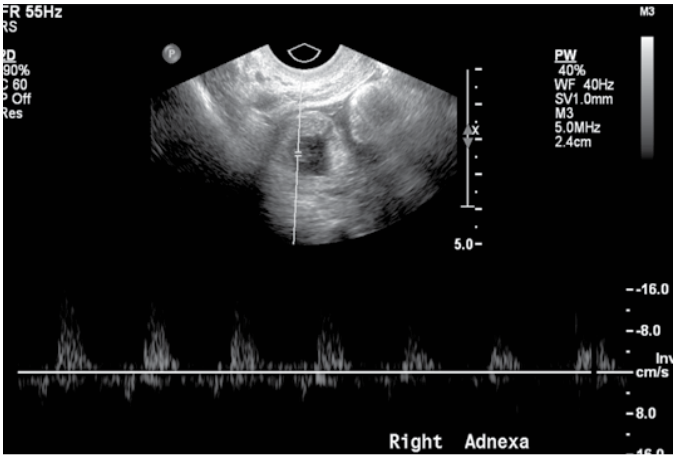

Figure 2: The adnexal pregnancy is shown with a perceivable fetal cardiac activity.

The patient was discharged home on the subsequent morning after being debriefed of the surgery. She was discharged on paracetamol and oral codeine for analgesia and was also prescribed for vaginal progesterone (susten) for the subsequent four weeks. She was also put on daily folic acid (400 μg) that she was to take up to the end of the first trimester of pregnancy.

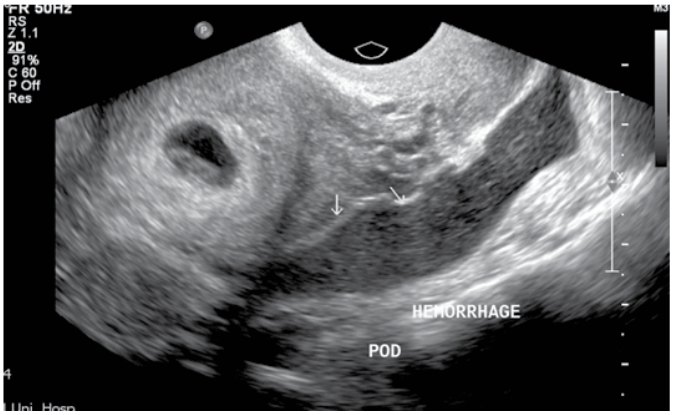

Figure 3: Sonogram showing free fluid in the pouch of Douglas pointing out to possible rupture.

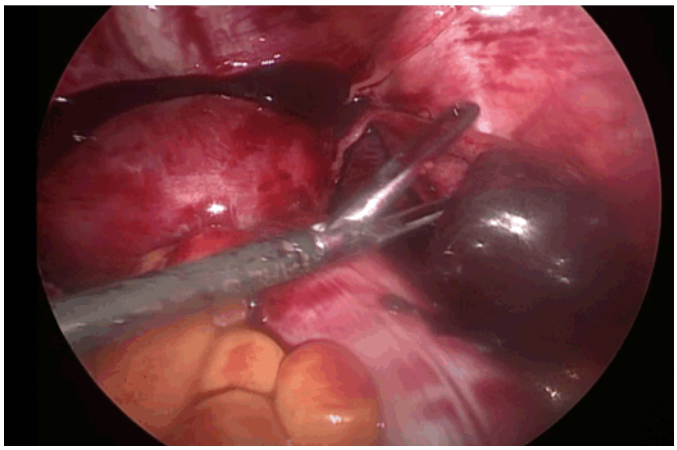
Figure 4: A laparoscopic still image showing a hyperemic uterus, the right tubal pregnancy and hemoperitoneum.

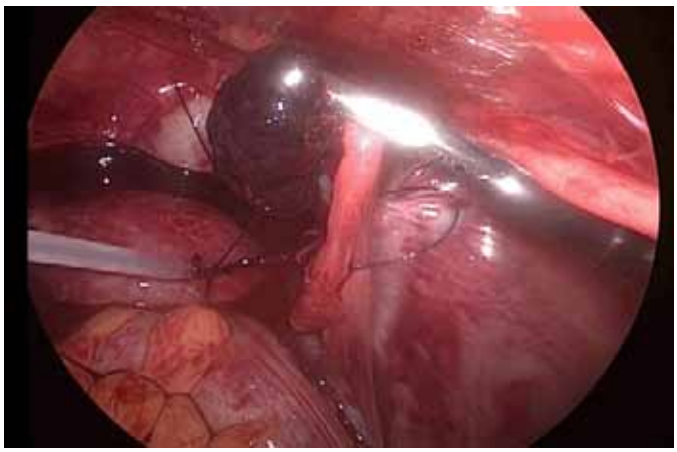
Figure 5: Endoloop is used to strangulate the tube proximal to the ectopic pregnancy.

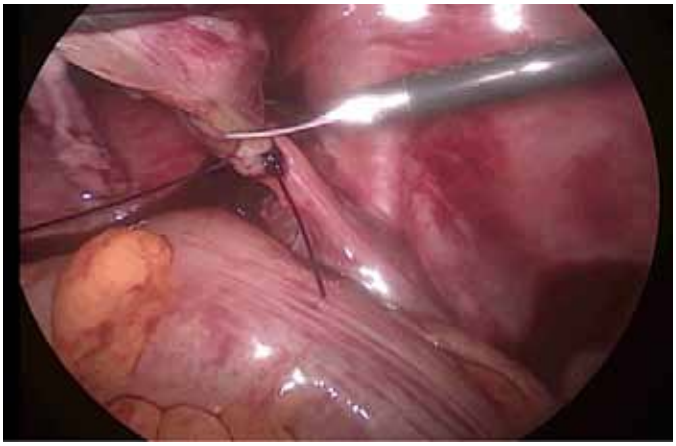
Figure 6: The salpingectomy is completed with a scissors.

The patient was seen in the outpatient clinic in two weeks for review. She was recovering well and was pain free. She had no vaginal bleeding or lower abdominal pain. She was further debriefed on the surgery and advised on starting antenatal follow-up.

Her subsequent antenatal follow-up was as follows: She had normal antenatal profile tests. She had a scan at 13th week that revealed the intrauterine pregnancy was viable and had no gross abnormalities. She had no abnormal pregnancy symptoms or complications. A 20-week anomaly scan revealed a normally formed intrauterine pregnancy that had adequate growth for dates. She had a normal 32 week growth scan and relatively uncomplicated pregnancy course. She had a term normal delivery with no reported perinatal morbidity.

DISCUSSION

The above case documents occurrence of a heterotopic pregnancy and its subsequent live pregnancy outcome. A heterotopic pregnancy occurs when an intrauterine and ectopic pregnancy occur simultaneously and this is a relatively rare occurrence [2].

The earlier reported incidence of heterotopic pregnancies was 1 in 30,000 pregnancies although with the advent of assisted reproductive technologies (ART), the incidence has been reported as 1 in 1500 in ART pregnancies [2, 3]. The case outlined was a spontaneous conception hence can fall in the former rather than the latter grouping. Although no strong risk factors have been identified for heterotopic pregnancies, there has been a documented increase in patients with certain factors. Women with history of tubal disease, pelvic inflammatory disease and those undergoing ART form the bulk of the predisposing factors to a heterotopic pregnancy [5, 6]. More so, in women who conceive with ART the factors that have been associated with an increased risk of

an heterotopic pregnancy include high numbers of stimulated oocytes or transferred embryos in a cycle, the volume and viscosity of the transfer medium and the technique of embryo transfer [7]. However, the patient outlined in the above case had none of these predisposing factors to a heterotopic or even ectopic pregnancy hence her occurrence may have been sporadic rather than risk factor based.

Heterotopic pregnancies have no specific clinical symptoms, although most of the women with a heterotopic or even ectopic pregnancy may present with abdominal pain [8]. Other symptoms will be a history of amenorrhea, symptoms of adnexal mass and even early pregnancy symptoms [9–11]. Heterotopic pregnancies may present at advanced gestation than an ectopic pregnancy, the reason being that once an intrauterine gestation is observed most may not consider an occurrence of an ectopic in the same pregnancy [12]. The current patient had abdominal pain that is commonly reported in ectopic pregnancies and hence the suspicion was towards an ectopic pregnancy rather than a normal intrauterine pregnancy.

The diagnosis of a heterotopic pregnancy is usually by ultrasound imaging. Any patient presenting with symptoms of an extrauterine pregnancy may require an ultrasound examination to determine the pregnancy location [5]. Features observed on ultrasound include the presence of an intrauterine gestation, an adnexal mass with a discernable gestational sac or even a fetal cardiac activity. Free fluid in the abdomen may point to possible rupture [13]. The patient had all these features on her ultrasound scan and the ectopic pregnancy also had a discernable sac with fetus and fetal cardiac activity hence her diagnosis was easily arrived at. Other diagnostic tests that may add value in these patients may include a complete blood count to assess their blood level and a serum β-hCG level that may be beneficial where no pregnancy has been identified on ultrasound [3]. Rarely, a diagnostic laparoscopy may be indicated in patients who may not have a clear diagnosis and in this instance the laparoscopy may be used for both diagnosis and treatment [4].

The management of heterotopic pregnancy is usually dependent on the site of implantation of the extrauterine pregnancy and should be the least invasive to offer favorable outcomes to the intrauterine pregnancy [14]. Systemic medical management is absolutely contraindicated in the presence of a viable intrauterine pregnancy [4]. Surgical management seems to be the recommended method of treatment of a heterotopic pregnancy, this is usually achieved by salpingectomy in patients with hemodynamic compromise and in whom rupture is suspected [8]. Where possible, a laparoscopic approach is preferred in view of better visualization and faster post-operative recovery [4, 5]. The current case was managed via the laparoscopic approach with salpingectomy being done as the patient was hemodynamically stable and had signs of rupture.

The other approach of management for a heterotopic pregnancy may be local injection under sonographic guidance of either hyperosmolar glucose or potassium chloride [6, 15]. These substance have a low toxicity to the co-existing intrauterine pregnancy and although the success rate [about 55%] may not be as high as surgical management, this may be a good option for patients who are hemodynamically stable and not keen on surgery [6]. In patients who are on management with local injections, it is important to note that more than half require subsequent surgical management with salpingectomy [6]. In patients in whom the ectopic is at a past cesarean scar in location treatment with embryo reduction using aspiration has been reported [16]. With regards to outcome of the pregnancy, about two thirds of patients with heterotopic pregnancies will carry the intrauterine pregnancy to term [3]. Moreover, although they have higher rates of spontaneous miscarriages compared to intra-uterine only pregnancies [33% versus 11%], there are no differences in perinatal outcomes between the two if the heterotopic pregnancy progresses to a live birth [3]. The present case resulted in a live birth with no associated pregnancy and birth complications.

CONCLUSION

The case presented is a case of heterotopic pregnancy resulting from spontaneous conception. Surgical management is the preferred method of management and this was required for the reported patient. The outcome of the intrauterine pregnancy is usually good after surgical removal of an ectopic pregnancy and the patient in this report had a relatively uncomplicated pregnancy with a good perinatal outcome. This case adds to the small body of evidence on heterotopic pregnancies, their management and subsequent outcome.

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Author Contributions

Steve Kyende Mutiso – 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

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

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Postoperative persistent hyponatremia: A case with metastatic lung cancer

Sibel Ocak Serin, Gulsah Karaoren, Ezgi Ersoy Yesil, Hakan Cakit, Sema Ucak Basat

ABSTRACT

Introduction: Hyponatremia is most commonly encountered electrolyte disorder in clinical practice. Syndrome of inappropriate anti-diuretic hormone secretion (SIADH), most frequent cause of euvolemic hyponatremia, is an important element that increases risk for morbidity and mortality and indicates severity of primary disease. SIADH can be seen in many clinical conditions or as multifactorial. Case Report: A 64-years old male presented to our facility emergency department with the complaints of shortness of breath and abdominal pain. According to the assessment, Morgagni hernia was in the thoracic and abdominal computed tomography (CT). The patient was hospitalized in the general surgery service and taken to the operation for hernia repair. On day-2 after operation, he had low serum Na+ value (124 mEq/L[124mmol/L]).SerumNa+valuedecreased to 114 mEq/L (114 mmol/L) on day 5 whereas 110 mEq/L (110 mmol/L) on the day-6; thus, 3% NaCl infusion was initiated. In further evaluation, several etiological factors were evaluated. On abdominal sonography, multiple metastatic lesions were detected incidentally. Thoracic and abdominal CT scan was re-evaluated, On thoracic CT scan, diffuse thickening (up to 1–1.5 cm) with irregular contours were observed. While isodense and hypodense lesions were seen in liver on abdominal CT scan. Diffuse metastatic disease was found in the patient by positron emission tomography (PET) scan and magnetic resonance imaging (MRI) scan. Small cell lung cancer (SCLC) diagnosis was made by biopsy samples obtained from liver. Our case had asymptomatic clinical course despite presence of diffuse metastatic SCLC and rapid decrease in Na+ values. Conclusion: Our case was presented to emphasize importance of detailed evaluation for all causes of SIADH, mainly malignancies in hospitalized patients at geriatric age group, and treatment based on differential diagnosis in the management of SIADH.

Keywords: General surgery, Hyponatremia, Small cell lung cancer, Syndrome of inappropriate anti-diuretic hormone secretion

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INTRODUCTION

Hyponatremia is seen in 30% of inpatients and syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is the most commonly encountered cause of hyponatremia. In general, it is characterized by uncontrolled and excessive anti-diuretic hormone (ADH) secretion from posterior pituitary gland and hyponatremia, and fluid retention can develop as a result of ADH secretion [1]. The SIADH can be seen in many clinical conditions such as malignancy, drug use, respiratory diseases and central nervous system diseases and as a multifactorial entity. Clinicians should perform a comprehensive evaluation to identify cause underlying SIADH [2]. Herein, we presented a case with asymptomatic small cell lung cancer (SCLC) which was detected during evaluations for secondary causes of SIADH identified as underlying cause of persistent hyponatremia.

CASE REPORT

A 64-year-old male presented to our facility emergency department with the complaints of shortness of breath and abdominal pain. According to the assessment, chronical reactive changes such as chronical bronchitis were determined in the thoracic computed tomography (CT) and Morgagni hernia was in the abdominal CT scan. The patient was hospitalized in the general surgery service and taken to the operation for hernia mesh repair. The patient was considered to have American Society of Anesthesiologists (ASA) I risk status in preoperative assessment and had no abnormal finding other than diaphragmatic hernia on chest radiograph (Figure 1). Laboratory tests and serum sodium (Na^+) concentration (142 mEq/L [142 mmol/L]) were found to be within normal range. The patient underwent hernia repair under general anesthesia; then, he was transferred to ward with Aldrete score of 9-10 after uneventful recovery period [3].

On day-2 after operation, the patient was consulted to our department as he had low serum Na^+ value (124 mEq/L [124 mmol/L]). In physical examination, the patient was considered as euvolemic, who had no findings of renal failure, congestive heart failure, hepatic failure, volume depletion, diuretic use, adrenal insufficiency or hypothyroidism or complaints of nausea, vomiting, polyuria or polydipsia. The fluid therapy and medications were reviewed in the patients. It was found that the patient received contrast material for thoracic and CT scan before surgery and that 2000 ml of normal saline was given during surgery; followed by maintenance fluid therapy with 1500 ml of 0.45% NaCl plus 5% dextrose. It was recommended to change fluid replacement therapy to normal saline, which was estimated as 1500 ml per day based on fluid gap. Metamizole sodium (4 g/day divided into 4 doses) used in postoperative pain management was withdrawn. In the follow-up, it was seen that hyponatremia did not respond to normal saline infusion. Serum Na+ value decreased to 114 mEq/L (114 mmol/L) on day-5 whereas 110 mEq/L (110 mmol/L) on the day 6; thus, 3% NaCl infusion was initiated. No finding of serious hyponatremia such as mental alteration, headache, nausea or vomiting was observed in the patient who had stable hemodynamic.

Serum Na^+ began to increase by addition of 3% NaCl. However, hyponatremia (125 mEq/L [125 mmol/L]) recurred when 3% NaCl was stopped; thus, further evaluation was performed to identify causes that might explain hyponatremia. In further evaluation, hematuria, ketonuria and trace proteinuria were observed in spot urinalysis. It was considered that there might be acute interstitial nephritis secondary to contrast material or metamizole sodium. However, there was no elevated creatinine value, eosinophilia, eosinophiluria or increased IgE levels in the patient. Urinary N-acetyl-ß-glucosaminidase (NAG) and ß2-microglobin levels could not be studied due to technical failure in the laboratory. No abnormal finding including fever, eruption, acid-base disorder, potassium disorder, hypotension or dehydration was observed in the patient. On urinary system sonography, bilateral renal parenchymal thickness and echogenicity were normal. On abdominal sonography, multiple metastatic lesions were detected incidentally. There was increased urinary osmolarity (475 mOsm/kg) in addition to hyponatremia and serum hypo-osmolarity (235 mOsm/kg). Blood Urea Nitrogen (BUN), urinary Na^+ concentration and serum uric acid level were 14 mg/dL (832 µmol/L), 141 mEq/L (141 mmol/L) (>40 mEq/L) and 3 mg/dL (178 µmol/L) (3.5-7.2 mg/dL), respectively.

Simultaneously, rigid fluid restriction was performed in the patient thought to have SIADH. Serum Na^+ value reached up to 137 mEq/L (137 mmol/L) within few days. There was no abnormal finding on preoperative chest radiograph (Figure 2). However, thoracic and abdominal CT scan was re-evaluated in the context of malignancy screening. On thoracic CT scan, diffuse thickening (up to 1–1.5 cm) with irregular contours were observed at the level of hilus on the left, while isodense and hypodense lesions were seen in liver on abdominal CT scan. Diffuse metastatic disease was found in the patient by positron emission tomography (PET) scan and magnetic resonance imaging (MRI) scan. SCLC diagnosis was made by biopsy samples obtained from liver and the patient was referred to oncology department.

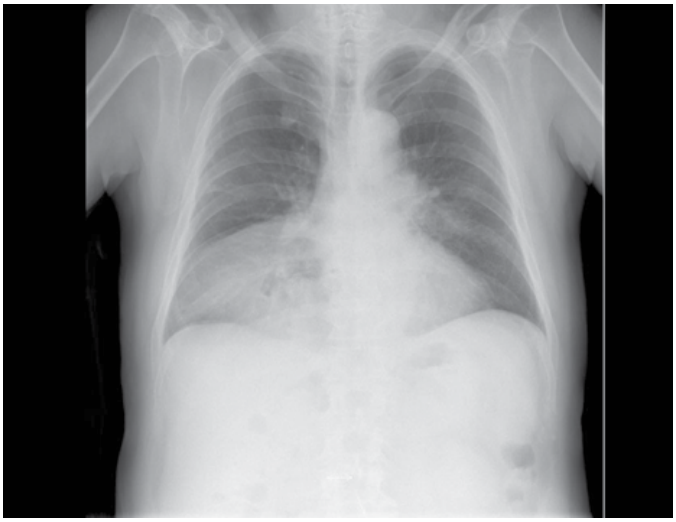

Figure 1: Preoperative lung image: Morgagni hernia, non-specific chronical bronchitis; bronchial wall thickening with increased bronchovascular markings.

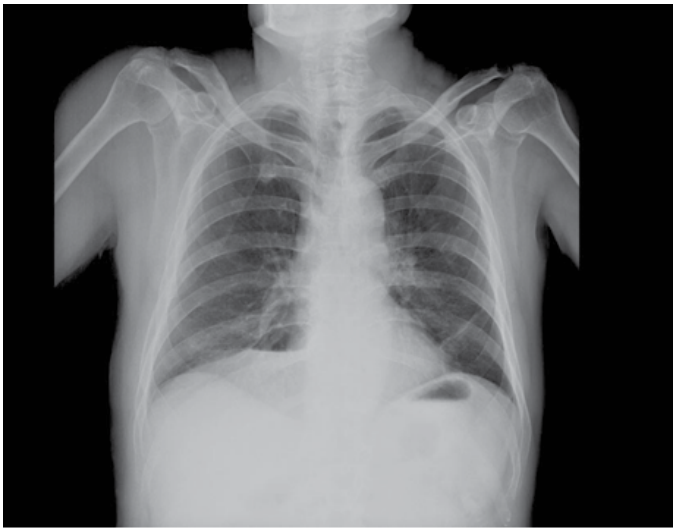

Figure 2: Postoperative lung image: Postoperative full expanded lung

DISCUSSION

In this case, we faced SIADH as the cause of persistent hyponatremia induced by repair of diaphragmatic hernia. In our case, many causes of secondary SIADH were evaluated in the differential diagnosis. As a result, we presented the case with asymptomatic SCLC which was detected incidentally as the cause of SIADH.

The syndrome of inappropriate anti-diuretic hormone secretion is characterized by hyponatremia, elevated urinary osmolarity, increased urinary sodium and decreased serum osmolarity in euvolemic patients not receiving diuretic therapy and having normal cardiac, renal, adrenal, hepatic and thyroid functions. SIADH can result from many causes varying from drugs to malignancies. It is strongly recommended to investigate secondary causes and this investigation should be done where possible [4]. In our case, cardiac, renal, adrenal, hepatic and thyroid function tests were found to be within normal range during evaluations for differential diagnosis.

The SIADH can develop from absorption of solutions containing sorbitol or glycine at varying degrees, which are used in laparoscopic procedures, hysteroscopy and transurethral prostate surgery [5]. In our case, diaphragmatic hernia repair was performed via laparoscopic approach; however, operation time was shorter than 40 minutes and no solutions containing sorbitol or glycine was used during surgery.

The SIADH occurred on day-3 after surgery in our case. Major surgeries involving abdominal and thoracic interventions can stimulate antidiuretic hormone (ADH) hyper-secretion via severe pain afferents [6]. In our case, visual analogue scale (VAS) pain score was found as 6-7 on the sixth hour after surgery and the patient reported gradually decreasing pain at postoperative period.

Aggressive fluid resuscitation during or after surgical interventions is another cause for postoperative SIADH [7]. No such clinical picture was observed in our patient monitored by balanced volume during perioperative and postoperative period.

Pulmonary tumors, especially small cell carcinoma, can produce ectopic ADH. In addition, tumors such as pancreatic adenocarcinoma, duodenal tumors and head-neck tumors can occasionally produce ADH. Hyponatremia is a common finding in elder patients with lung cancer accompanied by cardiovascular disorders and multi-drug use [8]. In a retrospective study, serum Na^+ value was found to be <135 mEq/L (135 mmol/L) in 97 (4.7%) of 2048 patients with lung cancer screened between 2006 and 2009. Hyponatremia incidence was approximately 5-folds higher in patients with SCLC 29/296 (14.2%) in SCLC versus 48/1752 (2.7%) in NSCLC) [9]. Similarly, our case was a 64-year-old man with lung cancer; however, there was no history of medication or systemic disease.

SIADH, most frequent cause of euvolemic hyponatremia, is an important factor that increases morbidity and mortality in patients and indicates severity of primary disease [10]. However, on contrary to literature, there was no paraneoplastic symptom or finding other than hyponatremia in our patient despite diffuse, metastatic SCLC.

Pulmonary diseases such as pneumonia, asthma, atelectasis, acute respiratory failure and pneumothorax can also cause SIADH [11]. In our case, diffuse thickening up to 1–1.5 cm with irregular contours at hilus on the left was striking on preoperative thorax CT scan. However, no pulmonary abnormality such as atelectasis, pneumothorax and acute respiratory failure was developed at postoperative period.

It is well-known that barbiturates, anticonvulsants, opiates, tricyclic anti-depressants, thiazide diuretic, monoamine oxidase inhibitors and some anti-diabetic

agents enhance ADH secretion or potentiate its effects in geriatric population. There are also cases with SIADH induced by non-steroidal anti-inflammatory drugs [12]. In our case, it was seen that hyponatremia and SIADH persisted after withdrawal of metamizole sodium used for postoperative analgesia.

In a cohort study in geriatric population, it was reported that hyponatremia can be seen in elder individuals without underlying disease. Moreover, Anpalahan et al. reported that there is a risk for SIADH development without any predisposing factor other than age [13].

Many central nervous system (CNS) disorders are associated to SIADH. Disorders such as stroke, infection, trauma, bleeding or psychosis enhance ADH secretion. However, hyponatremia that may be caused by cerebral salt wasting (CSW) is also seen in relationship with severe neurological events including intra-cerebral bleeding. Both conditions share common findings including hyponatremia, hypo-osmolarity, higher urinary osmolarity compared to serum osmolarity and urinary osmolarity >20 mEq/L. The most important discriminative feature is that extracellular volume is normal or slightly increased in SIADH while it is decreased in CSW. Differential diagnosis is essential to determine therapeutic approach, since fluid restriction corrects hyponatremia in SIADH while it enhances cerebral ischemia by exacerbating hypovolemia; thus, can cause vasospasm and death in CSW [14]. In our case, no neurological symptom or sign was developed during follow-up. In imaging modalities performed, no sign of neurological abnormality was observed in CNS. In addition, no clinical signs of extracellular volume loss such as hypotension, tachycardia, decreased skin turgor were present. CSW was excluded as the patient responded fluid restriction.

CONCLUSION

Postoperative hyponatremia and Syndrome of inappropriate anti-diuretic hormone secretion (SIADH), most common underlying reason, in the patients admitted for major surgery can be resulted from many conditions. In the management of SIADH, other causes should be kept in mind, particularly in refractory cases, and comprehensive evaluations should be performed in such patients including malignancy in the 6–7 decades.

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Author Contributions

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Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Adrenal ganglioneuroma: A rare case presentation

P. N. Tungenwar, A. H. Bhandarwar, Saurabh Gandhi, Rachana Binayke, Samarth Agarwal, Ajay Pai

ABSTRACT

Introduction: Ganglioneuromas are benign, well differentiated tumors arising from the sympathetic nervous system. However, they arise rarely in the adrenal glands. Ganglioneuroma (GN) is a very rare (0–6% of incidentalomas) tumor that arises from sympathetic ganglion/ chain and is made of mature ganglion cells, Schwann cells, neurites and nerve fibers. Most cases of adrenal ganglioneuromas are incidentally diagnosed since they are mostly asymptomatic and produce symptoms rarely due to compression of neighboring structures. Case Report: We hereby present a rare case of an adult female patient presented with pain in abdomen diagnosed with a non-secretory adrenal mass who underwent laparoscopic excision of the mass. She was finally diagnosed on pathological examination to be an adrenal ganglioneuroma, one of the very rare tumors reported in literature. Conclusion: Adrenal ganglioneuromas occur rarely and difficult in diagnosing preoperatively since symptoms vary and are mostly nonspecific. Ganglioneuroma should not be missed as a differential diagnosis of an adrenal mass. Histopathologic examination plays a crucial role in diagnosis.

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INTRODUCTION

Ganglioneuromas are benign, well differentiated tumors arising from the sympathetic nervous system. However, they arise rarely in the adrenal glands. Ganglioneuroma is a very rare (0–6% of incidentalomas) tumor that arises from sympathetic ganglion/chain and is made of mature ganglion cells, Schwann cells, neurites and nerve fibers. The most common sites are the posterior mediastinum and the retroperitoneal space [1]. Most cases of adrenal ganglioneuromas are incidentally diagnosed since they are mostly asymptomatic and produce symptoms rarely due to compression of neighboring structures. Retroperitoneal ganglioneuromas are usually non-secreting and asymptomatic but when they reach large sizes they cause pressure symptoms locally [2]. We hereby present a rare case of an adult female patient presenting with pain in abdomen diagnosed with a non-secretory adrenal mass who underwent laparoscopic excision of the mass. She

was finally diagnosed on pathological examination to be an adrenal ganglioneuroma, one of the very rare tumors reported in the medical world literature [3, 4].

Adrenal ganglioneuromas (GN) are rare tumors gaining origin from the neural crest cells of the sympathetic nervous system. This family of ganglion cell tumors includes GN which is benign, ganglioneuroblastoma which are of intermediate differentiation, and neuroblastoma which is a highly malignant lesion. Neuroblastoma and ganglioneuroblastoma mostly occur in infants and children, whereas GN has more prevalence in adolescents and young adults.

Laparoscopic adrenalectomy is now the gold standard in management of small adrenal masses. The standard treatment for benign adrenal tumors is laparoscopic or/ minimal access surgery. Large tumors (> 6 cm) are relative contraindications to laparoscopic adrenalectomy as they are more in favor of a diagnosis of adrenal carcinoma. We present in the following report a peculiar presentation of this condition and its laparoscopic excision followed by histopathology proving a diagnosis of ganglioneuroma.

CASE REPORT

A 40-year-old female presented with a history of vague pain in abdomen since 15 days and not associated with local flank swelling, constipation, or anorexia. There was no significant past surgical or medical history. No history of recent travel and family history of colitis or inflammatory bowel disease. On physical examination, the abdomen was soft, there was no distension or tenderness.

Computed tomography scan of the abdomen and pelvis with contrast study was suggestive of a right suprarenal mass lesion measuring approximately 4x2 cm with internal necrotic and calcified areas and moderate relatively homogenous with post contrast enhancement suspicious of neurogenic tumor (Figure 1A). Routine laboratory investigations including thyroid function tests were within normal range (Table 1).

Laparoscopic excision of the suprarenal mass was performed and sent for histopathological examination (Figure 1B).

On gross examination of specimen was a solid firm well delineated mass of size 4x3x2 cm brown in colour on the outside and cut section revealed pale greyish white appearance with peripheral golden yellow tissue with focal calcification (Figure 1C). Microscopic sections of the histopathological specimen showed ganglion cells and Schwann cells arranged in interlacing bundles suggestive of ganglioneuroma (Schwannian stroma dominant neuroblastic tumors) with peripheral normal adrenal parenchyma and no evidence of malignancy. On immunohistochemistry ganglion cells showed positivity for chromogranin and S-100 Protein was positive in fibres and focally in ganglion cells (Figure 2).

Table 1: Endocrine investigations showing non-secreting nature of tumor

	Unit	Normal range	Case
Triiodothyronine (T3)	ng/mL	0.58–1.59	1.32
Free thyroxine (FT4)	pmol/L	9.01–19.05	12.3
Thyroid-stimulating hormone (TSH)	IU/mL	0.35–4.94	3.05
Aldosterone (pmol/L) decubitus	-	22.2–477	ND*
Standing	-	83–985	-
Plasma Renin activity (ng/ml/hr) Decubitus		0.15–2.33	2.5
Standing	-	1.31–3.59	-
Plasma basal cortisol	µg/dl	6.2–19.4	18.39
Plasma Free Metanephrine	pg/dl	<90	18.90
Plasma Free Nor-Metanephrine	pg/dl	<180	-
Urine VMA	mg/24 h	2–14	3.4

* Not detectable

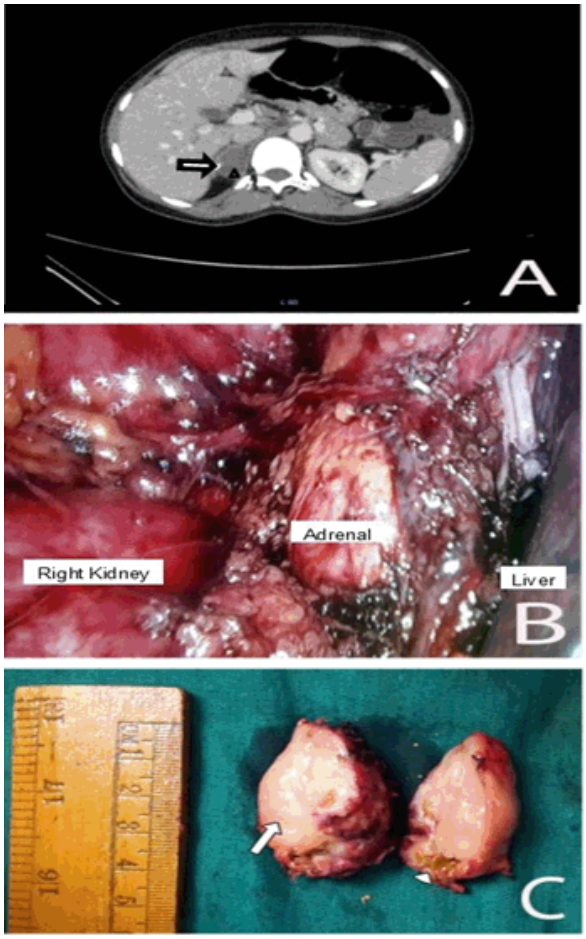

Figure 1: (A) Computed tomography scan of abdomen and pelvis showing right adrenal mass (arrow) with calcifications, (B) Intraoperative picture showing the adrenal mass in relation to the kidney and the liver, (C) Cut section revealing Greyish white surface of tumor (arrow) with small arrowhead showing adrenal parenchyma.

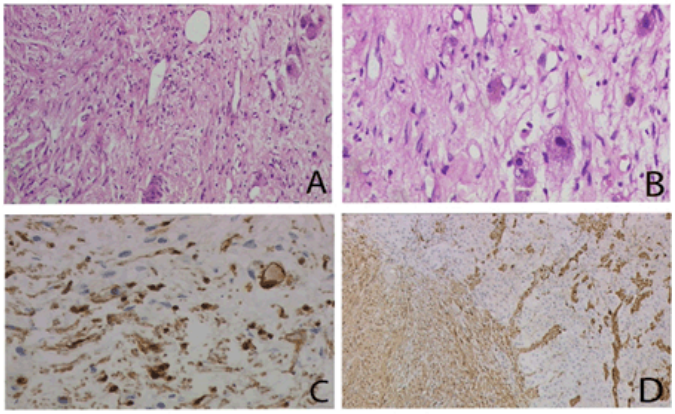

Figure 2: (A, B) Ganglion cells and Schwann cells arranged in interlacing bundles suggestive of Ganglioneuroma (H&E stain, (A) x200 and (B) x400), (C) On Immunohistochemistry (IHC) ganglion cells showed positivity for chromogranin, and (D) S-100 Protein was positive in fibres and focally in ganglion cells.

DISCUSSION

Ganglioneuromas can occur in the central nervous system or in the peripheral nervous system (sympathetic) [1]. It usually affects children and young patients below the age 20. Females are affected more than males [2]. The most common site of GN are retroperitoneum (40–50%) followed by mediastinal location (30–40%), or cervical region (up to 10%) and only rarely in adrenal gland [3–5].

The incidence of adrenal ganglioneuroma is 1/ million population being most commonly sporadic in occurrence but could be associated with other syndromes like multiple endocrine neoplasia type 2/neurofibromatosis type 2.

Ganglioneuromas are clinically asymptomatic and mostly hormonally inactive. Despite being benign and hormonally inactive in nature, GNs may cause pressure symptoms due to compression of their adjacent structures [5, 6]. Up to one-third of patients have elevated catecholamine levels but they rarely develop symptoms due to their excess.

Ganglioneuroma (GN) arises from the neural crest cells —the sympathetic ganglia and the adrenals. It is composed of Schwann cells, ganglion cells and fibrous tissues. The differential diagnosis of a tumor with high resemblance to ganglioneuroma is a neuroblastoma. In neuroblastoma, levels of urinary homovanillic acid (HVA) and vanillylmandelic acid (VMA) are usually raised, while the levels of urinary HVA and VMA in ganglioneuroma are within normal ranges [7]. Neuroblasts are not a part of mature GN. Thus the meta iodo benzyl guanidine uptake of a GN is lower than that of a neuroblastoma.

The GN should be diagnosed when the following findings are noted in a case of an adrenal mass: (1) non secreting, (2) absent vessel involvement, (3) calcifications in the gland, and (4) magnetic resonance imaging (MRI) findings of a non-enhanced T1-weighted signal with late and gradual enhancement. The final treatment for adrenal ganglioneuromas is resection by either open or laparoscopic method [8–10].

CONCLUSION

Adrenal ganglioneuromas occur rarely and difficult in diagnosing preoperatively since symptoms vary and are mostly nonspecific. Due to widespread utilization of imaging modalities like abdominal ultrasonography, computed tomography and magnetic resonance imaging, detection of such tumor has increased. Thus, ganglioneuroma should not be missed as a differential diagnosis of an adrenal mass. Histopathologic examination plays a crucial role in diagnosis.

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Author Contributions

P. N. Tungenwar – 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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Conflict of Interest

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CASE REPORT PEER REVIEWED | OPEN ACCESS

A fatal case of empyema due to *Streptococcus intermedius* associated pneumonia masquerading as acute pancreatitis in an otherwise healthy middle-aged woman

Anthea B. Mahesan Paul, Lary Simms, Abraham Ebenezer Paul, Jojo Yorke, Christopher Schmidseder

ABSTRACT

Introduction: Members of the *S. milleri* group *Streptococcus intermedius*, *Streptococcus anginosus*, and *Streptococcus constellatus intermedius*, are important pathogens implicated in respiratory illnesses such as bacterial pneumonia, pulmonary abscesses and empyema. Diagnosis of respiratory illnesses is largely dependent on accurate identification of symptomology and physical exam as radiological evidence is not always present. Case Report: In this case report, we present a fatal case of *Streptococcus intermedius* associated pneumonia causing empyema with an unusual constellation of symptoms and laboratory tests masquerading as acute pancreatitis in an otherwise healthy middle-aged woman. Conclusion: Our case adds to literature a novel clinical and laboratory presentation of *S. intermedius* empyema and the potentially fatal ramifications if not accurately diagnosed in an otherwise healthy woman.

Keywords: Empyema, Pancreatitis, Pneumonia, *Streptococcus intermedius*

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INTRODUCTION

Streptococcus milleri was first named in 1956 by O. Guthof when describing non-haemolytic species of commensal streptococci found in the oral cavity [1]. It has since been found as a normal commensal bacterium of the mouth, appendix, vaginal secretions and among fecal flora in 16–67% of healthy adults [2, 3]. The *Streptococcus milleri* group are anerobic gram-positive cocci in pairs or chains and contains three members, *Streptococcus intermedius*, *Streptococcus anginosus*, and *Streptococcus constellatus intermedius*. Members of the *S. milleri* group are important pathogens implicated in respiratory illnesses such as bacterial pneumonia, pulmonary abscesses and empyema [5, 9]. Diagnosis of respiratory illnesses is largely dependent on accurate identification of symptomology and physical exam as radiological evidence is not always present. Of the symptomology associated with pneumonia, the most common respiratory symptoms are cough, dyspnea, and sputum production, whereas the most frequently reported non-respiratory symptoms are fatigue, fever,

and chills [6]. In this case report, we present a fatal case of *Streptococcus intermedius* associated pneumonia causing empyema with an unusual constellation of clinical and laboratory symptoms masquerading as acute pancreatitis in an otherwise healthy middle-aged woman.

CASE REPORT

A 48-year-old Caucasian female presented to the emergency room with severe sharp non-radiating epigastric pain, associated with, coryza, nausea, diarrhea with generalized myalgia. The nonspecific symptoms began 10 days prior and gradually increased in severity despite over counter cough-and-cold medication. The patient was in good overall health with a medical history of anxiety, chronic lumbar back pain and lumbar laminectomy four years ago. She was taking both pain and anti-anxiety medication. The patient was a non-smoker and admitted occasional alcohol use. Vital signs on admission are temperature 98.5°C, blood pressure 106/59 mmHg, heart rate 114 bpm and respiratory rate 18/min. Pulse oximetry showed 96% oxygen saturation. Physical examination revealed tachycardia (114 bpm), a soft, tender abdomen and coarse crackles in the right lung field. Laboratory findings on admission showed significant leukocytosis (36.4 k/mm^3), thrombocytosis (799 k/mm^3), and mildly elevated lipase levels (111 IU/L) (Table 1). Our patient was admitted with the initial diagnosis of suspected acute pancreatitis and was started on IV fluids. Unfortunately, against medical advice the patient discharged herself before other confirmatory tests and treatment could have been given. She was given anti-inflammatories for pain and asked to return to the emergency room as soon as possible for re-admission. At home she continued to experience nonspecific symptoms until she was found deceased in bed three days later.

At autopsy, the external examination was unremarkable. Upon removing the breastplate, the right pleural cavity exhibited a large empyema composed of loculated purulent exudate around 300 ml in estimated volume (Figure 1). Removal and dissection of the right lung demonstrated the loculated exudate was firmly adherent to the visceral pleural surface (Figure 2).

Postmortem microbiology findings showed negative urine bacterial antigens of Group B Strep, *H. influenzae*, *Streptococcus pneumoniae* and *N. meningitidis*. Two different right pleural cultures were positive for *Streptococcus intermedius*; all other postmortem viral and bacterial tests were non-contributory. Microscopic examination of autopsy tissues showed acute fibrinopurulent inflammation of the surface of the right lung (Figure 3) associated with areas of necrosis and repair. The underlying lung showed broad areas of alveolitis and repair with scattered microabscesses, (Figure 4) and some small airways exhibited necrosis. Microscopic examination of the pancreas had normal number and appearance of islets of Langerhans with normal surrounding acinar tissue. The rest of the autopsy was unremarkable.

The final autopsy diagnosis was empyema of the right chest due to *Streptococcus intermedius* complicated by necrotizing pneumonia.

Table 1: Laboratory Values: (H: high levels, L: low levels)

Lab Test	Admission Value		Normal Values
White blood cells	36.4 k/mm^3	H	4.3–10.0 k/mm^3
Hematocrit	33.30%	-	33.0–48.0%
Hemoglobin	11.3 g/dL	-	11.0–16.0 g/dL
Platelets	799 k/mm^3	H	135–450 k/mm^3
Whole blood glucose	105 mg/dL	-	65–139 mg/dL
Serum BUN	10 mg/dL	-	7–25 mg/dL
Serum creatinine	0.75 mg/dL	-	0.59–1.07 mg/dL
Serum calcium	7.8 mg/dL	L	8.6–10.2 mg/dL
Total Bilirubin	0.7 mg/dL	-	0.2–1.2 mg/dL
Serum albumin	3.0 g/dl	L	3.6–5.1 g/dL
Serum alkaline phosphatase	105 U/L	-	33–115 IU/L
Serum AST	40 U/L	H	10–35 IU/L
Serum ALT	19U/L	-	6–40 IU/L
Serum sodium	137 mEq/L	-	131–145 mEq/L
Serum potassium	3.3 mEq/L	-	3.5–5.3 mEq/L
Serum chloride	90 mEq/L	L	98–110 mEq/L
eGFR	94	-	>59
Lipase	111IU/L	H	7.0–60.0 IU/L

Figure 1: The right pleural cavity with a large empyema composed of loculated purulent exudate around 300 ml in estimated volume.

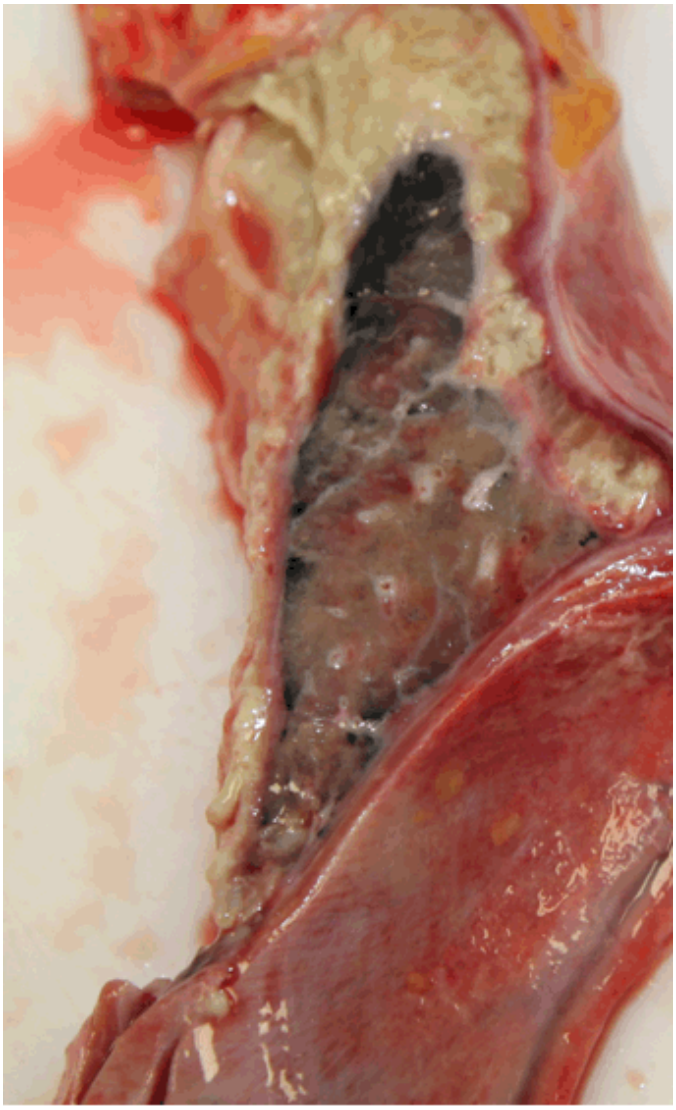
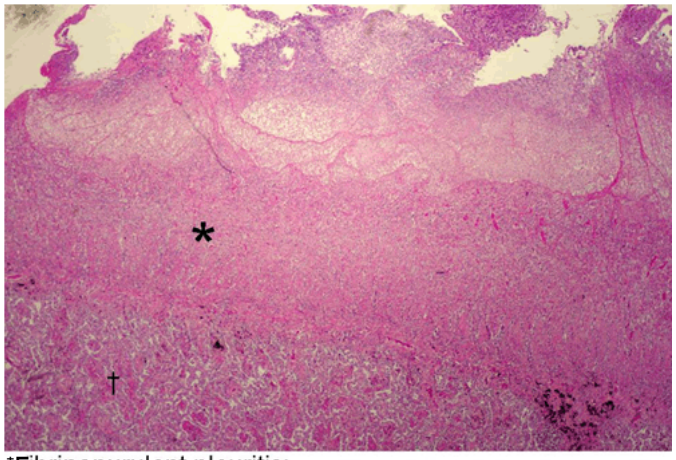
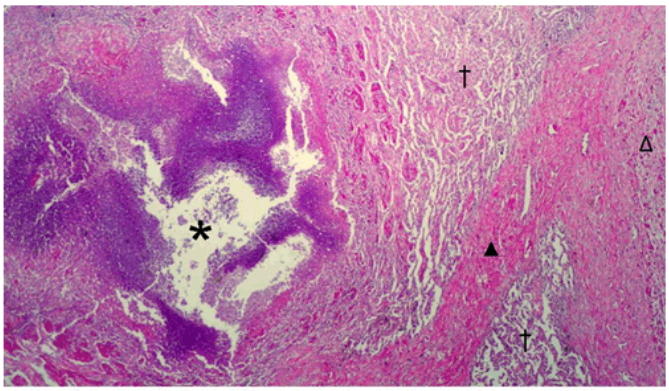


Figure 2: The loculated exudate that was firmly adherent to the visceral pleural surface.



*Fibrinopurulent pleuritis;
† Subpleural lung parenchyma

Figure 3: Acute fibrinopurulent inflammation of the surface of the right lung (H&E stain, x40).



*Microabscess in subpleural lung parenchyma;
▲Thickened interlobular septum;
† Subpleural lung parenchyma;
Δ Subpleural atelectatic lung parencyma

Figure 4: Scattered microabscesses within the right lung (H&E stain, x40).

DISCUSSION

Though the *Streptococci milleri* group is morphologically similar they appear to be associated with different clinical diseases and regions of the body. Whiley et al. found *Streptococcus anginosus* was the most prevalent of the three *S. milleri* bacteria accounting for 59% (89/151) of infections, most commonly found in the gastrointestinal tract and genitourinary tract [7]. *Streptococcus constellatus* intermedius accounted for 23% (33/151) of all *S. milleri* infections and was primarily found in the respiratory tract [8]. *Streptococcus intermedius* was only found in 19% (29/151) of *Streptococcus milleri* infections and was present most commonly in 86% (18/21) of head and neck infections [8]. In the respiratory tract, *S. intermedius* was found to be responsible for only 14% (1/12) of cases causing infection [8].

In literature, infections caused by *S. milleri* compared to those by *Streptococcus pneumonia* seem to affect hosts with underlying medical conditions and present with a longer course [9]. Of the five fatalities reported by Wong et al. with *S. milleri* associated empyema, all five had significant comorbid disease such as malignancy, invasive procedures, stroke, or dental disease [9]. This, however, was not the case in our patient who was in generally good health with no significant medical conditions, or recent procedures. Our case adds to literature the potential fatal ramification of infection by *S. milleri* if not accurately diagnosed in an otherwise healthy woman.

Respiratory symptomology associated with pneumonia has been reported to include cough, dyspnea, sputum production, pleuritic chest pain, and hemoptysis [7, 9]. Non-respiratory symptoms that have been reported with pneumonia have ranged from fatigue, fever, chills, anorexia, sweats, coryza, headache, earache, myalgia, nausea, sore throats, vomiting, diarrhea, and abdominal pain [7, 9]. Our patient exhibited many of the documented

symptoms in literature, however, interestingly in addition had elevated lipase levels (111 IU/L) which may have influenced the clinician to suspect acute pancreatitis. Elevated lipase levels have been reported in pancreatic etiology such as pancreatitis and in obstruction of the pancreatic duct, as well as in non-pancreatic etiology such as renal disease, alcoholism, diabetic ketoacidosis, post-endoscopic retrograde cholangiopancreatography and gastrointestinal diseases such as acute cholecystitis, nonspecific diarrhea, bowel obstruction, intestinal infarction, duodenal ulcers, and liver diseases [10]. A study by Tetrault found that isolated lipase levels were increased in 38/62 (61%) of patients with gastrointestinal disorders, specifically they found that 9/38 (23/6%) of patients with gastrointestinal disease and an isolated elevated lipase level had nonspecific diarrhea, as was the case in our patient [10]. In retrospect, we attribute the elevated lipase levels in our patient to her nonspecific diarrhea, as autopsy histopathology of all other organs, including the pancreas were unremarkable.

Empyema with clinical diagnosis has a very high mortality rate ranging between between 6–24% [4]. Though the symptoms exhibited by our patient are listed in the reported symptomology in literature, this constellation of symptoms was unusual in the circumstances presented. Our patient did exhibit significant relevant respiratory findings to warrant further investigation, however, the constellation of abdominal pain, elevated lipase levels, and diarrhea misled the diagnostic team to the incorrect initial diagnosis. We feel with patient cooperation, appropriate hospitalization and necessary diagnostic imaging and laboratory tests; our patient would have been appropriately diagnosed and treated. Our case demonstrates the need for awareness of the vast range of symptoms related to empyema by *Streptococcus intermedius* associated pneumonia to prevent further morbidity and mortality caused by this disease.

CONCLUSION

Our case adds to literature a novel clinical and laboratory presentation of *S. intermedius* empyema and the potentially fatal ramifications if not accurately diagnosed in an otherwise healthy woman.

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Anthea B. Mahesan Paul – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
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CASE REPORT PEER REVIEWED | OPEN ACCESS

Diagnosis and management of nephrotic syndrome in an adult patient: A case report

Samuel B. Reynolds, Ryan W. Lutz

ABSTRACT

Introduction: Nephrotic syndrome is a disorder characterized by proteinuria >3.5 g/24 hr, hypoalbuminemia <3 g/dL, and peripheral edema. The underlying etiology of the condition is influenced in large part by the age of the patient. In children under the age of 16, a large majority of cases are secondary to minimal change disease, whereas in adults the causes are more varied to include focal segmental glomerulosclerosis and membranous nephropathy. Case Report: A 68-year-old male with nephrotic range proteinuria who required workup with laboratory studies, immunological screening, and both light microscopy as well as electron microscopy to arrive at a diagnosis of minimal change disease. Conclusion: Also included is a review of previously published studies regarding minimal change disease and its association with non-Hodgkin lymphoma in the adult population, along with a discussion of current treatment approaches and a comparison of their efficacies.

Keywords: Adult, Change, Minimal, Nephrotic, Proteinuria

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INTRODUCTION

Nephrotic syndrome is a disorder characterized by proteinuria >3.5 g/24 hr, hypoalbuminemia <3 g/dL, and peripheral edema [1]. The underlying etiology of the condition is influenced in large part by the age of the patient. In children under the age of 16, a large majority of cases (76.6%) are due to minimal change disease (MCD) [2]. However, in adults aged 15–65 the cause of nephrotic syndrome becomes more varied to include primary kidney pathologies such as focal segmental glomerulosclerosis, membranous nephropathy, or less commonly minimal change disease. In addition, nephrotic syndrome can manifest itself secondary to a host of underlying conditions such as diabetes, amyloidosis, or systemic lupus erythematosus. This case in particular highlights the importance of determining the underlying etiology in patients with nephrotic-range proteinuria, which will guide future management and prognosis.

CASE REPORT

A 68-year-old male with a past medical history of hypothyroidism and urinary tract obstruction presented

to the Emergency Department with chief complaints of mild dyspnea on exertion, increasing abdominal girth, and weight gain over a period of 2–3 weeks. On arrival to the emergency room, the patient was found to have bilateral edema involving both the upper and lower extremities. He recalled a prior episode four months earlier, which prompted his primary care physician (PCP) to begin furosemide at 80 mg daily. He initially responded well to this treatment which was discontinued when his symptoms resolved. At the onset of this episode, his PCP re-started 80 mg furosemide, but this time with no therapeutic benefit. Given his worsening fluid retention and past history of urinary tract obstruction, the patient was admitted for further evaluation.

Initial laboratory studies revealed glucosuria, microscopic hematuria, proteinuria and an elevated urine protein to creatinine ratio of 12.16 mg/mmol. Patient was also found to have hyperlipidemia, with LDL and triglyceride levels of 355 and 238 mg/dL, respectively. An initial workup for adult onset nephrotic syndrome included measurements of ANA, ANCA, anti-DNA, C3 and C4 complement levels, free light chains, and anti-GBM as well as anti-streptolysin antibodies, which all came back negative. He was refractory to IV furosemide and had an improved diuretic response to intravenous torsemide. Blood pressure throughout admission ranged from 132–152 mmHg systolic and 75–90 mmHg diastolic.

Since his initial laboratory studies did not elucidate an etiology, the patient underwent an ultrasound-guided percutaneous needle biopsy of the patient's left native kidney. Pathological examination of this sample by light microscopy revealed normal-appearing glomeruli without any evidence of segmental sclerosis, endocapillary proliferation, crescents, or necrotizing lesions. More specialized testing also showed an absence of tram-tracking or spikes on silver stain and negative immunofluorescent studies. Renal vasculature was unremarkable for signs of thrombotic microangiopathy, micro-emboli, or vasculitis. Despite these negative findings, ultrastructural examination of several glomeruli revealed severe, widespread effacement of foot processes, a finding consistent with minimal change disease (MCD) (Figure 1).

For treatment of his MCD, he was started on prednisone 20 mg PO t.i.d. and his intravenous torsemide was continued. The patient responded to this regimen with a decrease in lower extremity edema as well as a drop in weight from 115.8 kg to 107.8 kg, during his hospital stay. The patient was discharged on hospital day eight on prednisone (60 mg total per day) and torsemide 40 mg PO b.i.d.

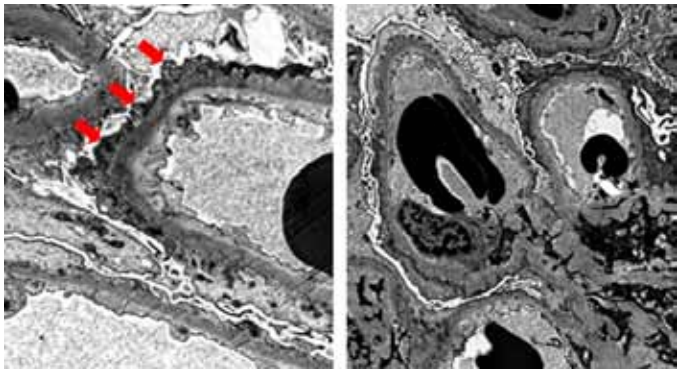

Figure 1: Two separate EM images of sample from patient's left kidney obtained via ultrasound-guided percutaneous needle biopsy, each showing notable podocyte effacement (demonstrated by red arrows) consistent with minimal change disease (*Source*: Health Network Laboratories).

DISCUSSION

Minimal change disease occurs most often in children, and nephrotic syndrome in adults is more commonly attributed to focal segmental glomerulosclerosis or membranous nephropathy and not often included in the differential diagnosis of adult onset nephrotic syndrome. A Brazilian study explored this topic by looking at the changing incidence of glomerular disease among 2068 adults from 1999–2005. The data obtained found the most common cause of primary glomerular disease to be focal-segmental glomerulosclerosis (29.7%), followed by membranous nephropathy (20.7%), IgA nephropathy (17.8%), and minimal change disease (9.1%) [3]. Similar results were found in a 2006 study out of Minnesota examining the incidence of glomerular disease among 208 patients [4]. It is important for clinicians to include variant presentations of nephrotic syndrome, particularly minimal change disease when evaluating a patient. As the treatment of nephrotic syndrome varies based on the specific etiology, the recognition and diagnosis of MCD is particularly important in the adult population.

Adult cases of minimal change disease, though less common than cases in children, are documented, specifically in patients actively diagnosed with or suspected of having non-Hodgkin lymphoma (NHL). A 2014 retrospective study examined this association in a series of 18 patients with established diagnoses of concurrent MCD and NHL. Researchers reported that, of these patients, 33.3% had Waldenström macroglobulinemia, 27.7% marginal zone B cell lymphoma and 22.2% chronic lymphocytic leukemia. Further investigation into the timing of disease presentation in this population, revealed four patients in whom MCD presented prior to NHL (with an average delay of 15 months), ten patients who were diagnosed simultaneously, and four who were found to have MCD after their NHL presented (average delay 25 months). Regarding management of the two conditions, reappearance of MCD was more likely in patients who had received only steroid therapy versus those who had been given steroids along with chemotherapy (77.8% and 25%, respectively). The authors concluded that MCD is most likely to appear in patients with NHL's of B cell origin,

and that the nephrotic syndrome is best managed with a combination of steroids and chemotherapy [5]. These conclusions are relevant to the patient described earlier, as he had been worked up for MCD but demonstrated no signs or symptoms consistent with NHL at the time. Since the latter condition confers a graver prognosis, the patient should have close monitoring for NHL going forward. However, if he were to be diagnosed with cancer and subsequently receive chemotherapy, he could be at increased risk for nephrotic syndrome depending on which medication he receives. A recently-published case described this risk, citing a 57-year-old female being treated with gefitinib for lung adenocarcinoma who was diagnosed with minimal change nephrotic syndrome, prompting her care providers to switch to erlotinib [6]. Awareness of this potential complication and consideration of minimal change nephrotic syndrome as a disease continuum will be also be important components of outpatient care.

Treatment for minimal change disease in adults has largely been accomplished by an approach with non-immunosuppressive in addition to immunosuppressive therapies. Non-immunosuppressive therapy is commonly instituted regardless of the etiology of nephrotic syndrome and typically consists of an angiotensin-converting enzyme inhibitor in order to preserve renal function. Immunosuppressive therapy is much more individualized to the underlying etiology of the nephrotic syndrome. Treatment of minimal change disease primarily employs glucocorticoids. In a study, Nolasco, et al. examined the efficacy of corticosteroid treatment in adult-onset minimal change disease. Researchers analyzed 75 patients who were treated with an initial dose of prednisone of 60 mg/day. 58 patients (81%) achieved complete remission [7]. A similar study out of Japan by Nakayama et al., found 38 out of 62 patients achieved remission within eight weeks of starting glucocorticoid therapy, and another 15 patients after eight weeks [8]. Although glucocorticoid therapy leads to a transient remission in 80–95% of adults with minimal change disease, approximately 50–75% of glucocorticoid-responsive patients will have a relapse at some point [9]. In patients with recurrent relapses, it is recommended to look at additional therapies, including cyclophosphamide, cyclosporine, tacrolimus, or rituximab.

CONCLUSION

Although uncommon in the adult population, minimal change disease carries a favorable response to glucocorticoid treatment, with 80-90% of patients achieving complete remission. It is important, therefore, for providers to maintain a broad differential when considering the underlying etiology of nephrotic syndrome in adults, as minimal change disease is treatable with a timely diagnosis and early intervention. In addition, it is prudent to look for secondary diagnoses in an adult patient with MCD for hematologic malignancies as they can be present upon initial diagnosis or appear at a later date.

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Author Contributions
Samuel B. Reynolds – 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
Ryan W. Lutz – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

A huge, pedunculated, multiseptated, cystic myoma misdiagnosed as an ovarian cancer in imaging studies

Chul Min Park, Sung Yob Kim

ABSTRACT

Introduction: A huge, pedunculated, multiseptated, cystic pelvic mass with normal uterus may cause misinterpretation of the computed tomography (CT) scan, magnetic resonance imaging (MRI) scan and PET-CT as a malignant ovarian epithelial tumor. Case report: A 56-year-old multipara woman complained of lower abdominal pain, abdominal distension and she consulted to local hospital. Cancer antigen 125 (CA-125) was 59.6 U/mL and the CT, MRI and PET-CT revealed that a large multiseptated cystic mass (20 cm) with soft tissue parts, multiple hemorrhage and fluid-fluid levels and that the uterus was normal finding with some ascites. Those images suggested that it might be a malignant ovarian epithelial tumor with hemorrhage. We performed an exploratory laparotomy with suspicion of ovarian malignancy and found out that the pedunculated mass was originated from the uterine fundus and that the ovaries were normal. There was a small amount of serous ascites. Conclusion: In this study, it is suggested that clinicians carrying out differential diagnosis of pelvic mass with increasing serum CA-125 level and ascites should consider not only ovarian cancer but also myoma with cystic degeneration.

Keywords: Cystic mass, Cystic myoma, Ovary malignancy, Ovarian cancer

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INTRODUCTION

In 1909, the first case of uterine myoma with ascites and hydrothorax was mentioned by Kelly et al. [1] and then Meigs reported that Meigs syndrome is characterized by the presence of benign solid ovarian tumors like fibroma associated with ascites and pleural effusion [2]. Other pelvic tumors such as teratoma, uterine myoma than fibroma associated with ascites and pleural effusion was reported as pseudo-Meigs syndrome [3].

The CA-125 (carbohydrate antigen 125, cancer antigen 125, or carcinoma antigen 125) is a type of cell surface antigens present in more than 80% of non-mucinous epithelial ovarian cancers. The CA-125 occurs in the serum of healthy females at low concentration (<35 IU/mL), however, the concentration appears to be moderately

elevated in patients with several benign conditions such as uterine myoma, adenomyosis, and endometriosis [4].

We report an uncommon case of huge, pedunculated, multiseptated, cystic myoma with ascites and high serum CA-125 level (59.6 U/mL) resembling ovarian cancer.

CASE REPORT

A 56-year-old multipara woman complained of lower abdominal pain, abdominal distension and she consulted to local hospital. She had an ultrasonography and serum CA-125 test. It revealed that 16x10 cm size, large inhomogeneous mass with some ascites and CA-125 was 59.6 U/mL. She was referred to our hospital under the impression of ovarian cancer. There was nothing remarkable in her medical history until then.

The CT scan and MRI scan revealed that a large multiseptated cystic mass (20 cm) with soft tissue parts, multiple hemorrhage and fluid-fluid levels and that the uterus was normal finding. Those images suggested that it might be a malignant ovarian epithelial tumor with hemorrhage (Figure 1). The PET-CT scan showed that large mass with mild, heterogeneous FDG uptake (SUV max 3.5) and metabolic defects in right abdomen and there is no significant abnormal FDG uptake to suggest metastatic lymph node or distant metastasis.

We performed an exploratory laparotomy with suspicion of ovarian malignancy. During the operation, we found out that the pedunculated mass was originated from the uterine fundus and that the ovaries were normal (Figure 2).

There was a small amount of serous ascites. So, we resected the mass, which was 20x18x8 cm in size and 1.593 g in weight, and the face of the mass showed cystic degeneration and multiple hemorrhagic lesion (Figure 3). The pathology confirmed leiomyoma with hemorrhage and no evidence of malignancy (Figure 4).

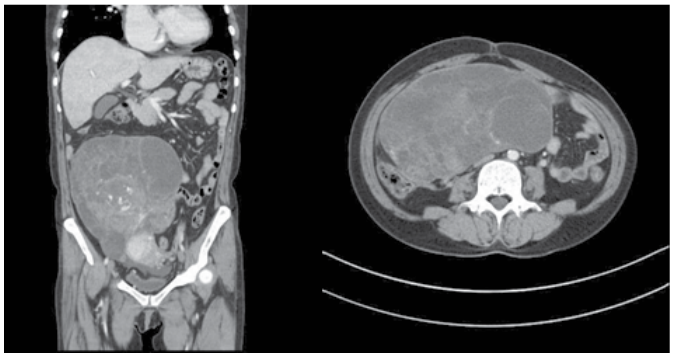

Figure 1: Computed tomography scan showed a large multiseptated cystic mass (20 cm) with soft tissue parts, multiple hemorrhage and fluid-fluid levels and uterus was normal.

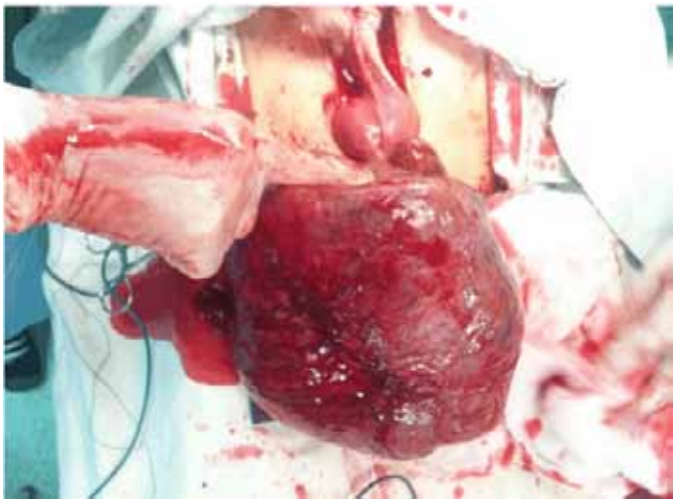

Figure 2: Pedunculated mass was originated from the uterine fundus and the ovaries were normal.

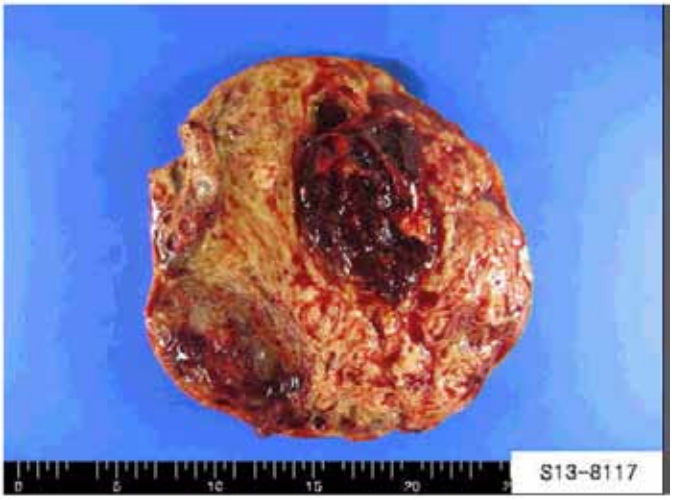

Figure 3: The face of the resected mass showed cystic degeneration and multiple hemorrhagic lesion.

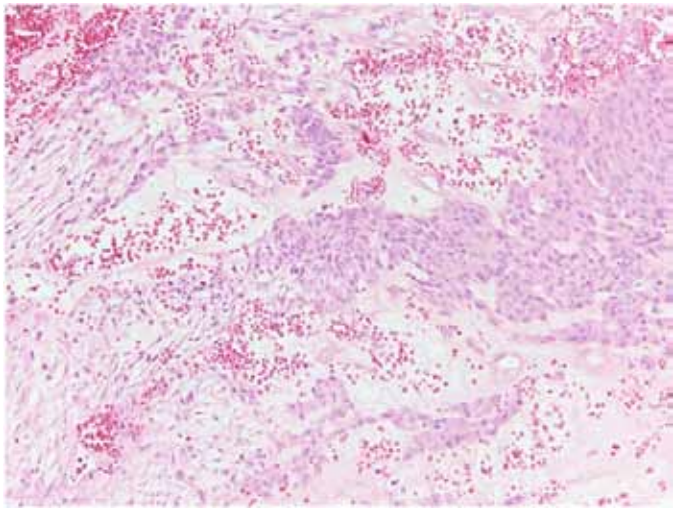

Figure 4: The pathology confirmed leiomyoma with cystic degeneration, hemorrhage and no evidence of malignancy.

DISCUSSION

A solid pelvic mass with ascites and elevated CA-125 level almost means malignant tumor with poor prognosis for patient. But Meigs and pseudo-Meigs syndrome are well-known as benign solid ovarian mass, less commonly uterine myoma, with high CA-125, ascites and pleural effusion [1–3]. Therefore, we report an uncommon case of huge, pedunculated, multiseptated, cystic myoma with ascites and high serum CA-125 level (59.6 U/mL) resembling ovarian cancer.

The mechanism of the generation of ascites in benign disease like uterine myoma is unclear. Meigs suggested that the ascites may originates from edematous fibromas, which can leak fluid [3].

In case of uterine myoma, a discrepancy between an excessive arterial supply to a large tumor and limited venous and lymphatic drainage might contribute to stromal edema and cystic degeneration with subsequent transudation into the peritoneal cavity [5]. Fluid leakage probably might result from a marked cystic degeneration and intratumoral pressure [6]. Especially in case of pedunculated myoma like our case, twisting of the pedicle of the tumor and its torsion resulting in fluid production has been suggested [7]. And the subserosal location like pedunculated myoma with cystic degeneration might facilitate leakage of fluid into the abdominal cavity [5].

Another theory of ascites in myoma is that cytokines, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and inflammatory cytokines(IL-1b, IL-6, IL-8) play roles in the development of ascites [8, 9]. The mechanical irritation in peritoneum from the tumor might cause peritoneal fluid production through a process of peritoneal inflammation [10]. Probably, both a leakage of intratumoral fluid and peritoneal inflammation could contribute to the production of ascites in pedunculated myoma with cystic degeneration like our case.

And peritoneal inflammation might be the primary cause of the elevated CA-125. The associated inflammatory reaction of mesothelial cells of peritoneum is probably the very important contributor to the very high serum level of CA-125 [11].

Lee et al. commented that giant multiseptated pyomyoma simulating an ovarian cancer showed mild FDG uptake in PET-CT and CA-125 level (59.2 U/mL) less than 500 U/mL as our case. Therefore, If PET-CT show mild FDG uptake and CA-125 level is less than 500 U/mL, although other imaging studies and clinical sign suggest ovarian malignancy, I think we could suspect myoma more than ovarian malignancy [12].

CONCLUSION

We should not rule out the possibility of the uterine mass in the pelvic mass with intact uterus on imaging studies like our case. Especially, gynecologists should always be aware of the possibility of uterine myoma, because that is one of the most common tumors of the female pelvic organ. Therefore, all clinicians carrying out differential diagnosis of pelvic mass with increasing serum CA-125 level and ascites should consider not only ovarian cancer but also huge, pedunculated, multiseptated, cystic myoma.

****

Author Contributions

Chul Min Park – 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

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

Guarantor

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Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

A case report of breast implant-associated anaplastic large cell lymphoma: The good, the bad, and the ugly

Alya Binmahfouz, Karin Steinke

ABSTRACT

Introduction: Primary lymphoma of the breast is very rare, comprising 0.5% breast neoplasms. The majority of breast lymphomas are of B cell type, postulated to originate from intramammary lymph nodes or breast lymphatics. Moreover, a still unresolved entity known as breast implant-associated anaplastic large T cell lymphoma (BIA-ALCL) has emerged over the last 20 years, its incidence believed to be on the rise, as the prevalence of women with breast implants is increasing. Case Report: We report an extremely uncommon presentation of BIA-ALCL in a 55-year-old lady who presented 23 years post-bilateral cosmetic breast implants with a locally aggressive mass in the left breast. The mass invaded the chest wall and was associated with left axillary and internal mammary lymph nodes. We review the medical imaging and histopathologic findings of this mass and briefly discuss the different presentations and recommended treatment options. Conclusion: This report reinforces the importance of understanding the possible inherent complications and variable clinical presentations associated with breast implants, in order to assist with early recognition and prompt management of this recently emerging, potentially fatal disease.

Keywords: Anaplastic T cell breast lymphoma, Breast implant, Implant associated breast lymphoma, Implant complication

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INTRODUCTION

Primary lymphoma of the breast is very rare, comprising 0.5% breast neoplasms, most of them being of B cell type, postulated to originate from intramammary lymph nodes or breast lymphatics [1]. Moreover, a still unresolved entity, known as breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) has emerged over the past 20 years [2], with its incidence is believed to be on the rise, as is the prevalence of women with breast implants.

CASE REPORT

A 55-year-old female presented to her general physician complaining of left breast swelling, pain and tenderness, first noticed five months prior. No nipple changes or discharge were reported. She has had a bilateral augmentation mammoplasty 23 years prior for cosmetic reasons. She was married, a smoker, a social drinker and had three children. She did not take regular medications, and had no family or personal history of breast cancer or lymphoma.

On examination, the breasts were asymmetric; the left breast was grossly enlarged and tender to palpation with overlying erythema. No nipple retraction, skin ulceration or axillary lymph nodes were noted. The right breast and axilla were unremarkable.

Her most recent mammogram and breast ultrasound scan done 1 year before presentation were unremarkable, apart from bilateral subpectoral intact saline implants.

A sonogram of the left breast was performed and showed an irregular contour of the implant suggestive of rupture, with edema and generalized increased vascularity. No definite solid mass or cystic lesions were detected. Bilateral mammography also showed an irregular contour of the left implant, with a suspicious density seen superiorly only on mediolateral oblique (MLO) view, no associated calcification (Figure 1). A contrast-enhanced dynamic bilateral breast MRI scan showed intact implants. However, an irregular, lobulated, thick-walled, rim-enhancing mass with central cystic changes, measuring 7x5 cm was detected posterosuperior to the left implant, invading the left chest wall and pleura and abutting the pericardium (Figure 2). The right breast and both axillae were unremarkable.

The differential diagnosis was malignancy versus aggressive infection, therefore a contrast-enhanced staging CT scan of the chest, abdomen and pelvis was performed, which re-demonstrated an irregular left breast soft tissue mass posterosuperior to the implant extending into the adjacent intercostal spaces, abutting the pericardium (Figure 3). No osseous destruction, pulmonary nodules, or mediastinal/axillary lymphadenopathy were seen at this stage. The abdomen and pelvis were free of disease.

An US-guided core needle biopsy using a 16G automatic gun (Bard Magnum® Biopsy Systems, Tempe, USA) revealed chronic inflammatory cells and reactive changes. No malignant cells were present, so an atypical infection was suspected, the implant was surgically removed, and the patient was commenced on empiric antibiotics.

The gross histological specimen measured 7.5x6.0 cm. Histopathology, cytology, and immunohistochemistry results of the removed implant and surrounding tissue showed an intact implant, with evidence of capsular fibro-inflammatory changes, silicone granulomas and CD30-positive/anaplastic lymphoma kinase (ALK)-1-negative abnormal large T cell infiltrate (Figure 4), confirming the diagnosis of BIA-ALCL. Bone marrow biopsy was negative.

A staging ^{18}F-FDG PET/CT scan was performed showing the persistent left breast mass with intense peripheral uptake and extension into chest wall abutting the pericardium. Mild to moderate uptake in left axillary and left internal mammary lymph nodes was reported (Figure 5).

The disease was stage IIE; the patient underwent surgical resection of the mass and is currently receiving high dose chemo-radiotherapy.

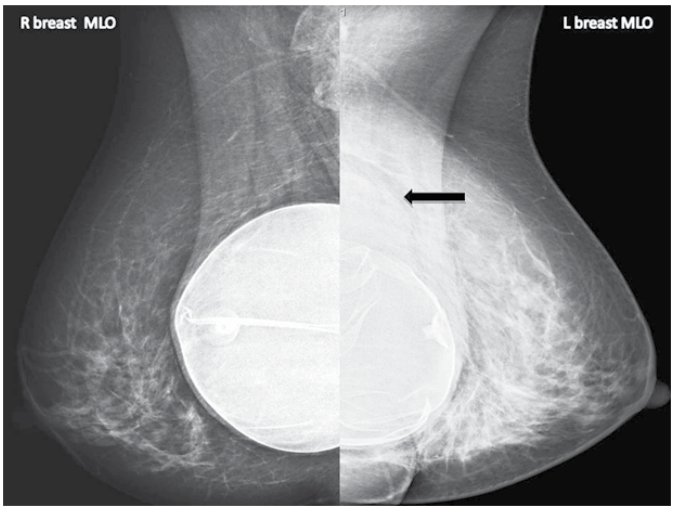

Figure 1: Bilateral mammograms MLO views show bilateral subpectoral saline breast implants. The left implant appears irregular and collapsed with global increased density of the left breast. An ill-defined density is seen superior to the left breast implant (arrow).

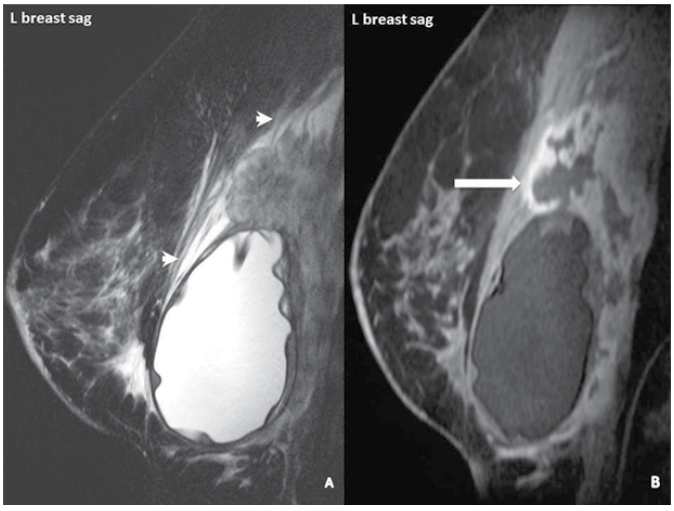

Figure 2: Left breast sagittal T2 fat-suppressed MRI image showing peritumoral edema (arrowheads) (A) and T1 post intravenous contrast administration (8 ml Gadovist®) subtracted image (B) shows an irregular, lobulated, peripherally enhancing mass posterosuperior to the left implant with invasion of the chest wall (arrow).

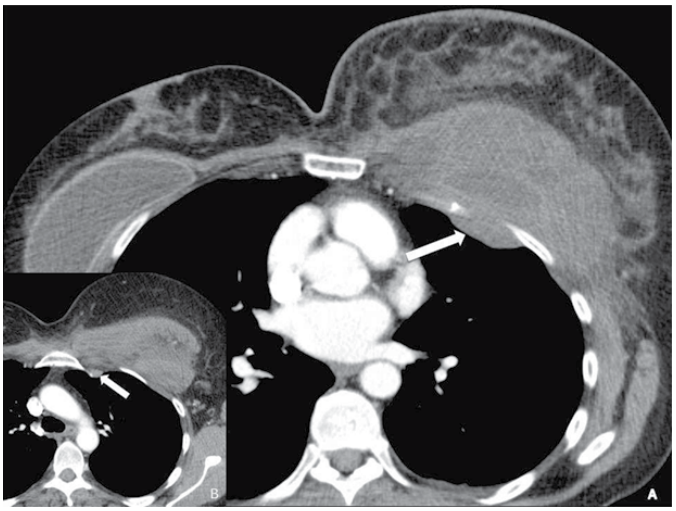

Figure 3: Axial post-contrast computed tomography scan of the chest shows an irregular mass posterosuperior to the left implant (A) invading the chest wall (arrow). A higher cut (B, inset) showing a pathologically enlarged left internal mammary lymph node (arrow).

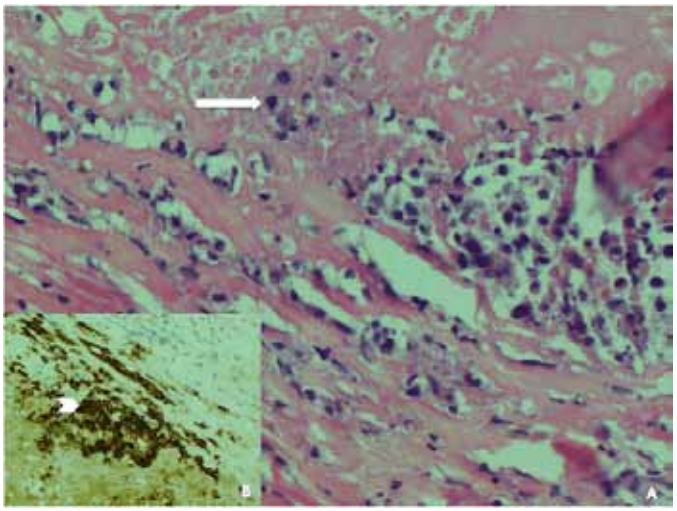

Figure 4: (A) Histopathology images showing scattered, poorly preserved atypical large cells admixed with copious necrotic debris (arrow) lining the capsule cavity (H&E stain, x200). (B, inset) Immunohistochemistry staining shows an aberrant immunophenotype with strong positivity for CD30 (arrowhead). The atypical cells are negative for CD3, ALK-1, CD8, and CD20.

DISCUSSION

Primary non-Hodgkin's lymphoma (NHL) of the breast is very rare with an incidence of 0.5% of breast cancers and is mostly of B cell type [3]. It can arise primarily from the breast or, more commonly, secondarily involves the breast. Sporadic cases of breast lymphoma associated with breast implants have been reported in literature, with around 83 cases documented worldwide. It is frequently of T cell type, specifically anaplastic large T cell lymphoma, which accounts for 3% of NHL.

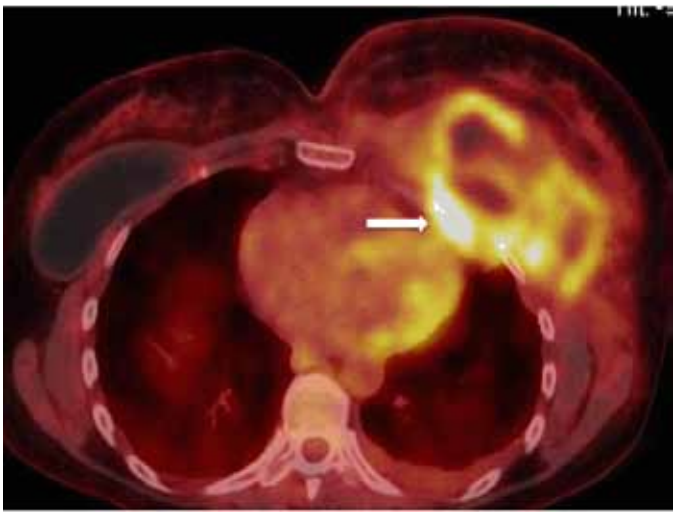

Figure 5: Fused 18F-FDG PET/CT scan of the chest axial plane showing abnormal heterogeneous increased FDG uptake of the left breast mass extending through the left chest wall (arrow).

It can occur with either silicone or saline breast implants, yet, all published studies in literature have confirmed the strong link between textured-shell implants and BIA-ALCL [2]. The median age at the time of diagnosis is 52 years, and the time interval from implant placement to diagnosis of ALCL ranges from 1 to 20 years, with a mean of eight years [4].

The pathogenesis is currently under investigation, but is assumed to be an immune response induced by silicone or polyurethane capsular material, which might then trigger an exaggerated reaction and induces a monoclonal neoplasm of activated T lymphocytes [3, 5]. Other postulated mechanisms are an indirect cytokine mediated reaction, and silicone induced toxic damage [6].

The most common clinical presentation is swelling, enlargement, and pain from a delayed seroma that is formed more than a year post implant placement. Occasionally, the lymphoma can present as a mass.

No interrelation between BIA-ALCL and the reason for implant (augmentation mammoplasty versus reconstruction) has been validated. Furthermore, a history of breast cancer or lymphoma does not worsen the prognosis of BIA-ALCL [2].

The first line imaging modality is breast sonography, which differentiates between a fluid collection and a solid mass [7]. The effusion is usually confined and adjacent to the implant. The mass, if present, is usually solitary, lobular, with irregular margins. Ultrasound is also used to guide aspiration of seroma or core needle biopsy of a mass. Mammography, on the other hand, can show a circumscribed lesion adjacent to the implant with a sensitivity of 73% [7], but does not determine the nature of the abnormality. Breast MRI scan is the most sensitive imaging modality to assess the lesion, implant, axilla, and contralateral breast. A seroma may appear as peri-implant fluid collection with enhancing wall. In contrast, the mass associated with BIA-ALCL likely appears as a

solid aggressive lesion with irregular margins, and at times areas of central necrosis, with rapid enhancement and early washout of the solid component.

In the given context, the differential diagnosis includes primary breast cancer (newly diagnosed or recurrent), metastasis, atypical infection, or implant-associated mesenchymal tumor - an implant related benign, locally aggressive fibromatosis very rarely can develop into a fibrosarcoma [8].

The final diagnosis is reached by cytological, histopathological, and immunohistochemical analysis of the aspirate or tissue specimen, showing large anaplastic T-cells with abundant eosinophilic cytoplasm, pleomorphic horseshoe shaped nuclei, and prominent nucleoli with frequent mitosis. The neoplastic cells commonly stain positive to CD30 and negative to ALK-1 proteins, which bares similarity to primary cutaneous ALCL as opposed to systemic ALCL. This immunostaining is key in dictating the prognosis of the disease [1,3].

When lymphoma is diagnosed by means of imaging and histopathologic examination, an FDG PET/CT scan is performed for staging of the disease and as a baseline for follow up after treatment.

The disease largely carries a favorable prognosis when it presents with a seroma without a mass, and the treatment consists of implant removal and total capsulectomy. However, if presenting as a mass, as in our case, the prognosis is usually poor and the treatment includes surgery with adjuvant chemotherapy. Local radiation therapy is considered if the disease is persistent after surgery or the patient cannot tolerate additional surgery [2].

A comprehensive study carried out in 2014 recommended surveillance of this group of patients by postoperative clinical follow up every six months for five years, and annual breast ultrasonography for two years [2].

CONCLUSION

This report reinforces the importance of understanding the inherent complications and variable clinical presentations associated with breast implants, specifically the aggressive BIA-ALCL, to assist in early recognition and prompt management of this recently uncovered, potentially fatal disease. This is, to our knowledge, the first case of aggressive BIA-ALCL infiltrating beyond the chest wall.

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Author Contributions
Alya Binmahfouz – 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
Karin Steinke – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

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Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Calcifying odontogenic cyst of mandible: A case report

G.V. Reddy, Javeed Akhtar Ankolvi, Arvind U.D., Irfan Ali Motiwala, Phanitej G., K. Sravan Kumar Reddy, J. Laxmi Sravya

ABSTRACT

Introduction: Calcifying odontogenic cyst was first described by Gorlin et al. in 1962. WHO defined it as "a cystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, an overlying layer that is often many cells thick and that may resemble stellate reticulum, and masses of ghost epithelial cells that may be in the epithelial cyst lining or in the fibrous capsule" Calcifying odontogenic cysts are 1.6% of all central odontogenic tumors. These are relatively rare odontogenic tumors occurring in the posterior mandible. Case Report: This report emphasizes a unique case of a 55-year-old male suffering with pain in lower right molar region and the management of the case. Conclusion: Even though the recurrence rate of calcifying odontogenic cyst is very rare, there are some case reports of development of ghost cell odontogenic carcinomas from calcifying odontogenic cyst. Our follow-up radiograph did not show any signs of recurrence. However, a clinical study with larger number of cases and long-term follow-up is required.

Keywords: Calcifying odontogenic cyst (COC), Calcifying cystic odontogenic tumor (CCOT), Ghost cell odontogenic carcinoma (GCOC)

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INTRODUCTION

In 2005, calcifying odontogenic cyst was classified as a tumor and designated as a calcifying cystic odontogenic tumor (CCOT) by the World Health Organization. Calcifying odontogenic cyst develops from the reduced enamel epithelium or remnants of odontogenic epithelium. Calcifying odontogenic cysts can occur at any age starting from first decade to seventh decade of life. It occurs more commonly in the second decade of

life. It occurs almost equally in both sexes with slight male predilection. The most common sites of occurrence are anterior maxilla 41.2%, posterior mandible 35.3%, anterior mandible (17.6%), and posterior maxilla (5.9%) [1–5].

CASE REPORT

A 55-year-old male reported with pain in the lower right molar region since one month. Pain was insidious in onset, continuous, throbbing type and localized. Intraoral examination revealed missing 38, 48. On palpation, there was tenderness over right mandibular ramus region. Orthopantomogram revealed a well circumscribed unilocular radiolucency in the right mandibular body and angle region, extending from mesial aspect of 46 to 48 which is impacted (Figure 1). Root resorption of 46 and 47 was seen. Endodontically treated 14, 16, 17, 24, 25, 36 and impacted 48. Aspiration has shown serosanguineous fluid. Based on these clinical and radiographic findings a tentative diagnosis of unicystic ameloblastoma or Keratocystic odontogenic tumor was attained.

Surgical enucleation and curettage of the lesion was planned under general anesthesia. Crevicular incision was placed from 45 to 47 and extended onto the ascending ramus of the mandible. Full thickness mucoperiosteal flap was reflected, extraction of 46 and 47 was performed. There was thinning of buccal cortical bone. De-roofing of the cyst was done to expose the cystic cavity. Careful enucleation and curettage of the lesion was performed (Figure 2). Impacted 48 were removed and the entire bony cavity was thoroughly irrigated with hydrogen peroxide and saline. Enucleated tissue specimen was sent for histopathological examination. Postoperatively wound healing was satisfactory and orthopantomogram at sixth month follow-up visit revealed new bone formation with no recurrence (Figure 4), still the case is under follow-up.

HISTOPATHOLOGY

The cystic luminal epithelium is non-keratinized stratified squamous type with luminal proliferations. The epithelium also shows numerous amorphous structures of various size and shape with well-defined borders without nucleus resembling ghost cells are seen. The eosinophilic dentinoid like material and basophilic round to irregular calcified masses are also seen. The cells in spinous layer show intercellular edema with intact desmosomal attachments. The basal cells are cuboidal to columnar with palisading arrangement and budding into underlying connective tissue at focal areas. The connective tissue wall shows densely arranged collagen fibers with mild inflammatory cell infiltrate predominantly lymphocytes. Suggestive of 'calcifying odontogenic cyst' (Figure 5).

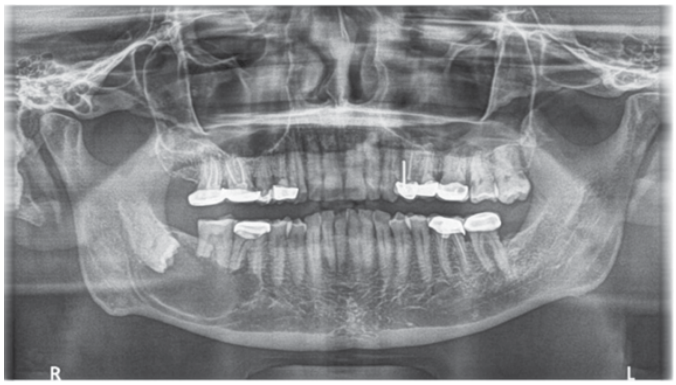

Figure 1: Preoperative orthopantomogram revealing the well circumscribed, unilocular radiolucency.

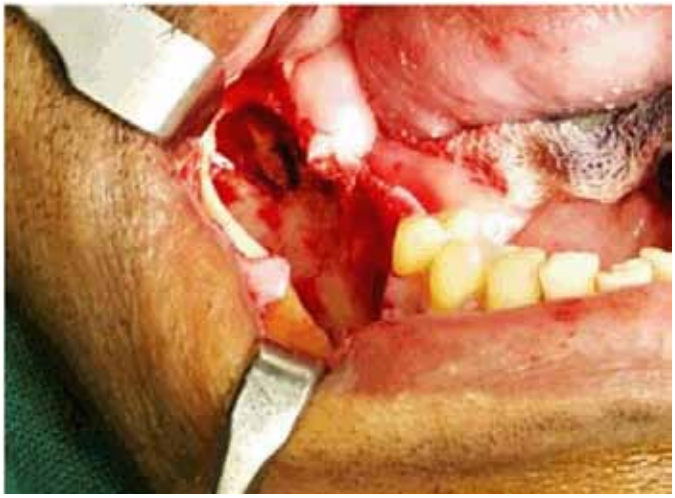

Figure 2: Bony cavity after enucleation.

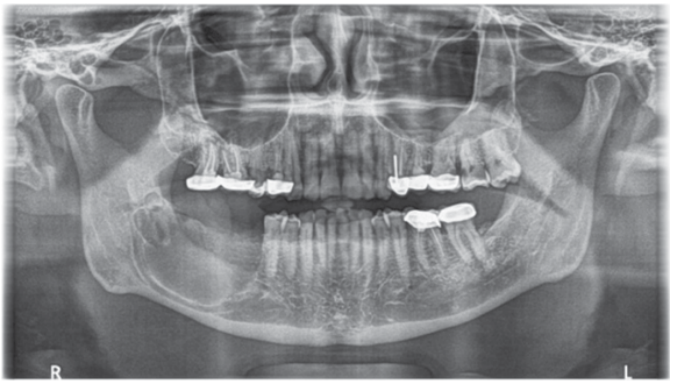

Figure 3: Two weeks follow-up radiograph.

DISCUSSION

Calcifying odontogenic cysts are usually non neoplastic with cystic features but, sometimes they appear as solid mass with neoplastic features. The solid lesions are named dentinogenic ghost cell tumor (DGCT), epithelial odontogenic ghost cell tumor (EOGCT). There has been confusion in classification and nomenclature of the lesion [6], because of its diversified histopathological features.

Praetorius in 1981 classified calcifying odontogenic cysts into a cyst entity and a neoplastic entity. The cystic entity was classified into three types [7].

Type 1: A simple monocsytic type of typical Gorlin cyst, with or without dentinoid calcified tissue

Type 2: Monocystic odontoma creative type, presence of ameloblastic fibroma tissue in the cystic wall extending into the surrounding tissue with all the characteristics of the previous type, except that the hard tissue was complex or compound odontoma

Type 3: Monocystic ameloblastomatous proliferating type with ameloblastomatous proliferation both in the walls and in the lumen, and dentinoid formation.

Calcifying odontogenic cyst presents as central lesion occurring intraosseously or as peripheral lesion occurring in the soft tissue. The more common are the central lesions [7, 8]. Clinically, Calcifying odontogenic cyst appears as a completely asymptomatic swelling with expansion of cortical plates [5]. In our case, the lesion is central with expansion of buccal cortical plate and the cyst was asymptomatic. Radiographically calcifying odontogenic cysts are seen as a unilocular or multilocular radiolucencies with well circumscribed borders. Unilocular appearance is more common than multilocular appearance. Multilocular appearance accounts for 5% to 13% of all lesions [7, 8]. Calcifications may appear as small opacities giving 'salt and pepper type of pattern' or may even show large solid amorphous masses [5].

In a case series of 11 cases published by Seiji lida et al. ten cases were associated with an unerupted tooth. Adjacent tooth displacement was observed in five cases and root resorption of adjacent teeth was observed in four cases [6]. In the present case the lesion appeared unilocular with well circumscribed borders. It was associated with unerupted 48 and there was resorption of roots in relation to 46,47.

Management of calcifying odontogenic cyst is usually surgical enucleation and curettage [7, 5].

Neoplastic variants of calcifying odontogenic cyst may require an aggressive surgical approach as they have the malignant transformation potential. However, the specific diagnosis is obtained only after histopathological examination.

Recurrence rate of calcifying odontogenic cyst is very rare, only eight cases of recurrence were noted in literature [7].

Ghost cell odontogenic carcinoma is malignant counterpart of calcifying odontogenic cyst, which is rare to occur. Utaroh Motosugi et al. noted ghost cell odontogenic carcinoma arising from calcifying odontogenic cyst in three cases out of 122 cases of calcifying odontogenic cyst [9]. So far 30 cases of ghost cell odontogenic carcinoma have been reported in literature [9]. We opted for enucleation of lesion and thorough curettage of bone cavity.

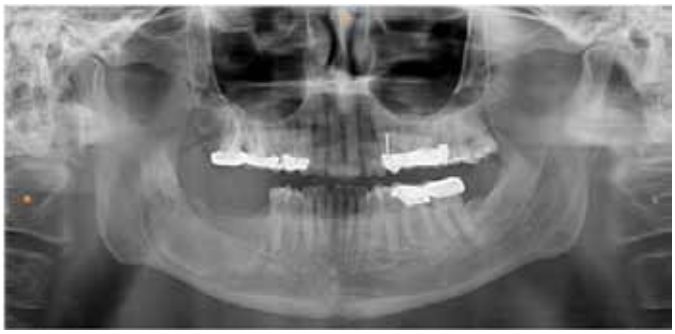

Figure 4: At sixth month follow-up, radiograph revealing new bone formation.

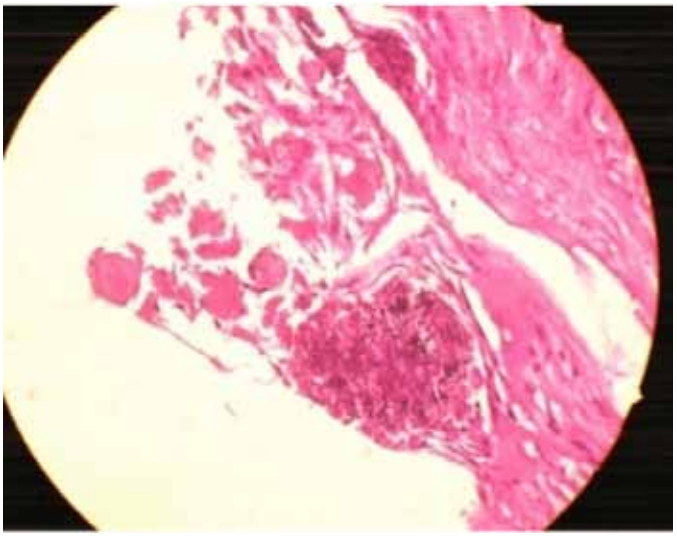

Figure 5: Histopathological section showing amorphous structures with well-defined borders without nucleus resembling ghost cells, and the eosinophilic dentinoid like material and basophilic round to irregular calcified masses are also seen.

CONCLUSION

Even though the recurrence rate of calcifying odontogenic cyst is very rare, there are few case reports of development of ghost cell odontogenic carcinomas from calcifying odontogenic cyst. Our follow-up radiograph did not show any signs of recurrence. However, a clinical study with larger number of cases and long-term follow-up is required.

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Author Contributions

Reddy GV – 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

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

Arvind U.D. – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
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J. Laxmi Sravya – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Human herpesvirus-8 related hemophagocytic lymphohistiocytosis with Kaposi sarcoma in an immunocompetent HIV negative adult

Talal Alnabelsi, Cecilia Jang, Ramzi Mulki, Amin Benyounes, Manju Balasubramanian, Mark Morginstin

ABSTRACT

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening disorder characterized by proliferation of the mononuclear phagocytic system resulting in marked hemophagocytosis. While HLH may occur as a consequence of a herpes viral infection, this usually arises in immunocompromised individuals. We report a rare case of HLH with Kaposi sarcoma triggered by human herpesvirus-8 (HHV-8) infection in an immunocompetent adult. Case Report: Our patient is a 58-year-old male with a recent diagnosis of Kaposi sarcoma of his lower extremities hospitalized for fever, chills and night sweats. Evaluation revealed pancytopenia, splenomegaly, diffuse lymphadenopathy and Kaposi sarcoma on lymph node biopsy in the absence of HIV infection. Investigations also revealed hemophagocytosis on bone marrow examination. A diagnosis of secondary Hemophagocytic Lymphohistiocytosis was made and the patient was initiated on etoposide and steroids with marked improvement of symptoms and blood counts. One month later, he was hospitalized for high grade fevers and was again found to be pancytopenic and septic with multi-organ failure. The patient's condition rapidly deteriorated and he succumbed to his illness five days later. Conclusion: Hemophagocytic lymphohistiocytosis is a rare and devastating condition typically arising in immunocompromised individuals. Our patient had non-specific symptoms in addition to pancytopenia and lymphadenopathy in the setting of Kaposi sarcoma. While this may seldom be compatible with an HHV-8 infection, a thorough search revealed associated HLH. Although extremely rare, HLH should be considered in immunocompetent patients with HHV-8 related manifestations particularly in the presence of pancytopenia.

Keywords: Hemophagocytosis, Kaposi sarcoma, Immunocompetent, Human herpesvirus-8

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening disorder characterized by proliferation of the mononuclear phagocytic system resulting in marked hemophagocytosis; macrophages engulfing hematopoietic cells. Familial and acquired forms of this disorder are recognized. Primary HLH refers to familial cases with underlying genetic abnormalities. Acquired forms on the other hand, are attributed to underlying infections, malignancy or autoimmune conditions. Infection-associated HLH has been documented in viral, bacterial, fungal and parasitic infections. The most notable viral cause of hemophagocytosis is Epstein-Barr virus. Human herpesvirus 8 (HHV-8), typically associated with Kaposi sarcoma, multicentric Castleman disease (MCD) and primary effusion lymphoma, is very rarely associated with HLH [1]. HHV-8 related HLH occurs mainly in immunocompromised hosts, such as post-transplant or HIV-positive individuals. Here we report on an unusual presentation of HLH related HHV-8 infection with KS in an immunocompetent, HIV negative adult.

CASE REPORT

Our patient is a 58-year-old Mediterranean male with a recent diagnosis of KS. Two months prior to his admission, the patient sought a podiatrist for abnormal skin findings on his lower extremities. He first noticed the lesions 12 months ago on his right lower back and several more developed on his lower extremities over time (Figure 1). The lesions were small and hyperpigmented papules scattered throughout both legs and feet. The largest lesion on his right foot was biopsied which showed KS with positive immunohistochemical staining for HHV-8. He was instructed to follow-up with a specialist for further workup. He then became symptomatic in the interim and presented to our hospital.

The patient presented with fevers, chills, malaise and night sweats. He also reported progressive weakness, dizziness and worsening pain in his lower extremities. His past medical history besides the recent diagnosis of KS was unremarkable. He denied receiving corticosteroids or immunosuppressant medication.

The patient was originally from Italy, but moved to the United States 10 years ago. He is recently unemployed and lives with his wife in Philadelphia, Pennsylvania. He had no allergies to medication or food substances. His family history was not significant for any hematological or oncological diseases. He was not a smoker and denied substance abuse or unprotected sexual exposure.

Vital signs on admission were: temperature 38°C peripheral pulse 95/bpm, respiratory rate 16/min, blood pressure 102/50 mmHg. Physical examination revealed marked conjunctival pallor, inguinal lymphadenopathy, splenomegaly and hyperpigmented papules on his lower extremities. The lymph nodes were large, firm but non tender with no overlying skin changes. Respiratory and cardiac examination was unremarkable. The patient was admitted to the medical floor for further workup.

Admission labs were noted as hemoglobin of 8.5 g/dl, white cell count of $3.9x10^3/\mu l$, platelet count $122x10^3/\mu l$. Serum electrolytes, coagulation studies, liver and kidney function tests were all normal. Multiple HIV tests (antibody and antigen-ELISA) were performed with negative results. The peripheral smear revealed a normal distribution of granulocytes with normal red blood cell morphology. An anemia panel revealed a markedly elevated ferritin 3465 ng/ml (22–275 ng/ml). Fasting triglyceride levels were also noted to be high at 336 mg/dl (0–150 mg/dl). A search for an acute infectious etiology was unrevealing.

Computed tomography scan of the chest, abdomen and pelvis showed extensive lymphadenopathy and splenomegaly. A subsequent positron emission tomography (PET) scan revealed metabolically active lymph nodes throughout the chest, abdomen and pelvis. The patient then underwent an excisional biopsy of a right inguinal lymph node. Immunohistochemical staining was positive for HHV-8 and the findings were compatible with KS. There was no evidence of lymphoma

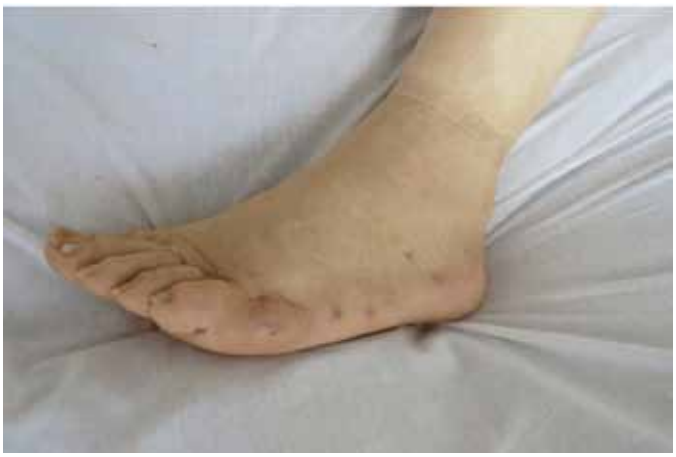

Figure 1: Hyperpigmented papules representing Kaposi sarcoma.

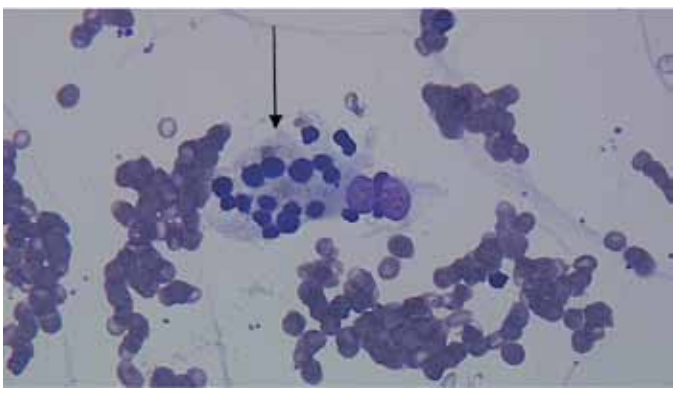

Figure 2: Bone marrow sample showing hemophagocytosis (arrow).

or Castleman's disease. Viral serology for EBV, CMV and HHV-6 were all negative.

Due to his persistent pancytopenia and unusual characteristics of symptoms a bone marrow biopsy was performed. Biopsy findings were consistent with a hypercellular marrow and hemophagocytosis with no evidence of lymphoma (Figure 2).

The patient met many of the diagnostic criteria for secondary HLH (Table 1), which in his case was triggered by an underlying HHV-8 infection. After consultation with the hematology and oncology service, the patient was started on the HLH-94 protocol regimen consisting of a 14-day course of 20 mg IV dexamethasone and three cycles of 300 mg of etoposide [2]. He also received supportive care with packed red blood cell transfusions.

The patient's constitutional symptoms and blood counts improved and he was discharged with planned outpatient evaluation for hematopoietic stem cell transplantation (HSCT). A month later while still undergoing etoposide chemotherapy, he presented to the emergency department with malaise and high grade fevers. He was found to be pancytopenic (hemoglobin 4.8 g/dl, WCC 0.6x10^3/µl, platelet count 32x10^3/µl) and in septic shock with multi-organ failure. He also had elevated ferritin 4813 ng/ml and triglycerides 1319 mg/dl. The patient was started on empiric antimicrobial therapy (intravenous vancomycin and piperacillin/tazobactam) and was admitted to the intensive care unit for circulatory and respiratory support but succumbed to his illness five days later.

Table 1: Diagnostic criteria for HLH adopted from Henter et al. [6]. A diagnosis can be established if the patient has a molecular diagnosis consistent with HLH or fulfills at least five of the above eight criteria.

2004 Diagnostic criteria for HLH	Criteria fulfilled in index case
Fever	Yes
Splenomegaly	Yes
Ctyopenia affecting ≥ 2 cell lineages: Hemoglobin < 9 g/dl Platelet < 100 x 103/dl Neutrophils < 1,000/dl	Yes Yes Yes No
Fibrinogen < 1.5 g/L or Hypertriglyceridemia (≥256 mg/dl)	Yes
Ferritin ≥ 500 µg/L	Yes
Soluble CD25 ≥ 2,400 U/ml	Not done
Low or absent natural killer cell activity	Not done
Hemophagocytosis in bone marrow, spleen or lymph nodes	Yes

DISCUSSION

Hemophagocytic lymphohistiocytosis is broadly classified into familial cases and secondary cases, typically triggered by underlying infections. The familial cases are further divided into two groups: familial hemophagocytic lymphohistiocytosis (FHL) and immune deficiencies such as Chediak–Higashi syndrome. The FHL usually presents in infants or young children with hepatosplenomegaly and pancytopenia. This form of HLH is caused by defects in immune regulation, such as mutations in genes controlling the function of cytotoxic T-cells and NK-cells [3]. Interestingly, even patients with genetic defects for HLH often have an infectious trigger to HLH in keeping with the two-hit hypothesis required for the development of many diseases [3].

The pathophysiology of HLH involves defective cytotoxic T-cell function coupled with unregulated macrophage activity leading to excessive cytokine production, immune dysregulation and tissue damage [3]. Of particular merit is IL-6, a cytokine reported to be involved in the pathogenesis HHV-8 associated disease [4]. The exact mechanism of virus mediated HLH is not clear. It has been hypothesized that the proliferation of HHV-8 infected plasmablasts might result in a cytokine storm leading to viral associated HLH, a mechanism similar to EBV-associated T cell lymphoproliferative disorder [5]. However, the trigger of HHV-8 reactivation has not been elucidated.

The diagnosis of HLH should be based upon the published diagnostic criteria used in the HLH-2004 trial [6]. Our patient had evidence of pancytopenia on laboratory investigations as well as markedly elevated ferritin and triglyceride levels. The key for our diagnosis was the demonstration of hemophagocytosis on bone marrow examination. We did not feel the need to pursue additional testing including soluble CD25 levels and natural killer cell activity because we were confident we reached a firm diagnosis.

We hereby report the fifth case of HHV-8 associated HLH in an immunocompetent, HIV negative adult. Li et al. were the first to report a case of HHV-8 related HLH in an immunocompetent, HIV negative individual with MCD [5]. Re et al. reported two more cases in immunocompetent patients but in the absence of HHV-8 related conditions [7]. A more recent article reported HLH secondary to HHV-8 in a patient with both MCD and KS [8]. Our patient had no history suggestive of immunodeficiency or malignancy and had developed KS twelve months prior to the discovery of HLH. All the patients mentioned in the cases above, including our patient, suffered a rapid and fatal clinical course.

Treatment of HLH is aimed at suppressing the hyperinflammatory state that leads to end organ damage. Treatment regimens vary according to the cause of HLH. Infection-associated HLH is usually managed by treating the underlying cause along with the standard HLH-94 protocol consisting of high dose steroids and

etoposide [2]. It has been shown that early introduction of etoposide is the only significant variable for improved survival [3, 9]. Nevertheless, HSCT remains the only hope for permanent control or cure of the disease [10]. Its main utility is in familial HLH, although many cases of acquired HLH should be treated with HSCT. Our patient received the appropriate therapy for HLH; however, as a result of pancytopenia these patients are prone to infections and bleeding episodes. He unfortunately died after developing severe sepsis syndrome with multi-organ dysfunction refractory to therapy with antibiotics, blood products and inotropic support.

CONCLUSION

Our patient expired despite being on evidence-based treatment for HLH. This not only highlights the aggressive nature of the disease and high mortality rates but also the need for improved therapy for these patients. Additionally, HLH presents with non-specific signs and symptoms resulting in delayed diagnosis. Therefore, HLH should be considered as a complication of HHV-8 infection particularly in the presence of pancytopenia, even in immunocompetent patients. We aim to raise awareness of this condition, as early recognition is crucial for any reasonable attempt at curative therapy to be made.

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Author Contributions

Talal Alnabelsi – 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
Cecilia Jang – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published
Ramzi Mulki – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published
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Manju Balasubramanian – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published
Mark Morginstin – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Monotherapy with erythromycin results in severe rhabdomyolysis

Lukas Birkner, Dimitri Zolotov, Mario Iasevoli

ABSTRACT

Introduction: Rhabdomyolysis is a potentially life-threatening condition caused by muscle necrosis and extravasation of intracellular muscle contents into the blood circulation. An elevation in serum creatine kinase is most confirmatory laboratory test. Erythromycin is an inhibitor of the CYP3A4 enzyme system which is responsible for the metabolism of several drugs, particularly some statins. Although rhabdomyolysis asssociated with macrolid-statin interaction has been previously described, we report the first case of erythromycin-induced rhabdomyolysis. Case Report: In our case, a 38-year-old male admitted with pneumonia developed rhabdomyolysis associated with erythromycin administration. Conclusion: Clinicians need to be aware of the risks this potential adverse drug reaction poses.

Keywords: Erythromycin, Penicillin intolerance, Pneumonia, Rhabdomyolysis

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INTRODUCTION

Rhabdomyolysis is a potentially life-threatening condition characterized by the leaking of creatine kinease and other intracellular proteins and electrolytes into the blood circulation [1]. The most common symptoms of rhabdomyolysis include muscle weakness, brown urine, electrolyte imbalances, acute renal failure and disseminated intravascular coagulation. An elevation in serum creatine kinase (CK) and myoglobin is the most confirmatory laboratory test for rhabdomyolysis since all cases are associated with it [2, 3].

Although there are multiple physical and nonphysical causes of rhabdomyolysis the most common cause is medication [4]. Especially, rhabdomyolysis related to macrolide-statin interaction, such as clarithromycin or ketoconazole interacting with simvastatin, has been previously described in literature [5].

CASE REPORT

We report a case of 38-year-old male presented with a clinical diagnosis of common acquired pneumonia.

He was treated with erythromycin (500 mg two times a day) for one and a half days due to a known penicillin intolerance. The patient subsequently developed joint and muscle pain after the first day of administration and an anuria with growing nausea after the second day without a documented source of infection. Consequently, the patient was admitted to our inpatient hospital complaining of an anuria. An extremely elevated creatine kinase concentration of 40205 U/L (normal <200) was discovered after the first day of hospitalization and reached 228456 U/L the following day. The estimated glomerular filtration rate (GFR) was reduced to <10 ml/min (normal 120 ml/min per 1.73 m^2). Other parameters indicating rhabdomyolysis were serum aspartate aminotransferase (AST) 5789 U/l (normal 5–34), serum alanine aminotransferase (ALT) 1093 U/l (normal < 55) and serum lactate dehydrogenase (LDH) increased to a maximum of 10,100 U/l (normal 125–243). Rhabdomyolysis associated with acute renal failure and hepatopathy was diagnosed. Erythromycin was immediately stopped and the patient received dialysis treatment as required over the course of two and a half weeks. The serum CK gradually decreased. Two weeks later creatine kinase returned to 2927 U/L. During the course of the dialysis treatment the micturition gradually increased and muscle pain subdued. No further laboratory tests were ordered.

Erythromycin was thought to be the precipitating factor for rhabdomyolysis because the patient was neither taking other medication nor had a conspicious anamnesis or relevant pre-existing conditions. Additionally, using the Naranjo adverse drug reactions probability scale a score of 6 was determined. Thus erythromycin can be considered a probable cause of rhabdomyolysis [6].

DISCUSSION

Rhabdomyolysis associated with macrolid-statin interaction has been previously described, however, rhabdomyolisis related to erythromycin has not been reported until now [7]. Erythromycin is an inhibitor of the CYP3A4 enzyme system, which is responsible for the metabolism of several drugs, particularly some statins as simvastatin or atorvastatin. Any documented cases of erythromycin induced rhabdomyolysis involved drug interactions with statins through inhibition of CYP3A4 enzyme system. It has a similar spectrum of activity as clarithromycin [8].

Of interest, clarithromycin induced rhabdomyolysis has been previously reported in a few cases. A five-year-old Asian-American girl was admitted with 102°F fever and a five-day history of productive cough. The patient was prescribed clarithromycin 125 mg twice a day. After five days a creatine kinase concentration of 949 U/L (normal <177) was discovered. Clarithromycin was immediately stopped and the child recovered [9, 10]. Undoubtedly, both cases show parallels, such as the elevation of serum CK associated with the respective drug and the course of recovery, although differences in the severity must be noted.

In our case, there was a definite connection between erythromycin exposure-withdrawal and the gradual recovery of the patient. Considering the sequence of events we ruled out infection as the possible cause of rhabdomyolysis. As a matter of fact the patients symptoms were inconspicious, while serum CK drastically increased one day after the start of treatment with erythromycin. Thus, the chronological relationship between the appearance of myalgia and the start of erythromycin suggest the conclusion that erythromycin is the responsible agent in our case.

CONCLUSION

We reported a probable case of erythromycin-induced rhabdomyolysis. The mechanism behind this adverse drug reaction is not understood, although there have been a few cases of rhabdomyolysis associated with macrolides. Clinicians need to be aware of the risks this potential adverse drug reaction poses, espeacially concerning patients at risk for rhabdomyolysis.

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Author Contributions

Lukas Birkner – 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
Dimitri Zolotov – 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
Mario Iasevoli – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Robot-assisted stereotactic laser ablation of residual epileptogenic focus in the setting of chronic low back pain

Alvin Y. Chan, Jack J. Lin, Lilit Mnatsakanyan, Mona Sazgar, Indranil Sen-Gupta, Frank Hsu, Sumeet Vadera

ABSTRACT

Introduction: Stereotactic laser-induced thermal therapy (LITT) is a minimally invasive procedure used to ablate a variety of intracranial pathology including tumors, epileptogenic foci and radiation necrosis. Potential benefits of LITT over open resection include avoiding a large craniotomy and pain associated with this. Case Report: We present a 58-year-old male who originally presented 15 years prior with new-onset seizures due to a low-grade astrocytoma in the left lateral temporal lobe. He underwent focal tumor resection at that time but continued to have seizures. The patient had a history of degenerative disease in the lumbar spine and had already undergone several surgeries in the past including a failed fusion. He presented to our center where video-electroencephalogram (vEEG) localized the ictal onset zone to the left mesial temporal lobe adjacent to the resection cavity. He was offered craniotomy and LITT therapy, and he elected to undergo LITT. Robotic assistance was utilized and bone fiducials were implanted for precise registration and implantation. A laser cannula was placed in the appropriate location and the ictal onset zone was ablated with MR-thermometry. The patient required no additional pain medications after surgery and has been seizure free since surgery. Conclusion: Our study demonstrates LITT can be beneficial over open craniotomy with regards to postoperative pain control in patients with severe chronic pain. Further, this case demonstrates the importance of considering tumors and epileptogenic foci as distinct and separate entities. Therefore, we advocate for evaluation and resection of ictal onset zones during initial tumor resection

Keywords: Chronic pain, Laser-induced thermal therapy (LITT), Lesionectomy, ROSA robot

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INTRODUCTION

Surgical resection of epileptogenic foci in patients who suffer from medically refractory epilepsy can be transformative [1, 2]. The results of epilepsy surgery are often a cessation or reduction in seizure activity and a better quality of life when compared with continued medical therapy [3, 4]. Patients with intracranial tumors

can present with seizures and appropriate treatment involves not only resection of the tumor but also isolation and removal of the ictal onset zone, as these are commonly distinct entities [5, 6].

Stereotactic laser-induced thermal therapy (LITT) is becoming increasingly utilized to ablate a variety of intracranial pathology including tumors, epileptogenic foci and radiation necrosis [7]. Although craniotomies are still considered first line therapy for a variety of treatments, LITT has been increasing in popularity as a minimally invasive alternative [8]. Laser-induced thermal therapy may offers several benefits over standard craniotomy including minimal postoperative pain, avoidance of a large craniotomy, a short hospital stay, better wound healing, and a lower rate of complications even in patients with comorbidities [9]. Furthermore, LITT has been shown to be safe and efficient in cases where an open craniotomy may not be an ideal treatment [10].

In this study, we present a case of a patient with chronic low back pain who originally presented 15 years prior to an outside hospital with medically refractory focal epilepsy and workup revealed a low-grade tumor in the left lateral temporal lobe. The patient underwent focal resection of the tumor but continued having seizures because the ictal onset zone was not localized or addressed during the initial surgery. The patient presented to our center with continued seizures and noninvasive testing revealed that seizures were arising from the mesial temporal lobe. The residual ictal onset tissue was ablated via laser with robotic assistance. This case outlines the need to consider the ictal onset region as being potentially distinct and separate from a tumor in epileptic patients, as this consideration may reduce the possibility of recurrence and thus another potential procedure. It also demonstrates LITT therapy as a good option in patients with chronic pain to minimize post-surgical pain, which can be difficult to treat after open craniotomy.

CASE REPORT

The patient is a 58-year-old male who originally presented to an outside hospital with new-onset seizures at the age of 43. Workup revealed a low-grade tumor in the left lateral temporal lobe. He underwent a focal resection of the tumor and postoperative MRI revealed gross-total resection. He was seizure free for one year after surgery and then developed recurrence of seizures of the same semiology. Of note, the patient had a history of lumbar decompression and fusion for back pain and developed chronic low-back pain requiring high doses of dilaudid and fentanyl. Patient presented to our institution with 14 years of medically refractor focal epilepsy and chronic low-back pain requiring high doses of dilaudid and fentanyl. Subsequent video-electroencephalogram (vEEG) data revealed a single focal area of cerebral dysfunction in the mesial temporal lobe adjacent to the prior resection cavity. The patient had failed multiple medications in the past and had no improvement in seizures. He had significant side effects from the medications and stopped taking them for this reason. Patient had 3–5 seizures per day prior to surgery.

The patient was offered an open resection of the residual epileptogenic foci or laser-induced thermal therapy (LITT) to treat the presumed ictal onset zone. He elected to undergo laser ablation to minimize post-surgical pain because of the patient's chronic pain and opioid dependence.

The patient underwent a preoperative volumetric MRI for stereotactic navigational purposes. The patient was placed under general anesthesia and then placed in a lateral position. We used the ROSA robot (MedTech Surgical, Inc, Montpellier France) to assist with implantation of a laser cannula through a transoccipital approach to the mesial temporal lobe. The patient was placed in a Leksell stereotactic head frame (Elekta, Crawley, United Kingdom) to connect him to the robot (i.e., not for stereotactic navigational purposes). Additionally, bone fiducials were used because facial registration is less accurate when the patient is in the lateral position. A mesial temporal trajectory was planned with the ROSA navigation software, including the entry point and trajectory needed to reach the target (Figure 1). A percutaneous burr hole was made on the scalp at the entry point and a PMT skull bolt (PMT Corporation, Chanhassen, Minnesota) was placed in the correct trajectory. We passed a cannula through the skull bolt and advanced it to the predetermined depth (Figure 2). The laser applicator was then placed within the cannula and secured. The patient was then transported to the MRI suite for the remainder of the procedure. Imaging confirmed correct placement of the laser applicator and then the LITT commenced.

The Visualase thermal therapy system (Visualase, Inc.) consists of a computer, a 15 W 980 nm wavelength diode laser, a cooling pump, and a disposable laser applicator that is approximately 1.65 mm wide [2]. Designated "safety points" would shut off the laser if the region of the brain near the laser applicator or surrounding parenchyma reached approximately 90°C, or if the protected cerebral structures reached temperatures around 50°C. The laser was pulsed at roughly 9 W for 60–90 seconds intervals. The laser cannula was pulled back and ablation continued until an adequate region was ablated. When the surgeon deemed the region to be sufficiently ablated, the applicator and bolt were removed and the wound was closed.

There were no complications associated with surgery and the patient was discharged on postoperative day one. The patient required no additional pain medications outside of his normal chronic pain regimen. During his follow-up appointment, he had no pain related to the surgery and has denied any seizures since surgery.

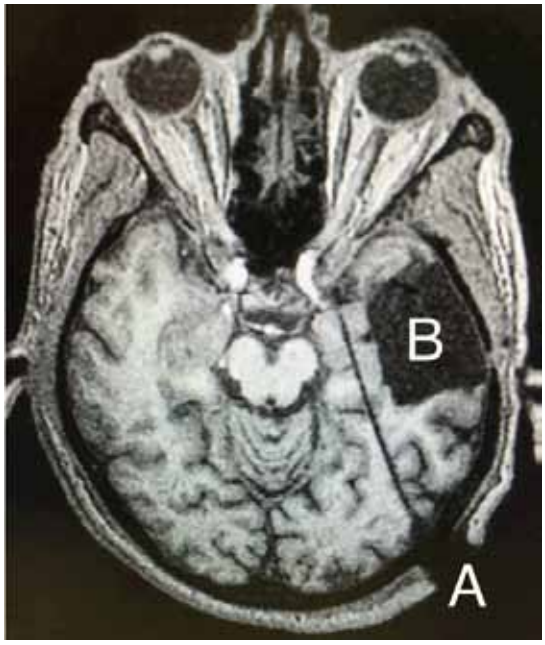

Figure 1: Panel A—ROSA display demonstrating planned and actual (A) Entry point, and (B) Target.

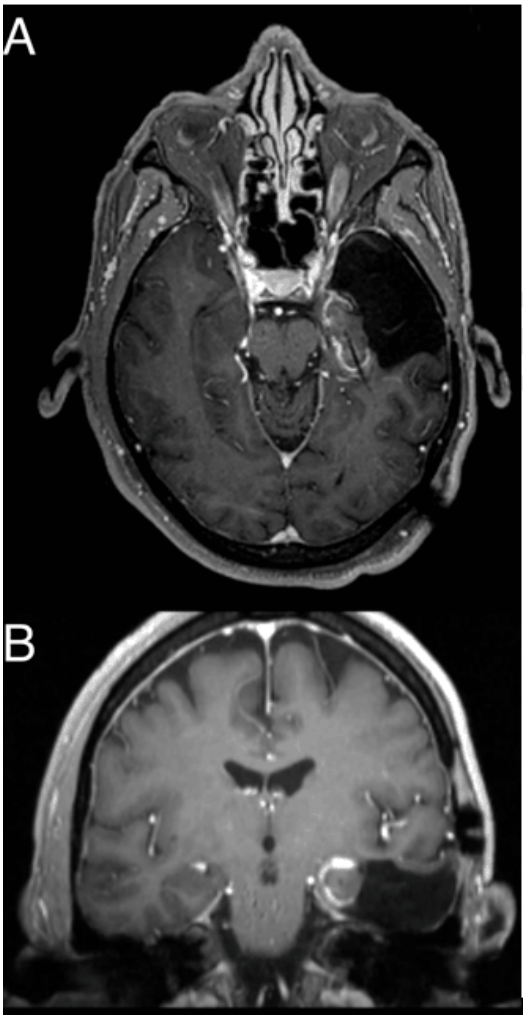

Figure 2: Axial image of the trajectory of the laser applicator taken from the posterior aspect of the head to the mesial temporal lobe; (A) Entry point, and (B) Cavitation.

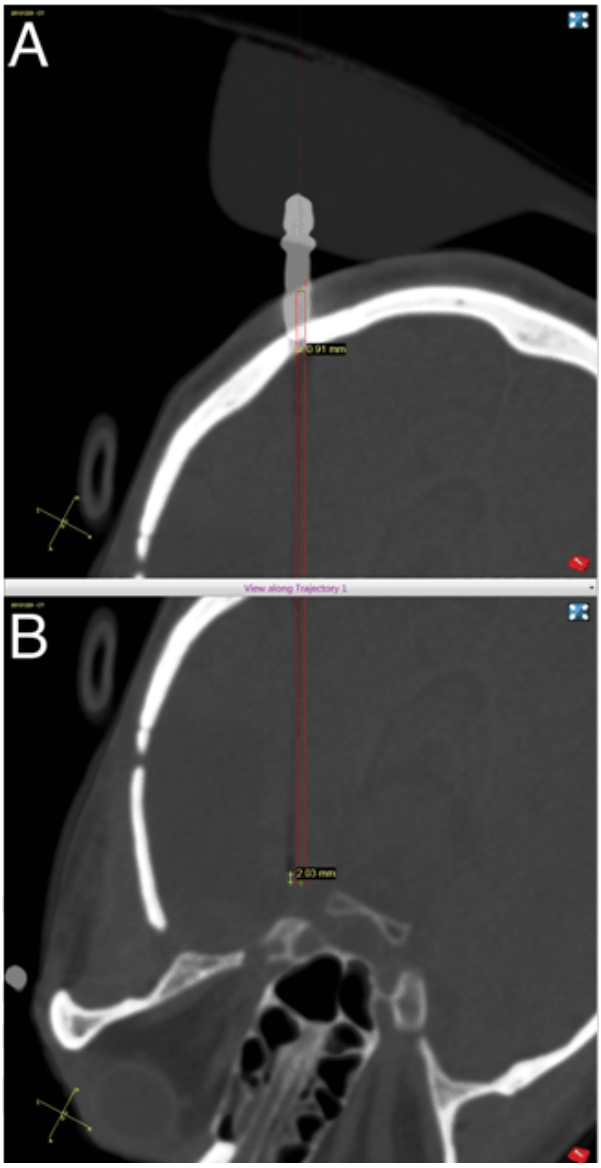

Figure 3: Post-ablation images; Enhancement surrounding the ablation area in the (A) axial and (B) coronal sections.

DISCUSSION

We present a case where stereotactic robotic assistance and LITT were used to ablate the ictal onset zone of a patient with chronic low-back pain and recurrent seizure activity following prior resection of a tumor in the left mesial temporal lobe. LITT was chosen as a viable alternative to an open resection because

(i) the patient had chronic pain and an open resection was likely to result in a more challenging post-surgical pain management than the less invasive LITT,
(ii) if LITT were ineffective, an open resection would still be an available option, and
(iii) the location and size of the residual tissue was ideal for laser ablation.

This case highlights the need to consider tumors and epileptogenic foci as distinct and separate entities and emphasizes the importance of isolating the ictal onset zone and resecting it as part of the tumor resection. Ictal onset zone may be localized through a variety of techniques including intraoperative electrocorticography (ECoG) and invasive monitoring (subdural grids or depth electrodes). If the patient originally had the entire mesial temporal lobe removed, he would likely be both free from the low-grade tumor as well as seizure activity. Therefore, identifying tumor location should be considered a separate process from localizing epileptogenic foci, as the two could be separate entities.

While not insurmountable, postoperative pain after craniotomy in patients with chronic pain can be difficult to treat. LITT therapy allows us to treat the ictal onset zone while minimizing additional tissue damage and injury. It also does not preclude further open surgery if required and some studies show better neuropsychological outcomes, as patients with refractory temporal lobe epilepsy undergoing laser ablation instead of an open temporal lobe resection may experience better cognitive outcomes in certain tasks [11]. Furthermore, postoperative pain is not inconsequential for patients and it is often poorly controlled despite a developing knowledge of pain mechanisms and treatments [12], therefore we wanted the opportunity to prevent postoperative pain by using LITT over a craniotomy.

CONCLUSION

Herein, we described a case where a patient underwent lesionectomy for a temporal lobe tumor, which resulted in the recurrence of seizures, and thus required removal of residual tissue that we chose to ablate by Stereotactic laser-induced thermal therapy (LITT) due to his pre-existing chronic lower back pain. This case emphasizes the need to identify and remove the ictal onset zone in addition to tumor resection in patients who present with new onset seizures in the setting of a tumor. Additionally, we demonstrate LITT can be considered as an alternative to craniotomy within pre-existing chronic pain to reduce the potential of additional chronic pain associated with the surgery.

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Author Contributions

Alvin Y. Chan – 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.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT PEER REVIEWED | OPEN ACCESS

Bilateral necrotizing scleritis isolated in patients with granulomatosis with polyangiitis and p-ANCA positivity

Anita Syla Lokaj, Blerta Rama, Ylfete Retkoceri

ABSTRACT

Introduction: Granulomatosis with polyangiitis (GPA) is a rare systemic disease of unknown etiology characterized with tissue granulomatous inflammation and vasculitis. The affected sites are the upper and lower respiratory system, skin, eyes, nervous system, kidney and rarely other organs. The disease exists in two forms; milder, regional located form (limited) and severe, progressive with renal involvement form (generalized). Case Report: In this study, we represent a case of bilateral necrotizing isolated scleritis, where we had difficulties to diagnose GPA with only p-ANCA positive titrate and negative c-ANCA titrate. His c-ANCA was negative whereas p-ANCA (seen in 5% of cases) was positive. The scleral biopsy revealed histology suggestive of granulomatosis with polyangiitis. He responded well with steroid and cyclophosphamide therapy with great caution because he had diabetes mellitus. Conclusion: In cases with few organ involvements or no active disease as showed in our case, where only scleritis is present and high suspicion of GPA clinically, a biopsy of organ with active disease is mandatory, as diagnosis cannot be made only on the presence of ANCA and signs of scleritis.

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INTRODUCTION

Granulomatosis with polyangiitis is a systemic disease involving granulomatous inflammation, necrosis and vasculitis that most frequently targets the upper respiratory system, the lower respiratory system and kidney [1]. As systemic disease, it can affect other systems like musculoskeletal system, skin, eyes and others. Therefore, granulomatosis with polyangiitis can cause a lot of ocular manifestation with different management approaches [2]

Determination of the specific antibodies can aid the diagnosis. Anti-neutrophil cytoplasmic antibodies (c-ANCA), which act against serine proteinase 3, are relatively sensitive and highly specific for granulomatosis with polyangiitis [3]. The perinuclear anti-neutrophilic cytoplasmic antibodies (p-ANCA), which act against myeloperoxidase, are not specific for any kind of vasculitis, but are found in some patients with GPA and other diseases [4].

ANCA associated diseases can be difficult to diagnose and treat [5], especially in cases with only p-ANCA positive titrate [6].

In this study, we represent a case of isolated bilateral necrotizing scleritis where we had difficulties to diagnose GPA with only p-ANCA positive titrate and negative c-ANCA titrate.

CASE REPORT

We report a case of 75-year-old male who presented to us with a history of episcleritis in his eyes for two months. He complained of some discomfort and pain in eyes and forehead. He gave a history of hypertension and diabetes mellitus which were controlled by medication therapy. On examination his visual acuity was nearly normal. There was mild congestion of conjunctiva in upper nasal quadrant. Sclera thinning in upper nasal quadrant with visible uveal tissue and no signs of inflammation was noted. He had very large patches of true scleritis in right eye and three small patches in left eye. Anterior chamber, iris, pupil and lens were normal. Applanation tension (intraocular pressure) was 16 mmHg. Ocular movements were normal. Dilated fundus examination was with normal limits.

Investigation revealed moderate ESR (60 mm/hr), red blood cell in normal range as well as white blood cell and platelets, negative rheumatoid factor, negative antinuclear antibodies, C3 and C4 complement were in normal value, negative cytoplasm staining pattern (c-ANCA) and positive p-ANCA. Anti-neutrophil cytoplasm antibody was performed by an enzyme-linked immunosorbent assay (ELISA) for the presence of anti-MPO antibodies. Chest X-ray was normal. Renal function was normal as assessed by urea, electrolytes and creatinine levels. At the end, we did sclera biopsy of left eye to verify the extra diagnosis and results were positive for GPA. Pathologically, scleral biopsy showed multinucleated giant cells. Perivascular was seen with epithelioid cells surrounding vessels. Blood vessels within sclera shows an intense inflammatory infiltrate with destruction of the blood vessels wall. Also in biopsy was collagen necrosis that suggested an aggressive ischemic process.

The patient was started on oral prednisolone (initial dose 40 mg/day), which were not effective to improve scleral inflammation. Therefore, we decided to start with A, oral cyclophosphamide (150 mg/day). Within 4–6 weeks, the scleral inflammation had subsided and the ANCA titers had become negative. After a follow-up of 18 months the scleritis remains on remission on a combination of cyclophosphamide (75 mg/day) and prednisolone (7.5 mg/day). So far, there was no evidence of extra ocular involvement. Serial ANCA titers remained negative.

Figure 1: Right eye showing sclera thinning in upper quadrant with visible uveal tissue and without peripheral corneal thinning. Note the avascular area of sclera.

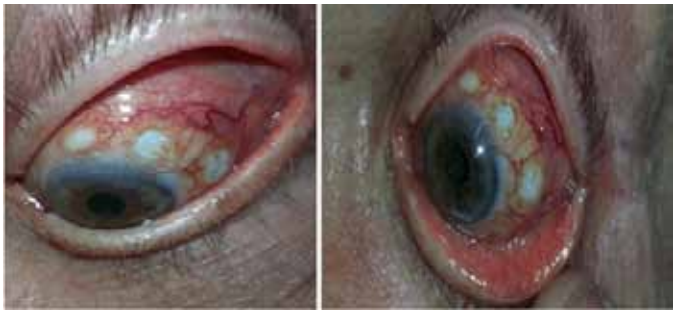

Figure 2: Left eye showing sclera thinning in upper nasal (correct nasal).

DISCUSSION

Granulomatosis with polyangiitis (GPA) may be in classic or limited form and ocular sign as scleritis, proptosis, corneal ulceration may be the major component of GPA [7]. In cases with bilateral scleritis, in addition to GPA, rheumatoid arthritis, ANCA-associated vasculitis associated scleritis as microscopic polyangiitis, polyarteritis nodosa, relapsing polychondritis, Churg-Strauss syndrome must also be taken into consideration. This is because they are associated with scleritis but the limited form is very rare in these diseases. In our case, peripheral ulcerative thinning, keratitis, uveitis, ischemic optic neuropathy, retinal artery occlusion were not present, even though they usually accompany this diseases. Scleritis in patients with GPA has a rate between 16–38%. Necrotizing scleritis can be manifested with other systemic disease, but in GPA it may be present and it has a great mortality rate if the patient are not undergoing immunosuppressive therapy [8–9].

The presence of cytoplasmic ANCA in a patient who is suspected to have Wegener's granulomatosis is strong circumstantial evidence in support of that diagnosis. However, it does not represent absolute proof and should be viewed with skepticism if the clinical presentation is atypical [10], because its implication was in other disease.

CONCLUSION

In cases with fewer organ involvements or no active disease as is in our case where only scleritis is present

and there is high suspicion of Granulomatosis with polyangiitis (GPA) clinically, a biopsy of organ with active disease is mandatory, as diagnosis cannot be made only on the presence of ANCA and signs of scleritis.

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Author Contributions

Anita Syla Lokaj – 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
Blerta Rama – 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

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Conflict of Interest

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