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An Unusual Case of Deep Vein Thrombosis and Mycotic Aneurysms Secondary to *Salmonella* Bacteraemia

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Abstract

Salmonella, a food-borne pathogen, can cause mild self-limiting gastroenteritis. However, immunocompromised hosts and older adults with complex medical conditions may develop a complicated form of bacteraemia, with a high mortality rate involving extra-intestinal foci of infection and mycotic aneurysms. We report the case of a 61-year-old man with poorly controlled diabetes mellitus, hypertension, dyslipidaemia, and congestive heart failure, who presented with unilateral left lower limb swelling, extensive deep vein thrombosis, and concomitant *Salmonella* bacteraemia. An oral anticoagulant and intravenous antibiotic therapy were initiated. Although the patient remained haemodynamically stable, he complained of constant left lower limb weakness and lower back pain. A computed tomography angiography scan of the thorax and abdomen revealed saccular aneurysms with contained hematoma of the left common iliac artery. The oral anticoagulant was discontinued, and an inferior vena cava filter was inserted as part of the venous thrombosis management. The patient was offered aorto-uni-iliac endovascular aneurysm repair and received intravenous antibiotic therapy, postoperatively, for six weeks. The postoperative blood cultures remained negative, and he was discharged with a course of ciprofloxacin administered orally. However, three months after the surgery, the patient died of recurrent septicaemia. This case illustrates the importance of remaining vigilant for potential endovascular complications of *Salmonella* bacteraemia, such as mycotic aneurysms and deep vein thrombosis, among high-risk patients. Further, this case highlights the challenges of eliminating *Salmonella* bacteraemia and its related complications, albeit treating it with both a prolonged course of medical therapy and surgical intervention.

Keywords

Deep Vein Thrombosis, Endovascular Aneurysm Repair, Infective Endarteritis, Mycotic Aneurysm, *Salmonella*

1. Introduction

Gastroenteritis is a common clinical feature of *Salmonella* infections and is often self-limiting, without complications. However, approximately 5% of affected patients develop *Salmonella* bacteraemia [1]. Disseminated infections are more likely to occur in immunocompromised hosts and older adults with complex medical conditions [2] [3] [4] [5]. These patients may develop complications involving endovascular infection and deep bone and visceral abscesses, which are challenging to treat and have a high mortality rate [6]. A recent study reported that *Salmonella* bacteraemia is the second most common cause of mycotic aneurysms and that its incidence is higher in Asian countries than in the West [7] [8]. In addition, *Salmonella* bacteraemia can present with atypical features, such as deep vein thrombosis [9] [10] [11]. Awareness of the rare and unusual clinical presentations of invasive *Salmonella* infection is essential for accurate diagnosis and prompt management.

Therefore, clinicians caring for high-risk patients with complex medical conditions need to remain vigilant and perform comprehensive evaluations to assess potential complications of *Salmonella* bacteraemia, such as mycotic aneurysms and deep vein thrombosis. Mycotic aneurysms involving multiple anatomical sites are challenging to treat, even when using a combination of medical and surgical interventions. Negative blood cultures, after a specific duration of antibiotic therapy and in the postoperative period, do not necessarily indicate complete bacterial elimination.

Here, we present the case of a 61-year-old man who presented with extensive deep vein thrombosis of the left lower limb with concomitant *Salmonella* bacteraemia and subsequently developed mycotic aneurysms.

2. Case Presentation

A 61-year-old man, with poorly controlled diabetes mellitus (Haemoglobin A1c: 12.5%), hypertension, dyslipidaemia, and congestive heart failure, presented with a gradual onset of unilateral left lower limb swelling for two weeks, which rendered him unable to walk. He had not been previously investigated for ischaemic causes of heart failure and had defaulted follow-up. He reported a subjective feeling of shortness of breath and had symptoms equivalent to the New York Heart Association Class III that were limiting his daily activities. He also reported significant tobacco use (smoking history of 40 pack-years).

On admission, his vitals were stable, with a low-grade fever of 37.6˚C; blood pressure of 128/78 mmHg; pulse rate of 96 beats/min; respiratory rate of 18

breaths/min and oxygen saturation of 100% breathing ambient air. Examination of the left lower limb revealed asymmetric calf swelling of more than 3 cm compared to the contralateral leg, without any pus discharge or skin excoriation. The active range of movement of the left hip, knee, and ankle was limited, owing to pain. Blood investigations revealed a white blood cell count of $9.46 \times 10^3/\mu L$ with a neutrophil predominance of 77% and an erythrocyte sedimentation rate of 79 mm/h (Table 1). Based on the elevated inflammatory markers and low-grade fever, a presumptive diagnosis of left lower limb cellulitis was made, and the patient was started on intravenous ceftriaxone. A chest radiography scan revealed cardiomegaly. Based on elevated D-dimer levels of 2251 ng/ml and a Wells score of 3, an urgent lower-extremity venous ultrasound examination revealed extensive thrombi in the left common femoral, superficial femoral, and popliteal veins (Table 1). There were no focal loculated fluid collections indicative of septic arthritis in the hip, knee, or ankle joints. He denied any long-distance travel, recent surgery, or a malignancy history. To prevent further clotting and an embolism, he was started on subcutaneous enoxaparin and bridged with dabigatran.

Table 1. Progress of patient's relevant blood investigations throughout hospital admission.

	Normal Values	Day 1	Day 7	Day 14	Day 28	Day 42
WCC (10^3/uL)	3.60 - 10.20	9.46	13.71	7.14	7.90	9.9
Neutrophil percentage	43% - 73%	77%	80.6%	74%	70%	72%
Haemoglobin (g/dL)	12.5 - 16.0	11.2	10.5	9.2	7.8	7.7
MCV (fL)	80 - 100	79.3	75	75	81.6	90
MCH (pg)	27 - 33	27	27	26	27	26
Platelet (10^3/uL)	152 - 347	188	335	292	311	279
ESR (mm/h)	≤15 mm/h	79	49	100	104	64
D-Dimer(ng/ml)	0 - 253.5	2251				
PT (sec)	11 - 16	16.1	17	20	14.7	15.9
PTT (sec)	30 - 40	54.3	52	74	49.7	61.9
INR		1.3	1.3	1.4	1.2	1.3
Urea (mmol/L)	1.7 - 8.3	8.2	7.8	3.7	2.9	4.0
Creatinine (umol/L)	80 - 115	83	97	67	75	78
Sodium (mmol/L)	133 - 145	126	131	128	128	134
Potassium (mmol/L)	3.3 - 5.1	4.7	4.1	3.8	4.3	3.7
Albumin (g/L)	38 - 51	24	24	21	29	29
AST (U/L)	5 - 41	116	93	73	60	63
ALT (U/L)	5 - 37	93	45	31	30	25
Hepatitis B & C		NR				
HIV		NR				
Syphilis		NR				

Continued

Stool Culture		Neg	Neg	
Blood Culture and Susceptibility		*Salmonella enteritidis* Susceptible to: - Ceftriaxone - Ampicillin - Co-trimoxazole	Neg	Neg
PSA (ng/mL)	1 - 1.5	0.9		
CEA (ng/mL)	0 - 2.5	0.21		
AFP (ng/mL)	10 - 20	4		
CA 19-9 (U/mL)	0 - 37	2.1		
ANA		Neg		
Anti-ds DNA		Neg		
RF		Neg		
Direct & Indirect Coomb's		Neg		
Haemoglobin A1C	<6.0%	12.5%		
Total Cholesterol (mmol/L)	0.1 - 5.2	5.4		
HDL (mmol/L)	0.91 - 3.12	1.25		
LDL (mmol/L)	0.9 - 3.9	4.2		
Triglycerides (mmol/L)	0.1 - 2.27	1.1		

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ANA, anti-nuclear antibodies; Anti dsDNA, anti-double-stranded DNA antibody; AST, aspartate aminotransferase; CA 19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; INR, international normalized ratio; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; Neg, negative; NR, non-reactive; PTT, partial thromboplastin time; PT, prothrombin time; PSA, prostate specific antigen; RF, rheumatoid factor; WCC, white cell count.

A preliminary report showed a gram-negative organism in the blood culture. Intravenous ceftriaxone was continued, and the patient remained haemodynamically stable and afebrile. The inflammatory markers improved, whereby the erythrocyte sedimentation rate decreased from 79 mm/h to 49 mm/h (Table 1). However, the patient continued to report a subjective feeling of fatigue and constant lower back pain, with a pain score of 4/10, which did not improve even after receiving intravenous antibiotics for a few days. Later, it became apparent that he was harbouring *Salmonella enteritidis*, which was susceptible to ampicillin, ceftriaxone, and co-trimoxazole (Table 1). The patient was co-managed by an infectious disease team, and the antibiotic was changed to intravenous ampicillin.

Collaborative history from the patient and his family members did not reveal prior gastroenteritis symptoms and significant risk factors for infection, such as travel, consumption of fast foods, poultry, raw eggs, or contact with pets were absent. The patient denied having constitutional symptoms, weight loss, or a prior history of thrombosis, and his family history was unremarkable. The stool culture and susceptibility tests were negative (Table 1). Infective screening for

hepatitis B and C, human immunodeficiency virus, and syphilis were negative (Table 1). Extensive investigations, including tumour markers and computed tomography (CT) scans of the thorax and abdomen, did not reveal any evidence of a solid organ tumour (Table 1). A peripheral blood smear revealed microcytic hypochromic anaemia but otherwise unremarkable for haematological malignancies. The result of comprehensive panel of rheumatological markers also tested negative (Table 1).

During the second week post admission, the patient reported worsening of lower back pain that hindered his walking abilities. The neurological examination was unremarkable, with localised pain over the left gluteal area and a severely restricted range of movement of the left hip owing to pain. The patient continued to remain haemodynamically stable and afebrile. Blood investigations revealed worsening inflammatory markers with a white blood cell count of 7.14 $\times 10^3/\mu L$ with a neutrophil predominance of 74% and an elevated erythrocyte sedimentation rate of 100 mm/h. The patient's haemoglobin levels decreased from 11.2 g/dL to 9.2 g/dL. An urgent esophago-gastro-duodenoscopy and colonoscopy did not reveal active gastrointestinal bleeding. Subsequently, an urgent multi-slice spiral CT combined with computed tomography angiography (CTA) of the thorax, abdomen, and pelvis was performed to identify potential invasive complications of *Salmonella* bacteraemia such as discitis, psoas abscess, and mycotic aneurysms. The CTA scan of the thorax, abdomen and pelvis revealed the presence of a 1.0 cm anteroposterior (AP) × 0.8 cm width (WT) saccular aneurysm at superolateral wall and 5.7 cm (AP) × 7.7 cm (WT)× 6.4 cm craniocaudal (CC) lobulated saccular aneurysm at the inferomedial wall of the left common iliac artery with contained hematoma (Figure 1 and Figure 2). Large saccular aneurysm does laterally displace the psoas muscle and compress the left distal ureter, which results in mild proximal hydroureter and hydronephrosis. The CTA abdomen also revealed infrarenal dissecting abdominal aortic aneurysm (AAA) measures 3.2 cm in its widest diameter (Figure 1). The true and false lumens measure 1.6 cm in diameter respectively. An echocardiogram revealed an ejection fraction of 20%, with hypokinesia in the apical and septal regions, with no evidence of valvular vegetation.

With these observations, the oral anticoagulant was discontinued due to the risk of aneurysmal rupture. As an alternative, the patient received an inferior vena cava filter to prevent embolic events from the extensive left lower-limb deep vein thrombosis. Further discussions occurred with the vascular team about the surgical interventions. After six weeks of intravenous antibiotic therapy and negative blood cultures, the patient was transferred to their facility. Considering the patient's poor cardiac reserve and multiple comorbidities, which carry an enhanced perioperative risk, the patient was offered aorto-uni-iliac endovascular aneurysm repair (EVAR) of the left common iliac artery. Postoperatively, the patient remained haemodynamically stable, received six weeks of intravenous ceftazidime, and had negative blood cultures with no evidence of leakage. However, endovascular cultures were not evaluated. At six-weeks post EVAR and

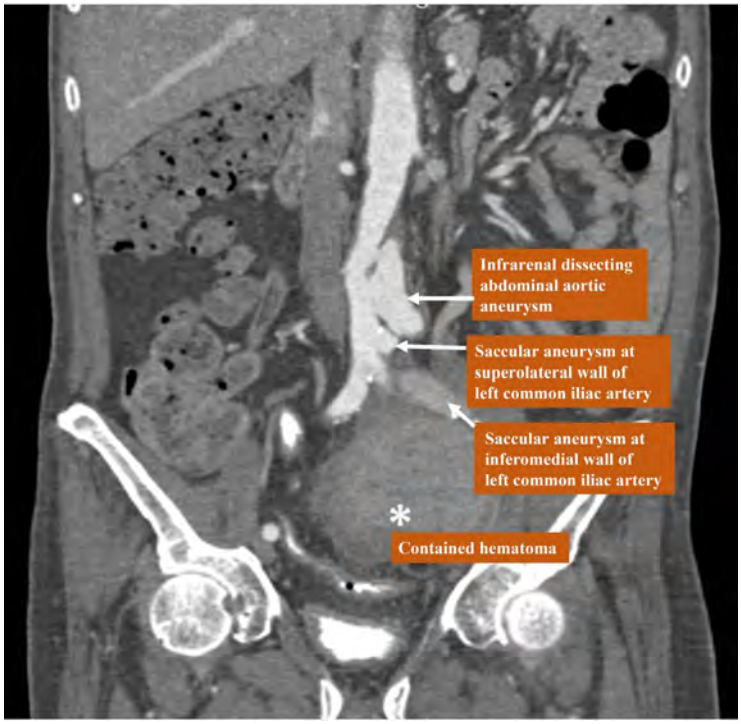

Figure 1. Computed tomography angiography (CTA) of abdomen, coronal view shows presence of two contrast filled lobulated saccular anurysms seen at left common iliac artery. The smaller aneurysm at superolateral wall of left common iliac artery measures 1.0 cm × 0.8 cm (AP × WT) with the defect opening measures 0.8 cm in diameter. Another larger aneurysm arising from inferomedial wall of left common iliac artery measures 5.7 cm × 7.7 cm × 6.4 cm (AP × WT × CC) with the defect opening measures 1.2 cm in diameter. The area marked with * shows contained hematoma from the aneurysms. CTA abdomen also shows infrarenal dissecting abdominal aortic aneurysm (AAA) measures 3.2 cm in its widest diameter. The true and false lumens measure 1.6 cm in diameter respectively.

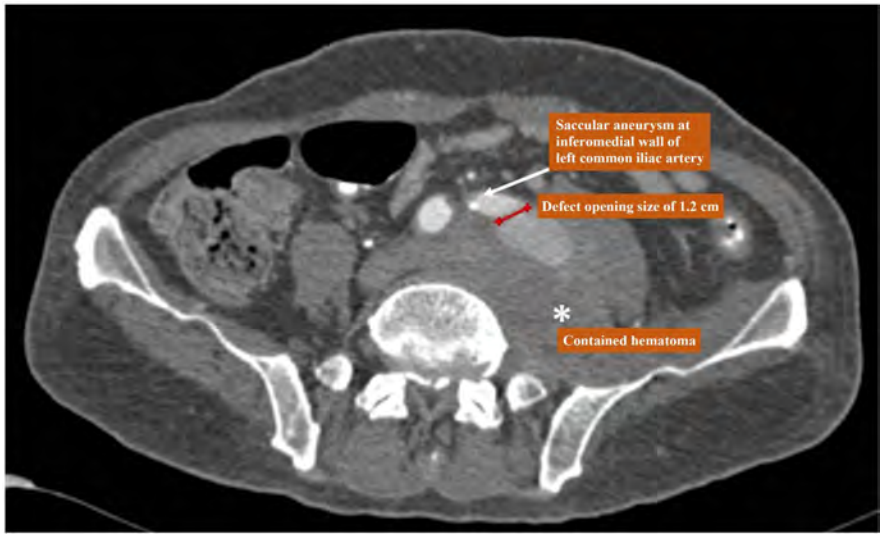

Figure 2. Computed tomography angiography (CTA) of abdomen, axial view shows presence of saccular aneurysm arising from inferomedial wall of left common iliac artery measures 5.7 cm × 7.7 cm × 6.4 cm (AP × WT × CC) with the defect opening measures 1.2 cm in diameter. The area marked with * shows contained hematoma from the aneurysm.

based on a susceptibility test, he was discharged with an extended course of oral ciprofloxacin. However, during the third postoperative month, the patient presented with extensive left lower limb gangrene and severe septicaemia. The patient later died despite extensive medical and surgical intervention.

3. Discussion

Invasive *Salmonella* infections can present with a variety of clinical features and varying degrees of complications, particularly in high-risk patients. These patients are notably immunocompromised and warrant a comprehensive evaluation. Clinicians caring for these patients need to increase their awareness, improve their clinical acumen, and should anticipate and manage any potential complications during the course of the disease (Table 2).

This case report is unique and relevant. The patient presented with severe *Salmonella* bacteraemia and extensive deep vein thrombosis and later developed multiple saccular mycotic aneurysms of the left common iliac artery. A thorough evaluation did not reveal other potential causes for the extensive deep vein thrombosis, except the severe *Salmonella* bacteraemia. Severe infection inducing a hypercoagulable state and thrombosis may explain the development of extensive deep vein thrombosis [12]. Atypical manifestations of invasive *Salmonella* infection with deep vein thrombosis have been previously reported but are notably rare [9] [10] [11]. Another possible explanation could be the compression of the ipsilateral iliac vein by a mycotic aneurysm arising from the left common iliac artery; however, this was not evident on a CTA scan of the abdomen. It would have been interesting if thrombophilia panels had been used to investigate the possibility of inherited or autoimmune causes of venous thrombosis. Thrombophilia panels were not done for this patient as inherited or autoimmune prothrombotic conditions seemed unlikely based on his negative family and personal history

Table 2. Patients with enhanced risk factors to develop invasive *Salmonella* bacteraemia.

Category	Risk Factor
Non-modifiable	Extreme age group (Age > 65 years old and neonates)
Cardiovascular	Chronic smoking Hypertension Poorly controlled diabetes mellitus Previous history of stroke Hyperlipidaemia Congestive heart failure
Immunocompromised State	Long term steroid usage Rheumatological disease Liver cirrhosis End stage renal failure Acquired Immunodeficiency Syndrome Active Malignancy Recent Chemotherapy

of thromboses. The extensive venous thrombosis was strongly suggestive of severe invasive *Salmonella* bacteraemia, a sepsis-induced hypercoagulable state and possible external compression of the ipsilateral iliac vein from the large mycotic aneurysm, causing venous stasis and thrombosis. Although the adjunctive clinical history and inflammatory markers were strongly suggestive of the extensive venous thrombosis because of severe salmonellosis and external compression, without additional thrombophilia screening, it was difficult to arrive at a definite conclusion that this was indeed the case.

It is possible that the patient had developed a mycotic aneurysm earlier, but this was missed during the initial admission and assessment, as the focus remained largely on the extensive left lower limb deep vein thrombosis. Later, the development of enlargement of the mycotic aneurysms with contained hematoma led to severe and persistent lower back pain along with a concomitant decrease in haemoglobin level. This led to further evaluation and a final diagnosis of multiple saccular mycotic aneurysms of the left common iliac artery. It is very difficult and challenging to determine whether deep vein thrombosis or mycotic aneurysms was the first potential complication of the invasive *Salmonella* bacteraemia. This case highlights the importance of closely monitoring a patient's progress and re-evaluating the initial diagnosis whenever there is a clinical doubt, especially when more information becomes available or if there is a change in the patient's condition. This case report is unique because mycotic aneurysms of the iliac artery are rarely reported in the literature, with previous reported cases of mycotic aneurysms predominantly occurring in the abdominal aorta [13] [14].

Salmonella has a strong affinity to adhere to damaged vessel walls, which causes inflammation, destruction, and localised abnormal dilatation, ultimately leading to mycotic aneurysm formation [2]. The process of infective endarteritis is postulated to be enhanced in patients with increased risk for developing atherosclerosis [2] [13]. Therefore, in such patients, imaging examinations should be performed to identify endovascular complications. Although mycotic aneurysms are a rare occurrence, once they develop, they can be severe and expand rapidly, leading to rupture, contained hematoma, and abscess formation. This patient did report poorly controlled diabetes, hypertension, dyslipidaemia, and possibly undiagnosed coronary artery disease, which increased his risk of atherosclerosis. The adjunctive clinical and biochemical markers, such as persistent lower back pain, increased inflammatory markers, and decreasing haemoglobin levels, prompted further investigation and evaluation of the mycotic aneurysms using CTA of the abdomen. Extensive venous thrombosis is life-threatening, and it becomes even more challenging when venous thrombosis and mycotic aneurysms coexist. This patient had aneurysms at multiple anatomical sites with contained hematoma that made the management of the venous thrombosis difficult. An inferior vena cava filter was inserted to prevent further embolization.

Currently, medical treatment for mycotic aneurysms alone has no lasting curative effect. Owing to aneurysmal rupture, formation of septic emboli, recurrent bacteraemia, abscess formation, and multi-organ failure, mortality may reach

100%. Therefore, treatment should involve a combination of intensive targeted antibiotic therapy and surgical interventions, such as open vascular surgery or EVAR, to prevent aneurysmal rupture and remove the infected vessel foci. As the patient was unfit for open vascular surgery, he was offered EVAR. The EVAR is beneficial in preventing lethal aneurysmal rupture in the acute phase but provides less protection from recurrent sepsis complications [15] [16]. Despite achieving negative cultures from the peripheral blood before and after EVAR and continued intensive antibiotic therapy, the patient experienced septic complications and succumbed to these complications. Endovascular cultures may have provided more accurate results than peripheral blood cultures. Clinicians must remember that peripheral blood cultures have poor sensitivity and specificity for mycotic aneurysms, particularly when the patient has received long-term antibiotic therapy. In such patients, negative cultures do not guarantee elimination of the foci of infection. However, this patient was already at an increased risk for mortality given his older age, poorly controlled comorbidities, and the delay in seeking care at a facility during the initial illness.

4. Conclusion

The main observations from this case report are first, clinicians should be vigilant and consider potential endovascular complications arising from *Salmonella* bacteraemia in patients with multiple comorbidities. Second, *Salmonella* bacteraemia can present with rare, atypical manifestations such as deep vein thrombosis, either in isolation or with infective endarteritis. Clinicians need to be aware of this association, and such cases need to be reported to the scientific community. With more reported cases, identification of the temporal relationship between *Salmonella* bacteremia, infective endarteritis and deep vein thrombosis will be eased in the future. Third, among high-risk patients, *Salmonella*-induced mycotic aneurysms are associated with exaggerated morbidity and mortality. These patients may have severe medical conditions that reduce the benefits of open vascular surgery. Currently, treatment options available for such patients are limited and prolonged medical therapy alone or in combination with EVAR is yet to achieve satisfactory results. Further, more in-depth research on effective treatment of severe endovascular infection among high-risk patients, where open vascular surgery is considered unsuitable, is urgently needed.

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Data Availability

The patient data used to support the findings of this case report are available

from the corresponding author upon request.

Informed Consent

Written informed consent was obtained from the patient's daughter for the publication of this article (including a case history and radiographic imaging).

Author's Contribution

MS was directly involved in the treatment of the patient, literature search, and scientific writing. APR participated in providing expert opinion on patient care and review of the manuscript.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Acute Kidney Injury with Levetiracetam in Patient with Epilepsy: A Case Report

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Abstract

Epilepsy is a common neurological disorder in neurology clinic. Levetiracetam is considered as one of common antiepileptic drugs used to manage epilepsy with good efficacy and tolerability profile. It is renally excreted and not depending on the cytochrome p450. It has adverse effects reported as somnolence, headaches, dizziness, depression and anxiety. Also, it was reported that levetiracetam can cause Acute kidney injury (AKI), renal profile disturbance, that may be related to its way of excretion and possible nephrotoxicity especially with high loading dose. We are reporting a young female patient with epilepsy presented to hospital with status epileptcus and started on loading dose of levetiracetam 3 grams and then maintenance dose of 1 gram twice daily seizure were controlled but she developed acute kidney injury that improved after discontinue leveriracetam and medical management without renal dialysis and discharged home in stable condition. Physician and health care providers should be aware of such rare adverse reaction and available management options for better patient care and outcome.

Keywords

Acute Kidney Injury, Epilepsy, Levetiracetam

1. Introduction

Epilepsy is a common neurological disorder, it is ranks fourth in the world's neurological disorders burden with lifetime prevalence of 6 - 7 per 1000 people [1]. It is affecting all age group and both gender and requiring long-term, sometimes lifelong, treatment. Antiepileptic drugs (AEDs) are the main treatment option for epilepsy patients, and two-thirds of epileptic seizures can be controlled by AEDs. Levetiracetam (LEV) is relatively new AEDs which were approved as

an adjunctive therapy for adults with focal epilepsy since 1999 in the US. It was approved in 2006 as monotherapy for adults and adolescents above 16 years of age with newly diagnosed focal-onset seizures with or without secondary generalization in Europe [1] [2]. Levetiracetam is considered as one of the most common antiepileptic drugs used to manage epilepsy. It is important to know that the way of elimination of levetiracetam is mainly occurs by renal excretion, and because of that, the mechanism of action is not depending on the cytochrome p450 [3] [4]. Levetirracitam can be administered intravenously or orally and it is effective medication and considered as a good option to be used in treatment of status epileptcus which is a prolonged or repeated attacks of seizures without regaining of conciseness. The most common adverse reaction of levetiracetam is asthenia, headaches, dizziness, somnolence, and behavioral changes [5] [6] [7]. Recent studies reported that there are some patients who have seizures and not known to have renal issues can have acute kidney injury when using levetiracetam, and surprisingly they are getting much better when they stopped take levetiracetam and using other antiseizure medication to control their seizures [8] [9] [10]. We are reporting a case of acute kidney injury induced by levetiracetam for a patient with history of epilepsy who presented to emergency room with status epilepticus.

2. Case Presentation

A 34-year-old female patient known to have epilepsy for 12 years she was carbamazepine 400 mg orally twice daily with history of poor compliance to her medication brought to emergency department with status epilepticus as she had tonic-clonic seizures four times without regaining her consciousness. Vital signs showed a blood pressure (BP) of 137/86 mmHg, heart rate (HR) of 96 beats per minute (bpm), and Weight of 86 kg, height of 169 cm, her BMI was 30. Neurological examination she was conscious and drowsy with equal pupils and reactive to light, intact cranial nerve examination, and no signs of meningeal irritation, with normal motor and sensory examination.

2.1. Investigation

Her laboratory investigation result with normal reference (**Table 1**), Patient had brain Computer topography (CT) which was unremarkable and negative for acute pathology later Brain magnetic resonance imaging (MRI) was done and was unremarkable.

2.2. Treatment and Course in Hospital

Patient received lorazepam 2 mg IV two doses separate to stop seizures then was started on intravenous levetiracetam 3 grams as loading dose diluted in at 100 ml of a normal saline and administered over 20-minute intravenous infusion and was continued with levetiracetam 1000 mg intravenously every 12 hours and was admitted to intensive care unit, Seizure was controlled with no recurrence; however, urine output was decrease and the patient developed oliguria. The patient

Table 1. Laboratory investigation result on admission with normal reference.

Test	Result (Normal Reference)
White Blood Cell Count	13.90 (4.10 - 10.10 × 10^3/uL)
Hemoglobin	12.1 (12.9 - 16.7 g/dL)
Neutrophils	16.2 (1.40 - 6.80 × 10^3/uL
Lymphocytes	2.5 (1.10 - 2.90 × 10^3/uL)
Monocytes	0.9 (0.20 - 1.00 × 10^3/uL)
Platelets	302 (153 - 328 × 10^3/uL)
Serum Glucose	125 (74 - 106 mg/dL)
Serum Blood Urea Nitrogen (BUN)	14 (9.0 - 20.0 mg/dL)
Serum Creatinine	1.1(0.66 - 1.25 mg/dL)
Serum Sodium	141 (133 - 145 mEq/L)
Serum Potassium	4.2 (3.5 - 5.1 mEq/L)
Serum Chloride	102 (98 - 107 mEq/L)
Serum Calcium	9.6 (8.4 - 10.2 mg/dL)
Serum Total Protein	9.2 (6.3 - 8.2 g/dL)
Serum Albumin	4.6 (3.5 - 5.0 g/dL)
Serum Total bilirubin	1.1 (0.2 - 1.3 mg/dL)
Alanine transaminase (ALT)	56 (21 - 72 U/L)
Aspartate transaminase (AST)	45 (17 - 59 U/L)
Serum Lactate	6.2 (0.70 - 2.10 mmol/L)
Creatinine Kinase (CK)	467 (55 - 170)
Urine protein	42 (5.0 - 11.0 mg/dL)
Urine sodium	93 (30.0 - 90.0 mEq/L)
Urine urea nitrogen	62 mg/dL
Urine creatinine	124 mg/dL

was assessed by a neurology and nephrology teams and urinalysis showed large blood, and 1.010 of specific gravity, and increased urine sodium (96 mEq/L). No signs of hydronephrosis showed on abdominal ultrasound. Patient had no history of renal disease, intravenous contrast, or nephrotoxic medication. levetiracetam was discontinued after 4 days as a possible cause of AKI and received intravenous furosemide, 1/2 normal saline, and it was interchangeable with 5% dextrose in water for volume expansion then urine output was improved gradually with follow up of Creatinine, BUN and CK levels continued to improve (Table 2) till normalized without requiring renal dialysis. Later lamotrigine 50 mg, and to be taken twice daily was added to avoid seizure recurrence with no side effect, patient has no recurrence of seizure and renal function was normal till discharge from hospital after 20 dayd of admission with a follow up at outpatient neurology clinic after 2 month where she continue to have controlled seizures and normal renal function test.

Table 2. Trend of laboratory result during admission.

Day in hospital	Creatinine (mg/dL) (Reference: 0.66 - 1.25 mg/dL)	BUN (mg/dL) (Reference: 9.0 - 20.0 mg/dL)	CK (Reference: 55 - 170 U/L)
On admission	1.13	14	467
Day 2	2.53	17	426
Day 3	4.62	24	512
Day 4	7.36	41	734
Day 5	8.14	57	1270
Day 6	7.78	62	1082
Day 7	7.16	64	927
Day 8	6.48	58	644
Day 10	4.13	47	489
Day 12	2.62	36	261
Day 14	1.21	26	192
Day 15	1.13	19	153

BUN: Blood urea nitrogen, CK: creatinine kinase.

3. Discussion

Levetiracetam is considered as a new and favorable antiepileptic drug because it is well-tolerated drug for many types of seizures and has minimal side effects. With generally good efficacy and safety profile [11] [12]. Due to its way of excretion, some renal adverse effects can occur, and rarely acute kidney injury can be caused by levetiracetam. In this report, we demonstrate the clinical and biomedical profile of a patient with relation between acute kidney injury and levetiracetam as an inducer, especially with high loading dose.

Our patient started to have decreased urine output and oliguria after taking levetiracetam for 4 days, and urinalysis showed large blood, 1.010 of specific gravity, and increased urine sodium (96 mEq/L), and the creatinine and CK were gradually increase and reached their highest level on the 5th day, while BUN reached its highest level on the 7th day. Levetiracetam was discontinued as it was thought to be the offending agent and all the creatinine, CK, and BUN were improved after the discontinuation of levetiracetam and later using lamotrigine 50 mg twice daily as an alternative antiepileptic medication to avoid seizure recurrence, as levetiracetam founded to be the likely cause in our case to induce acute kidney injury.

On reviewing the literature; Cases were reported that levetiracetam can cause AKI. One case about 26 years old male with history of epilepsy had tonic-clonic seizures for five times without regaining his consciousness. Prior his presentation, his medication at home was levetiracetam 750 mg but he has poor compliance. He received 10 mg of midazolam intramuscularly with the ambulance, then after he was arrived at ED, 4 mg of midazolam was given to him to stop his

seizures. The patient then noticed by the ED that he is in a status epilepticus phase, and after intubation, 4 grams loading dose of levetiracetam was given intravenously, then he was continued on levetiracetam 1000 mg. His initial laboratory investigations were elevated levels of lactate, creatinine, creatinine kinase, and BUN. levetiracetam discontinued, and 500 mg of valproic acid was given to control seizures. The creatinine level returned to the baseline level after 20 days [13] [14]. In this patient he was young and presented with status epileptics similar to our patient. Whoever, the loading dose was higher compared to our patient and the duration of improvement of his renal function was longer than our patient.

Another case for 23 years old female presented with two episodes of generalized tonic-clonic seizure lasting for 1 minute for each one without regaining her level of consciousness. She received lorazepam 2 mg and levetiracetam 1 gram as loading dose. The initial laboratory investigations were all normal. Also, MRI and EEG were unremarkable. She was admitted under neurology observation, and she was given 500 mg of levetiracetam on the next day. After that, the patient had raised creatinine level. After nephrology evaluation, they found that the most likely reason for elevated creatinine is levetiracetam. Urinalysis has 1+ blood, and abdominal ultrasound showed increased echogenicity of bilateral renal cortexes. For that reason, they discontinued levetiracetam, and they used phenytoin as an alternative and fluids. By the 4th day in the hospital, the creatinine level was started to improve and back to its baseline [8] [15].

A third case reported about 45 years old male medically free was presented with dizziness and gait unsteadiness, and on neurological examination the patient had impaired tandem gait and increased deep tendon reflex with left sided brisk reflexes. A brain MRI was done for him and showed T1 hypointense lesion within the right thalamus. After taking biopsy, it showed low grade infiltrating astrocytoma. Before the surgery, the patient received levetiracetam 500 mg BID for seizure prophylaxis. Therefore, his symptoms worsened to seizures and the levetiracetam was increased over 2 months period to 3000 mg/day. After that, he was noted to have elevated creatinine level and fraction excretion of sodium (FENa) was >1% [16].

Levetiracetam considered to be nephrotoxic in some patients with Granulomatous interstitial nephritis (GIN), which can lead to hemodialysis requiring acute renal failure, and by withdrawal of the medication, complete recovery can be made [17] [18].

Date suggest that It is important to consider the possibility even in rare occasions of renal function deterioration secondary to levetiracetam as one of the differential diagnoses for any unexplained acute kidney injury, mainly during the first few weeks of levetiracetam administration [19] [20].

4. Conclusion

Levetiracitame in an effective and well tolerated new antiepileptic medication with good safety profile. Due to the renal excretion of levetiracetam, in this case

report we have a young female patient who develops an acute kidney injury after that was in relation after starting her on levetiracitam with improvement after medical treatment with intravenous fluid and discontinue the possible offending agent which was thought as levetiracetam, she respond well and discharged in stable condition with good control of seizure with other antiepileptic medication. It is important for physician and health care provider to close monitor all patients who started on new antiepileptic medication especially if patient required a loading dose for rare adverse reactions like nephrotoxicity and acute kidney injury for better patient care and clinical outcome.

Consent

Approval was obtained from relevant regulatory committee, and informed consent was taken.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acquired Gerbode Defect Secondary to Severe Bicuspid Aortic Valve Endocarditis

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Abstract

An annular aortic abscess is a fatal complication of infective endocarditis. Echocardiography is the initial imaging modality to confirm the diagnosis in suspected infective endocarditis. Here, we present a case of a bicuspid aortic valve infective endocarditis caused by *Staphylococcus aureus* and complicated with annular aortic abscess resulting in acquired Gerbode defect (type II) with tricuspid valve vegetation which was undiagnosed preoperatively. The intraoperative transoesophageal echocardiography yields a new finding prior to the surgical incision, which impacted the clinical decision-making and increased the burden of the procedure.

Keywords

Acquired Gerbode Defect, Infective Endocarditis, *Staphylococcus aureus*, Bicuspid Aortic Valve

1. Background

Gerbode defects are rare congenital cardiac anomalies that account for less than 1% of all congenital cardiac abnormalities and only 0.08% of intracardiac shunts [1]. It is defined as abnormal shunting between the left ventricle and right atrium resulting from either a congenital defect or prior cardiac insults (**Figure 1**). The pathophysiology underlying the development of Gerbode defect is a disease process that injuries the atrioventricular septum and leads to the abnormal shunting of blood. Although the most common cause of Gerbode defect has historically been congenital, an increasing trend towards acquired cases has recently been reported in the literature.

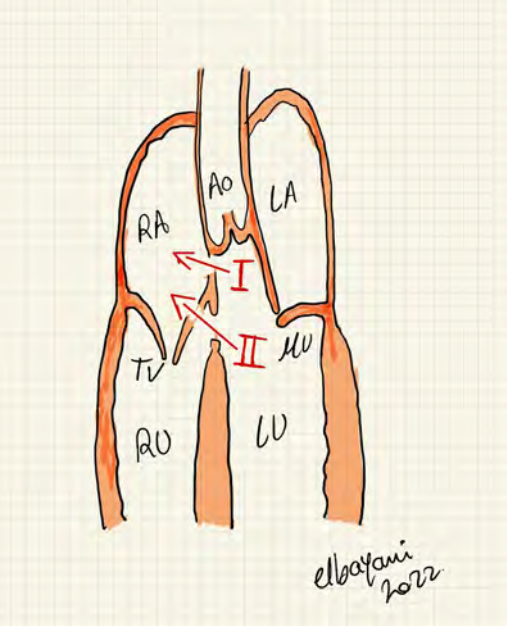

Figure 1. Schematic representation of Gerbode defect types. Defect number one (I) is the supravalvular (direct) type. Defect number two (II) is the infravalvular (indirect) type. LA—left atrium, LV—left ventricle, RA—right atrium, RV—right ventricle, TV—tricuspid valve, MV—mitral valve, AO—aorta.

2. Case Presentation

A 38-year-old white, non-smoker male (1.83 m, 75 kg, BSA 1.9 m^2, BMI 22) presented to the Emergency Department (ED) in secondary healthcare facility complaining of fever, cephalgia, and delirium. He denied intravenous illicit recreational drug use. He had no history of known congenital heart disease. Prior to his current illness, there was no administration of any immunosuppressive medications. He had no physical limitations and regularly engaged in sports activities.

On presentation, blood pressure was 120/90 mmHg, heart rate 120 beats per minute, respiratory rate of 21 per minute, temperature 38,9 degrees Celsius using ear thermometer, and oxygen saturation of 94% on ambient air. The arterial blood gas analysis was unremarkable except for hypokalaemia (K * 3 mmol/L). Physical examination was remarkable for a soft diastolic murmur; Lung auscultation revealed bibasilar crackles. Neck veins were non-distended, and lower extremity edema was not detected. Due to the febrile infection, the patient was admitted to the COVID ward for isolation. SARS-COV-2 infection could not be seen in the PCR tests performed so that the patient could be a few hours later de-isolated.

2.1. Investigations

Initial laboratory test results were remarkable for white blood cell count of 11.5 × 10^3/ul (4 - 10 × 10^3/ul) with elevated neutrophils, platelets of 64 × 10^3/ul (150 - 400 × 10^3/ul), C-reactive Protein of 26.7 mg/dl (0.0 to 0.8 mg/dl), procalcitonin

of 9.8 ng/ml (0 - 0.5 ng/ml) and abnormal liver function with elevated total Bilirubin 3.1 mg/dl (<1.23 mg/dl). Renal function tests were within normal limits. Four sets of blood cultures were initially positive for gram-positive round-shaped cocci, which were identified as *Staphylococcus aureus* later (Methicillin-sensible, MSSA). Abdominal sonography showed mild splenomegaly. An electrocardiogram showed normal sinus rhythm.

Because of the medical health providers' arousal towards the pandemic and the patient's vaccine opponent attitude, a low dose CT scan was performed to exclude pneumonia, which revealed no typical COVID-19 changes in the lungs.

Transthoracic echocardiography revealed a sclerosed aortic valve with bicuspid morphology, severe aortic valve insufficiency with no evidence of vegetation, and slightly impaired systolic Left ventricular function with an estimated left ventricular (LV) ejection fraction of 45%.

Subsequently, trans-oesophageal echocardiography (TEE) was performed, which confirmed the aortic valve of bicuspid nature with progredient insufficiency. However, there were no endocarditis-susceptible vegetations on any of the heart valves.

Ultimately, definite acute endocarditis was diagnosed according to the Duke criteria, including two blood culture results of *Staphylococcus aureus*; the severe progredient regurgitation of the aortic valve revealed by an echocardiogram; and such clinical and laboratory features as fever, splenomegaly, and heart murmur.

2.2. Management

Initially, the patient was treated empirically for infective endocarditis with intravenous antibiotics. The patient was then transferred to our heart center for surgical intervention. The cardiac catheterization showed no evidence of obstructive coronary artery disease.

Intraoperatively and prior to the surgical incision, the trans-oesophageal probe was introduced, and TEE was performed, which confirmed aortic valve of bicuspid nature, and aortic annular abscess with left ventricular outflow tract defect to the right atrium (LVOT-RA) consistent with Gerbode defect (**Figure 2**).

After median sternotomy, the patient was heparinized with checking activated clotting time. Aortic and bicaval cannulation was installed, and cardiopulmonary bypass was initiated for 141 minutes. The aortic cross-clamp was then applied for 96 minutes. A normothermic blood cardioplegia was administrated through the aortic root, directly through the coronary Ostia, and retrograde through the coronary sinus, which achieved a satisfactory diastolic arrest. Aortotomy was performed, and stay sutures were placed. The aortic valve was inspected, and it was heavily calcified and bicuspid. Cusps were resected, and the annulus was debrided. After resection of the abscessed tissue, a shunt connection from the Left ventricle to the right ventricle entering the right atrium was revealed (**Figure 3**). After right atriotomy, involvement of the tricuspid valve was confirmed. An aneurysm with vegetations was seen at the septal leaflet of the

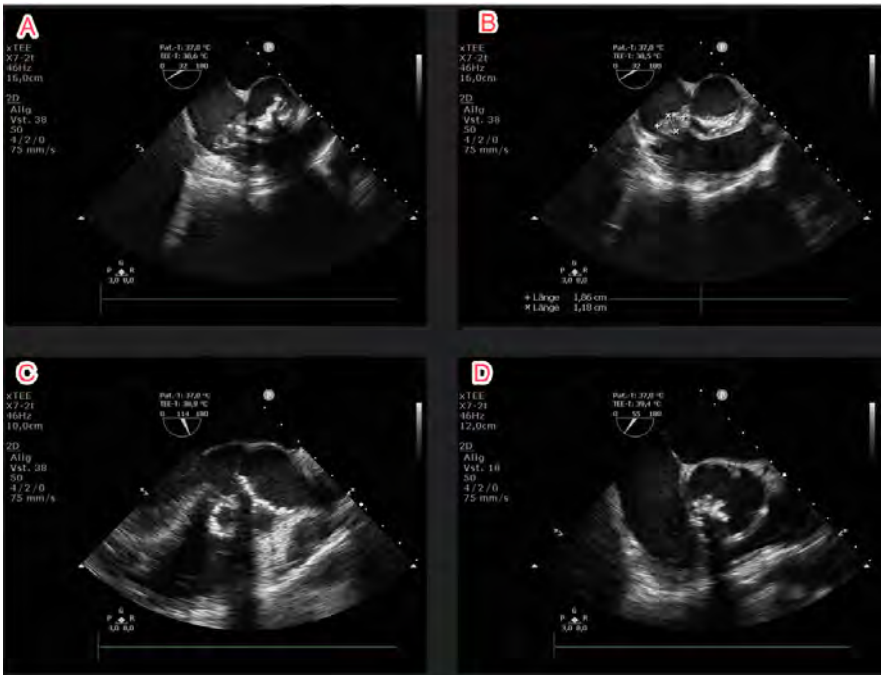

Figure 2. intraoperative trans-oesophageal echocardiography. (A) mid-oesophageal short-axis view demonstrating large vegetation in RA and ruptured/flail leaflet of the bicuspid aortic valve; (B) mid-oesophageal short-axis view shows the dimensions of the vegetation (1.86 cm × 1.18 cm); (C) mid-oesophageal long-axis view demonstrates Gerbode ventricular septal defect; (D) mid-oesophageal right ventricular inflow-outflow view demonstrating the hyperdense vegetation.

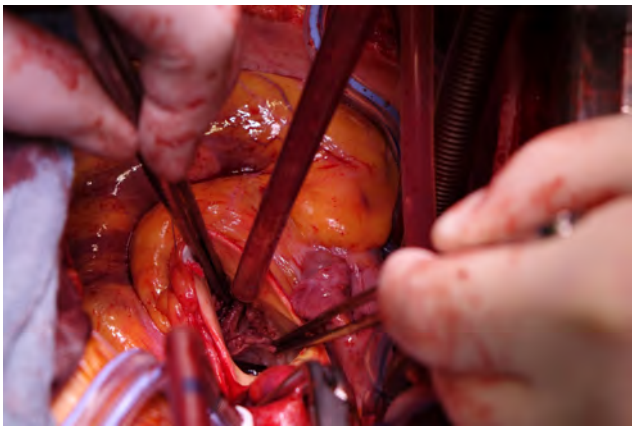

Figure 3. Surgical aortic valve replacement to a mechanical valve prosthesis after debridement of the aortic annulus a septal defect could be detected.

tricuspid valve. Below the tricuspid annulus to the ventricle, a shunt leading to the LVOT could be seen.

Vegetations on the tricuspid valve could be surgically resected, and the integrity of the tricuspid valve could be preserved (**Figure 4**). The decision was already made to proceed with aortic valve replacement with a 23-mm Regent mechanical valve (St. Jude Medical, St. Paul, MN) and primary closure of a septal defect using pledgeted sutures. The right coronary ostium was confirmed to be patent

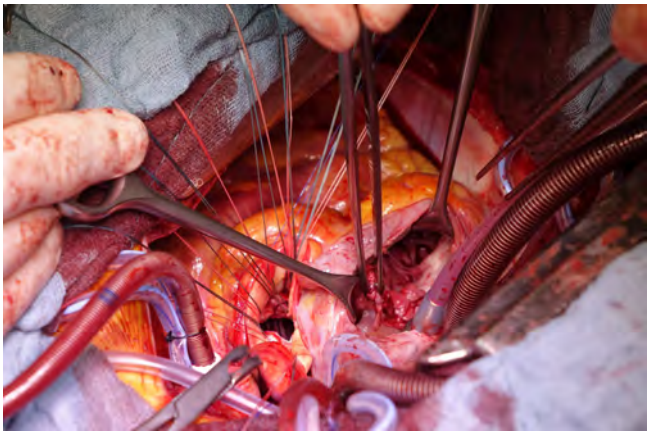

Figure 4. Intraoperative picture where the right atrium was opened, and the vegetations on the septal leaflet were grasped and gently pulled with forceps, preserving the tricuspid valve's integrity.

multiple times during the procedure. The aortotomy was then closed in layers, and the root was vented. The heart was de-aired, and the aortic cross-clamp was removed. The weaning off the cardiopulmonary bypass was performed as usual after the spontaneous return of the heartbeats. Protaminized decannulation was done, and hemostasis was secured. The chest was closed in layers. The patient tolerated all the mentioned procedures well and was monitored in an intensive care unit for 24 hours and then shifted to the surgical ward later for further postoperative care, which was uneventful. The patient was isolated through the whole period of hospital admission is due to the detection of vancomycin-resistant enterococci (VRE) in the rectal and mouth, nose, and throat smear.

The intraoperatively resected valve and vegetation were sent for histopathological and microbiological studies to isolate and identify the pathogen. Histopathological examination of the excised aortic valvular tissue showed fibrous, dystrophic calcification, inflammatory cell infiltration, and bulky vegetation comprised of fibrinous exudative material with areas of neovascularization and areas of granulation tissue. Findings were suggestive of subacute bacterial endocarditis. And the DNA samples from tissues of the aortic valve and the vegetation of the tricuspid valve were both positive for *Staphylococcus aureus* in the Polymerase chain reaction (PCR) test.

The patient had a stable functioning prosthesis with preserved ejection fraction in the follow-up transthoracic echocardiography. He was then discharged resilient and asymptomatic. He successfully recovered post-operatively with inpatient rehabilitation and continuation of intravenous antibiotic therapy.

3. Discussion

Staphylococcus aureus bacteremia (SAB) is an urgent medical problem due to its growing frequency and its poor associated outcome. As healthcare delivery increasingly involves invasive procedures and implantable devices, the number of patients at risk for SAB and its complications is likely to grow. The mechanisms

leading to SAB involve host factors and environmental factors predisposing to infection, whereas the impact of genotypic features on the ability of different strains to cause infection is still controversial [2]. Unfortunately, it is the leading cause of infective endocarditis, and its mortality has remained high despite better diagnostic and therapeutic procedures over time. However, recent studies suggest that valve replacement improves outcome [3]. Transoesophageal echocardiography (TEE) is essential in intraoperatively monitoring adult and congenital heart surgery. It gives us real-time data about the heart during the whole procedure that the adequacy of the repair can be ensured immediately through a review of TEE images directly after surgery; in our case, the intraoperative TEE yield a new finding of the left ventricular outflow tract defect to the right atrium (LVOT-RA), which was not known at the time of the surgery. Therefore, we believe the intraoperative TEE increased the burden of that procedure but helped us make the right decision to deal with the case.

The pathophysiological mechanisms of Gerbode defect usually are reopening of a congenital defect, widening of a small defect, or destruction of the membranous ventricular septum [1]. The Gerbode defect observed in our patient is an acquired defect rather than congenital given the subvalvular location and proximity to the ruptured aortic valve abscess.

The current approach in managing acquired Gerbode defect secondary to IE is surgical repair of the defect as a transcatheter device is not an option due to the presence of infection [4].

The current American Heart Association/American College of Cardiology (AHA/ACC) guidelines do not include a bicuspid aortic valve in a high-risk group category for pre-operative IE antibiotic prophylaxis [5]. However, in a recent study, the bicuspid aortic valve was found to carry a substantially increased risk of IE and intracardiac complications [6].

4. Conclusion

This case highlights the potential of the intraoperative TEE to influence clinical decision-making for cardiac surgical patients. It also illustrates that the use of TEE in high-risk populations can yield a higher incidence of new findings. Furthermore, it emphasizes the need to revisit the infective endocarditis prophylaxis guidelines in the future to include antibiotic prophylaxis in patients with the bicuspid aortic valve.

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Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation to any qualified researcher.

Ethics Statement

The patient signed informed consent related to the clinical course; therefore, the Institutional Review Board was waived due to the retrospective nature of the educational case report.

Authors Contributions

All authors contributed to the patient care, diagnosis, treatment, and authoring this article.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abbreviation and Acronyms

- TEE Transoesophageal echocardiography
- TV Tricuspid valve
- CT Computer tomography
- LVOT Left ventricular outflow tract
- IE Infective endocarditis
- BSA Body surface area
- BMI Body mass index
- CPB Cardiopulmonary bypass
- RA Right atrium
- DNA Deoxyribonucleic acid

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Primary Small Bowel Melanoma or Small Bowel Metastasis with Vanishing Primary Cutaneous Lesion

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Abstract

The small bowel represents one of the main sites for cutaneous melanoma metastasis; however, numerous cases of primary intestinal melanoma have recently been described. In view of this, we present the case of a 39-year-old woman admitted for nausea, heartburn, abdominal pain, change in bowel habits and weight loss. Contrast-enhanced CT revealed a small bowel mass. Surgical resection of a 6 cm ileal tumour with regional mesenteric lymphadenectomy and end-to-end anastomosis was performed. Histopathological findings indicated the presence of an ileal melanoma metastasis. Subsequent dermatological examination identified a cutaneous lesion on the right forearm, however no malignant cells were found at the histopathological exam. Whole body PET CT with FDG identified multiple frontal and parietal lesions. Genetic testing was positive for BRAF gene V600 E mutation. The patient underwent multiple neurosurgical procedures for the resection of cerebral metastases. Palliative external radiation and chemotherapy was also attempted. After approximately 2 years after the diagnosis, the patient died following multiple episodes of intracranial hypertension.

Keywords

Melanoma, Small Bowel, Cerebral Metastasis

1. Introduction

The incidence of malignant melanoma exhibited an ascending trend in recent

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years. This type of malignancy is characterised by an elevated affinity for the small bowel as metastasis site, more than half of melanoma patients exhibiting intestinal metastasis at autopsy. Although numerous cases of primary intestinal melanoma have been published, the possibility of melanoma developing directly from the intestinal mucosa represents an ongoing matter of debate, some authors suggesting that other organ involvement is associated with the regression of the primary cutaneous melanoma.

Most intestinal melanoma initially present with symptoms of small bowel obstruction. The mean survival of patients with metastatic melanoma amounting to approximately 5 months, possibly improved by surgical tumour resection.

The aim of this paper is to provide further insight into this disease and draw attention to the difficulty of differentiating between primary intestinal melanoma and intestinal melanoma metastasis with vanishing primary cutaneous lesion.

2. Case Presentation

A 39-year-old woman, with no previous medical history, presented with nausea, heartburn, diffuse abdominal pain, bloating, alternation between diarrhoea and constipation and involuntary weight loss of 4 kg in the past month.

Physical exam revealed slight tenderness on palpation in the hypogastrium. Bloodwork showed mild iron-deficiency anaemia (Hb 9.3 g/dl, ferritin 39 ng/ml) and a mild inflammatory syndrome (ESR 45 mm/h).

Abdominal ultrasound identified a digestive structure with thickened wall in the hypogastrium, in contact with the sigmoid colon and uterine body, without being able to distinguish its origin. Subsequently, lower digestive endoscopy was performed. No lesions were discovered at this level.

Contrast-enhanced CT scan of the abdomen and pelvis described a parenchymatous heterogeneously enhancing structure, of approximately 53/45 mm, involving the terminal jejunum or proximal ileum (**Figure 1**). Additionally, multiple lymphadenopathies along the superior mesenteric vascular pedicle were described.

Tumour markers CEA and CA125 were within normal values. Upper digestive endoscopy was also performed in order to exclude a celiac disease, but with no modification in this context. An antral gastritis was described, without any correlation with the actual disease.

Laparotomy was performed, with the resection of a 6 cm ileal tumour, located at 40 cm from the ileocecal valve, with regional mesenteric lymphadenectomy and end-to-end anastomosis. No postoperative incidents were reported and the patient was discharged after 4 days.

Pathology examination of the resected tumour identified a malignant cell proliferation with a mitotic rate of 11 atypical mitosis/10 HPF (**Figure 2**). None of the 35 ganglia removed exhibited malignancy features. Additional immunohistochemistry tests were positive for Melan-A, S100 and HMB45 (**Figure 2**). Thus,

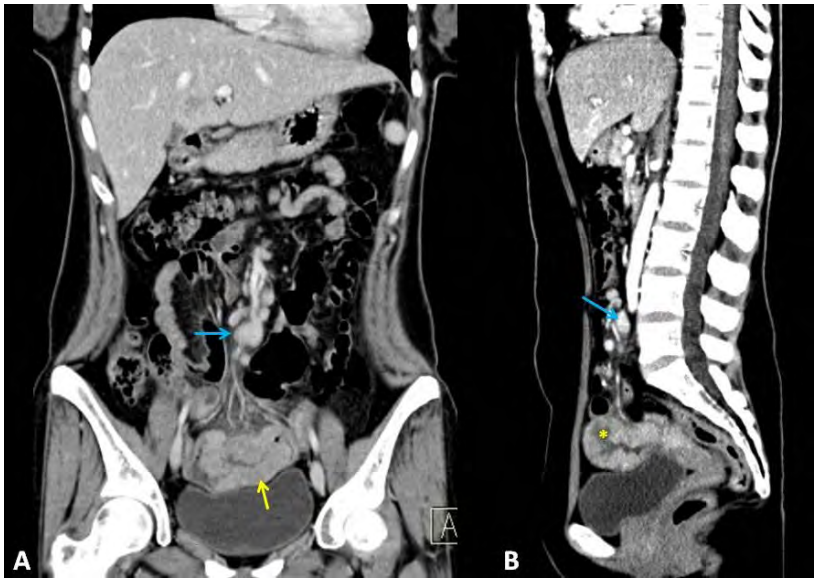

Figure 1. Abdomen and pelvis contrast-enhanced CT scan findings: The coronal (A) and sagittal (B) reconstructions depict a segmental small bowel thickening at the jejunal-ileal junction (yellow arrow), with necrosis (asterisk) and multiple satellite mesenteric lymphadenopathies (blue arrows).

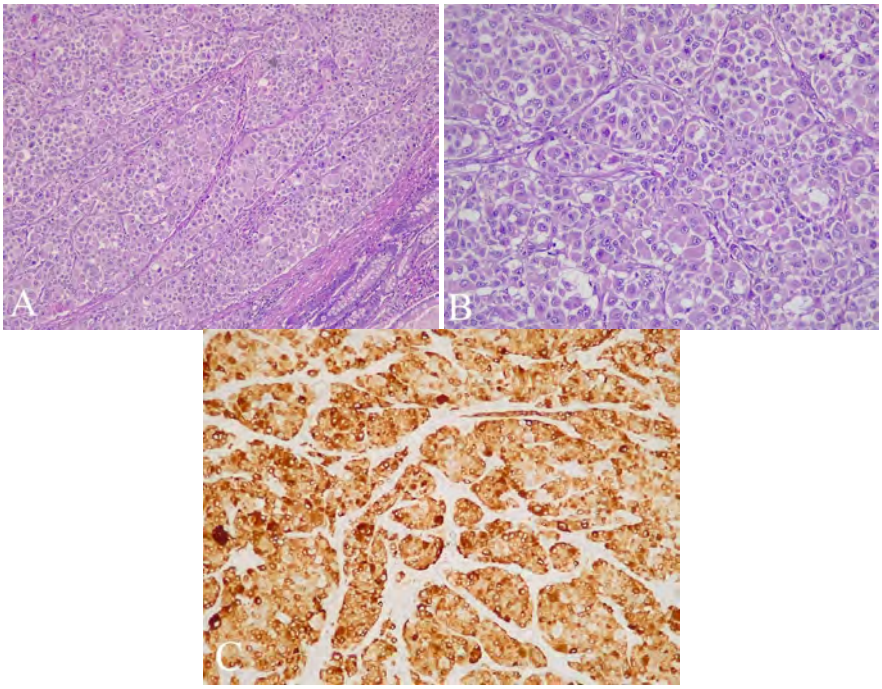

Figure 2. Histopathological findings: Hematoxylin and eosin stain (A 10×, B 40×) showing a malignant cell proliferation with a mitotic rate of 11 atypical mitosis/10 HPF. Immunohistochemical depiction of a melanocytic intestinal lesion positive for Melan-A (C 40×).

these histopathological features indicated the presence of a melanoma ileal metastasis.

In consequence, the patient underwent thorough dermatology examination,

which identified a lesion suggestive of a superficial spreading melanoma on the right forearm. The lesion was promptly surgically removed. Pathology examination described a small number of melanophages spread across the superficial dermis and inflammatory infiltrate around capillaries, suggestive of chronic irritation. No malignant cells were identified on the examined specimens.

Whole body PET CT scan with 18-fluor-deoxi-glucose (FDG) was performed in order to identify the primary tumour or other concurrent metastases (Figure 3). The examination revealed no other lesions in the thorax, abdomen or pelvis. However, significant vasogenic cerebral oedema of the left centrum semiovale and multiple frontal and parietal hypermetabolic lesions were identified.

The PET CT findings prompted brain MRI evaluation which identified a total of 7 metastases both in the supratentorial and infratentorial regions (Figure 4).

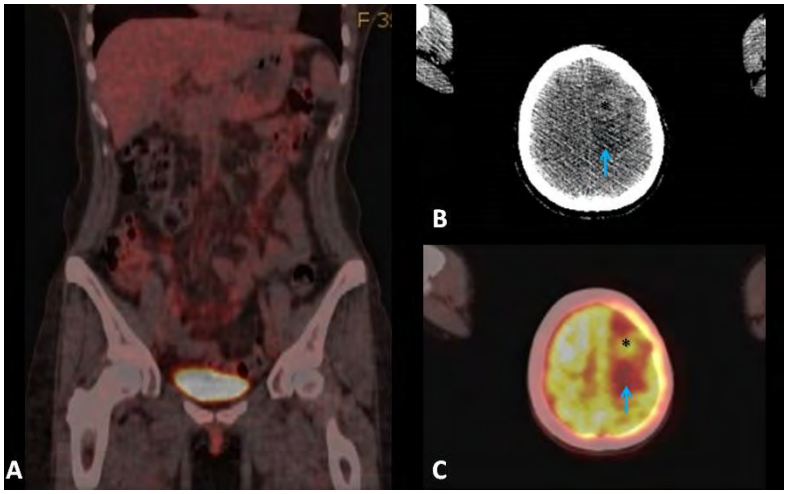

Figure 3. FDG PET-CT findings: The coronal reconstruction (A) showed no signs of relapse or abdominal or pelvic metastases. Cerebral axial reconstruction (B) (C) revealed left frontal vasogenic oedema (blue arrows) surrounding a nodular aria suggestive of a cerebral tumour (asterisk).

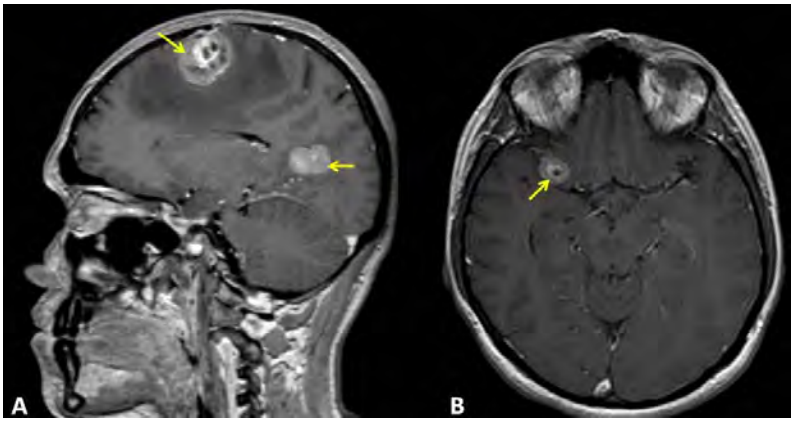

Figure 4. Contrast-enhanced MRI findings: T1 sagittal (A) and axial (B) reconstructions reveal multiple nodular cortico-subcortical lesions located in the supratentorial and infratentorial regions suggestive of cerebral metastases. The largest ones are located in the left frontal and parietal-occipital lobe and right frontal lobe (yellow arrows).

To complete the investigations, mutational status of BRAF gene was determined, V600E (c.1799T > A) mutations being detected.

From this moment on, the patient underwent four neurosurgical gamma-knife procedures for the resection of cerebral metastases in the span of 18 month. Moreover, palliative external radiation (30 Gy in 10 fractions) and chemotherapy (dabrafenib 150 mg twice daily and trametinib 2 mg twice daily) were attempted. The patient maintained a good clinical status throughout treatment, although progressive disease was detected after 12 months under this treatment. Chemotherapy was therefore supplemented with nivolumab 3 mg/kg every 2 weeks.

The patient neurological status gradually worsened and further progression of the disease was confirmed after 5 months from the addition of nivolumab. The patient was multiple times admitted for episodes of intracranial hypertension treated with iv corticoids and mannitol, eventually succumbing after approximately 2 years from diagnosis.

3. Discussion

The small bowel is rarely a site for development of primary tumours, most tumours arising at this site being metastatic in nature [1].

Skin melanoma is the most frequent malignancy to develop small bowel metastasis, namely up to one third of small bowel metastasis are due to melanoma [2], followed by breast and pulmonary cancer [3]. A possible explanation for the affinity of melanoma for the small bowel resides in the presence of surface chemokine CCR9 on melanoma cells that binds to the CCL25, particularly found on intestinal cells [4]. Most melanoma metastasis are located in the jejunum and ileum [5], but it can spread to any gastrointestinal segment. Although 60% of autopsies on melanoma patients reveal intestinal involvement, only 4% of intestinal metastases are diagnosed ante-mortem [6].

We found a few other case reports that described the presence of melanoma at different levels of the gastrointestinal tract, such as the oral cavity, oesophagus, small and large bowel, rectum and anal canal, with no detectable cutaneous melanoma at the time of diagnosis [7]-[15]. Through immunohistochemical stains such as HMB-45 and S100, the presence of melanocytes has been detected at the aforementioned digestive sites [16]. The migration of melanoblastic cells originating in the neural crest to the distal ileum by means of the omphalomesenteric canal, might account for the development of primary intestinal melanoma [17]. Another possible mechanism involves the development of primary intestinal melanoma from the Schwannian neuroblast cells that form the enteric nervous system [18].

Some authors argue that there is no primary intestinal melanoma, implying that either cutaneous lesions were failed to be diagnosed or underwent complete regression by the time of metastasis detection [19]. Cutaneous melanoma regression is a fairly common finding, encountered in up to 37% of all melanomas [20], occasionally leaving no trace of the initial malignant lesion. The histologi-

cal aspect left behind cutaneous regression is characterised by decreased number of melanoma cells, dermis fibrosis, inflammation, melanophages, ectatic blood vessels, epidermal attenuation and/or apoptosis of keratinocytes or melanocytes [21]. In our case, some of these histopathological elements have been described after examining the excised cutaneous lesion, but no certain cutaneous melanoma regression diagnosis could be reached.

The degree of spontaneous regression of the primary cutaneous lesion has been linked with survival in melanoma patients. Thin melanomas are more likely to metastasize depending on the degree of cutaneous regression; after 77% of the primary cutaneous tumour has regressed, solid organ metastases are more likely to be diagnosed [22].

While some authors argue that there is no such entity as primary gastrointestinal melanoma, notwithstanding cases where no primary cutaneous lesion could be identified after rigorous dermatological examination [19], others defined a series of diagnostic criteria for primary small bowel melanoma. Sachs *et al.* [23] outlined the following criteria according to which a primary small bowel diagnosis could be reached: 1) solitary melanoma lesion confirmed by histopathology, 2) no other organ involvement except regional lymph nodes and 3) disease-free survival of 12 months minimum following diagnosis. According only to the aforementioned criteria, our case does not qualify for the diagnosis of primary small bowel melanoma, as only one of the three criteria was met, namely the histopathologic confirmation of the presence of melanoma at a small bowel site. In our case, approximately four months had elapsed before the diagnosis was confirmed and further investigations were performed for the identification of other organ involvement, therefore the second criterion cannot be considered fulfilled.

Usually, intestinal melanoma manifests as an acute bowel obstruction [24], the underlying mechanism being enteric intussusception [25]. Other possible symptoms are abdominal pain, change in bowel habits, haematemesis, melena and weight loss [26]. Our patient presented no signs of acute bowel obstruction or digestive bleeding.

Usually, abdominal ultrasound is the first examination employed in the evaluation of cutaneous melanoma patients with digestive symptoms, although it renders a weak diagnostic performance, as in the case of our patient where the exact location of the tumour could not be established only through abdominal ultrasound. In addition, upper and lower digestive endoscopy systematically fails to identify small bowel lesions [27]. Therefore, additional diagnostic procedures are being investigated. Our patient presented a tumour at approximately 40 cm from the ileocecal valve, a site not accessible by conventional endoscopy. As enteroscopy could not be performed in our medical unit, further radiological examinations were employed (contrast enhanced CT scan).

Considering the frequent small bowel involvement in patients with cutaneous melanoma, Albert *et al.* [28] attempted with a multicentric prospective study, to design an algorithm for the detection of small bowel metastasis using faecal oc-

cult blood test, gastroscopy, ileo-colonoscopy and video-capsule endoscopy (VCE). 390 patients with stage I-IV melanoma patients were evaluated. Small bowel melanoma metastasis was identified in 28.6% of stage IV patients, 1.7% of stage III and in none of the stage I-II patients. The study underlines the potential role of VCE in the detection of small bowel metastasis, as no additional lesions were identified by further conventional endoscopy in these patients. Moreover, a positive faecal occult blood test indicated a poor survival rate in stage III and IV melanoma.

Gastrointestinal melanoma metastases are usually diagnosed at 2 to 180 months after the detection of the primary tumour [29], but their development remains possible even years after the curative treatment of the primary lesion [30]. Stage IV melanoma patients usually have a mean survival of 5.3 months [31], however in addition to symptomatic relief, considerably increased survival time has been observed in stage IV patients who underwent tumour resection [32]. In the case of our patient, a 2-year survival was achieved after the resection of the initial small bowel tumour, followed by multiple resections of the cerebral metastases.

According to Janavicius *et al.* [33], patients with melanoma brain metastases achieved better overall survival when treated with combined treatment modalities: surgery followed by radiotherapy (26.6 months overall survival), combining surgery, radiotherapy and systemic therapy (18.7 months overall survival), and also radiotherapy followed by systemic therapy (13.8 months overall survival). In the presented case, combined therapy was offered (surgery, radiotherapy and chemotherapy with dabrafenib, trametinib and nivolumab) achieving a longer survival than the average presented by Janavicius *et al.*

In conclusion, although in most cases it cannot be distinguished between primary intestinal melanoma or small bowel metastasis with no detectable primary cutaneous lesion, all patients require urgent diagnosis and management, as its prognosis remains poor.

Conflicts of Interest

None of the authors declared a conflict of interest.

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An Extensively Drug Resistant *Acinetobacter baumannii* from Soft Tissue Isolated in a Hospital in Senegal

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Abstract

Emerging and rapidly spreading multidrug resistant bacteria constitute a rising public health concern worldwide. *Acinetobacter baumannii* is one of these bacteria that cause different infections including pneumonia, bacteremia, meningitis, soft-tissue, and urinary tract infections, and are associated with high mortality and economic burden. We present a case of a 43-year-old woman, admitted at the department of orthopedics, regional hospital of Ourossogui, North-East of Senegal for soft-tissue injuries. Initially diagnosed with *Yersinia pestis* infection, the patient was well managed before being released. Supplementary sampling for confirmatory tests allowed the detection of an extensively drug-resistant *Acinetobacter baumannii* clone.

Keywords

Acinetobacter baumannii, Extensively Drug Resistance, Soft-Tissue, Senegal

1. Introduction

Acinetobacter baumannii has become a leading cause of nosocomial infections, especially in patients in intensive care units (ICUs). *A. baumannii* clones are often multidrug-resistant (MDR), leaving limited options for antibiotic treatment [1]. The World Health Organization (WHO) recently ranked carbapenem-resistant *A. baumannii* as the most critical bacterial pathogen for public health [2]. Invasive procedures and patients' exposure to certain antimicrobials are risk factors for colonization and infections by MDR *A. baumannii*. Moreover, cross-transmission among hospitalized patients is favored by poor adherence to hand hygiene practices and by repeated contact with contaminated environments [3]. Despite the

increase incidence of MDR *A. baumannii* in many parts of the world, data from sub-Saharan Africa are scarce. We present a case of an extensively drug-resistant *A. baumannii* isolated from the soft tissues of a 43-year-old woman.

2. Case Presentation

This case represented a 43-year-old woman living in Ourossogui, North-East of Senegal, who was admitted on May 18th, 2021 to the orthopedic department of the regional hospital as shown in Figure 1. The motif of consultation was an oozing wound on the back of the sole of her right foot and the patient attested not having any particular pathological history, except hypertension. During the medical examination, she said that signs began in September 2020 with a blackish point with an oozing clear fluid. About two months later, her situation deteriorated such that she could not stand on her feet and developed a fever. She visited a peripheral healthcare facility in November 2020, where she received aseptic cleaning and an antibiotic treatment that was presumed to be cotrimoxazole. With a slight improvement, she resumed her daily activities until six months later when her situation severely worsened, necessitating her admission to the regional hospital.

At the admission, the wound appeared slightly budding and suppurating, and the patient was taken to the orthopedic department for surgical excision. A pus sample was collected for microbiological analysis. The results returned the presence of Gram-negative bacilli suspected to be a *Yersinia pestis*, which was resistant to

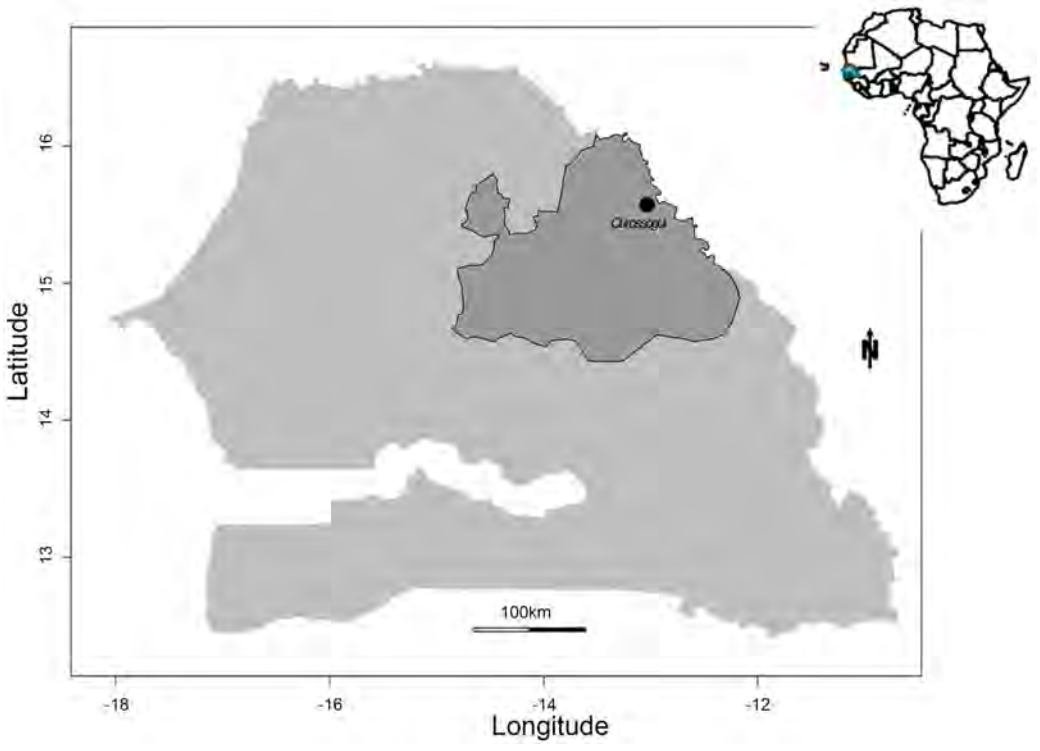

Figure 1. Map of Senegal, highlighting Ourossogui area, where the case was investigated. (Map representation was done by R software).

aztreonam, cephalothin, ceftriaxone, chloramphenicol, and colistin. Nonetheless, the strain was susceptible to carbapenems (imipenem), aminoglycosides (gentamicin, kanamycin, tobramycin), quinolones (ciprofloxacin), and penicillin's (ticarcillin, Amoxicillin-clavulanic acid) (see **Supplementary Table**). Thereafter, the patient was treated with a combination of intravenous antibiotics (clavulanic acid, Clavuject for 1 g × 3/day), antalgic (Perfalgan for 1 g × 3/day and Dynapar 1 amp × 2/day), and anticoagulant (Lovenox 0.4 mg/day). After two weeks, she showed a positive evolution and was released from the hospital on June 1st, 2021 for home or nursing office care. She was following up for at least 4 weeks with aseptic cleaning, and from the latest news, her health condition was stable, even thought she was not completely healed. It must be stressed that results on *Yersinia pestis* detection should be taken with caution, due to the drastically decreasing incidence of plague in Senegal and overall in Africa since 1949 [4]. Since plague is a reportable disease in Senegal, an epidemiological investigation was initiated and a wound swab was collected on the day of the patient discharge and sent to Institut Pasteur de Dakar (IPD) for confirmation and further investigation. Microbiological analysis revealed Gram-negative cocobacilli. Culture on different medial (chocolate, MacConkey and bromocresol purple agars) showed smooth and rounded colonies identified as *A. baumannii* with API biochemical tests. Antimicrobial susceptibility testing performed by disk diffusion and automated (Vitek 2 system, bioMérieux) methods revealed resistance to penicillin's (ticarcillin, piperacillin, ticarcillin-acid clavulanic, piperacillin-tazobactam), sulphonamides (trimethoprim-sulfamethoxazole), carbapenems (meropenem, ertapenem, imipenem), cephalosporins (cefotaxime, ceftazidime, cefepime), gentamicin, tetracyclines (tetracycline, minocycline) and fluoroquinolones (ciprofloxacin), and susceptibility to colistin, amikacin, and tobramycin (**Table 1**). Based on these results, we classified this clone as an XDR *A. baumannii* that is resistant to at least one drug from all categories except two or fewer [5].

Table 1. Antimicrobial susceptibility testing in XDR *Acinetobacter baumannii*.

Antibiotic class	Antibiotics	value (mm)	value (mg/L)	Interpretation
Penicillin's	Piperacillin-tazobactam	6	≥128	R
	Piperacillin	6	≥128	R
	Ticarcillin	6	≥128	R
	Ticarcillin-clavulanic acid	6	≥128	R
Aminoglycosides	Tobramycin	21	≤1	S
	Amikacin	22	≤2	S
	Gentamicin	6	≥16	R
Cephalosporines	Cefotaxime	6	NT	R
	Ceftazidime	6	≥64	R
	Cefepime	10	NT	R

Continued

Carbapenems	meropenem	6	≥16	R
	Imipenem	NT	≥16	R
	Ertapenem	6	NT	R
Quinolones	Ciprofloxacin	6	≥4	R
Sulphonamides	Trimethoprim-sulfamethoxazole	6	≥40	R
Tetracycline	Minocycline	NT	≥16	R
	Tetracycline	6	NT	R
Miscellaneous	Colistin	NT	≤0.5	S

R: resistant; S: sensitive; NT: not tested; mm: millimetre; mg/L: milligram per litre.

3. Discussion

The emergence and dissemination of MDR *A. baumannii* are a global public health concern. *A. baumannii* belongs to the ESKAPE group of pathogens, which are characterized by their ability to rapidly develop resistance to numerous antibiotics. In Senegal, the epidemiology of MDR *A. baumannii*, including carbapenem-resistant clones, is poorly documented. Available literature shows its presence both at the community and hospital level, even though no epidemiological data on its burden is available yet [6] [7]. From our results, we cannot firmly conclude that the isolated XDR *A. baumannii* was the aetiological agent of the wound that the patient suffered from. It was unfortunate that the suspected *Y. pestis* clone initially isolated was not stored, preventing any confirmation. However, since the patient's condition improved following the initial treatment and given that *A. baumannii* was isolated 13 days after admission corresponding to her day of release, we believe of a case of hospital-acquired infection, likely during wound cleaning. In Africa, the prevalence of hospital-acquired infections (HAIs) ranges from 10% to 60%, and they are the third, second and first leading causes of maternal mortality, early neonatal mortality and postoperative morbidity, respectively. HAI prevalence is estimated at 10% in Benin, 10.9% in Senegal, 12% in the Ivory Coast, and 14% in Mali [8]. A review that examined the incidence and prevalence of HAIs by *A. baumannii* in Europe revealed that this bacterium is more frequent (>20%) than other common nosocomial pathogens like *Klebsiella pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus* [9]. A similar pattern was described in Southeast Asia [10], China [11], and Latin America [12], but it was different in the United States, where HAIs with *Acinetobacter* spp in ICUs were estimated to be only 1.1% [13]. Data on the burden of MDR *A. baumannii* infections, including carbapenem-resistant clones are very scarce in Africa. Nonetheless, available data suggest a widespread distribution of carbapenemase-producing strains with prevalence ranging from 2.3% to 67.7% in North Africa and 9% to 60% in sub-Saharan Africa [14]. Studies to delineate the magnitude and spread of *A. baumannii* infections across Africa are therefore urgently needed. To our knowledge, this study is the first reporting a potential

HAI with XDR *A. baumannii* in Senegal. It stresses the importance to strengthening and enforcing guidelines for patient management, especially those in ICUs. Moreover, surveillance systems should be implemented to study the evolution, dynamic of transmission and biological role of important nosocomial pathogens like *A. baumannii*.

4. Conclusion

Emergence of MDR *A. baumannii* in clinical settings is of critical importance. This case illustrates a potential HAI XDR *A. baumannii* infection in Senegal, where data on this bacterium are scarce. This stresses the need of an active surveillance of *A. baumannii* in LMIC hospitals as well the development and enforcement of effective guidelines for patient management.

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Authors and Contributors

Conceptualization: CF, BSB, YD; methodology: OS, FPL; validation: CF, OS, FPL, YD; investigation: BD; original draft preparation: CF; writing-review and editing: CF, OS, FPL, BSB, YD. All authors have read and agreed to the published version of the manuscript.

Ethical Approval

The authors declare that the privacy of the patient was respected according to the CIOMS rules, regarding the privacy of the data collected.

Conflicts of Interest

All the authors declare no conflict of interest.

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Supplementary Table: Antimicrobial Susceptibility Testing in *Yersinia pestis*

Antibiotic class	Antibiotics	Interpretation
Penicillin's	Amoxicillin	Resistant
	Amoxicillin-clavulanic acid	Sensitive
	Ticarcillin	Sensitive
carbapenems	Meropenem	Sensitive
cephalosporines	Azitreonam	Resistant
	Cephalotine	Resistant
	Ceftriaxone	Resistant
Aminoglycosides	Gentamicin	Sensitive
	Tobramycin	Sensitive
	Kanamycin	Sensitive
Phenicol's	Chloramphenicol	Resistant
quinolones	Ciprofloxacin	Sensitive
miscellaneous	Colistin	Resistant

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Surgical Repair of Growing Skull Fracture: A Case Report

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Abstract

Background: Growing skull fractures (GSF) are a rare complication of pediatric head trauma that comprises post-traumatic skull defect associated with an underlying dural tear and an intact arachnoid membrane. They are often misdiagnosed, and delay in management can lead to progression of the disease with neurological sequelae. GSF are rare and their incidence has been estimated as 0.05% - 1% of all pediatric skull fractures. This low incidence and the subtlety of its presentation often make diagnosis challenging with consequent delay in management. Surgery is recommended to treat GSF and involved dural repair with or without cranioplasty. In this paper, we report a case of a patient with GSF in whom the surgical repair was successful with good cosmetic and functional outcome. **Case Report:** A 12 months old girl was admitted to our neurosurgical department with right parietal swelling that had been gradually enlarging over 3 months. The history of the disease began when the girl was 1 month old with a fall with cranial impact resulting in head trauma with initial loss of consciousness. At presentation the girl was alert with normal consciousness. Clinical examination revealed the deformed skull with large pulsatile and painless swelling lesion in the right parietal region and hemiparesis on the left side. The CT scan revealed type 3 GSF including parietal bone diastasis with hypodense fluid collection that mimicked the leptomeningeal and porencephalic cyst. Surgical repair was performed. The post-operative course was uneventful and the child was discharged home five days after surgical intervention. **Conclusion:** GSF can lead to serious neurologic complications. Therefore educating parents on this potential outcome and close follow-up with clinical and imaging screening is recommended to screen children at risk for the development of the disease.

Keywords

Growing Skull Fracture, Head Trauma, Dural Tear

1. Introduction

Growing skull fractures (GSF) are a rare complication of pediatric head trauma that comprises post-traumatic skull defect associated with an underlying dural tear and an intact arachnoid membrane. They are often misdiagnosed, and delay in management can lead to progression of the disease with neurological sequelae. GSF are rare and their incidence has been estimated as 0.05% - 1% of all pediatric skull fractures [1] [2]. This low incidence and the subtlety of its presentation often make diagnosis challenging with consequent delay in management [3] [4] [5] [6] [7]. CT scan or MRI is the imaging modality study to confirm the diagnosis. Early surgical intervention is recommended to treat GSF and involved dural repair with or without cranioplasty. In this paper, we report a case of a patient with GSF in whom the surgical repair was successful with good cosmetic and functional outcome.

2. Case Report

This 12 months old girl was admitted to our neurosurgical department with right parietal mass that had been gradually enlarging over 3 months. The history of the disease began when the girl was 1 month old with a fall with cranial impact resulting in head trauma with initial loss of consciousness with no clinical lesion at the time. The patient was discharged home. At presentation 11 months later the girl was alert with normal consciousness. Clinical examination revealed the deformed skull with large pulsatile and painless swelling lesion in the right parietal region (**Figure 1**) and hemiparesis on the left side. The CT scan (**Figure 2**) revealed type 3 GSF including parietal bone diastasis with hypodense fluid collection that mimicked the leptomeningeal and porencephalic cyst. Results of routine laboratory studies were normal. Surgical repair was performed. The surgical technique consisted of performing duraplasty alone using autologous tissue with pericranium and watertight closure (**Figure 3**). The post-operative course

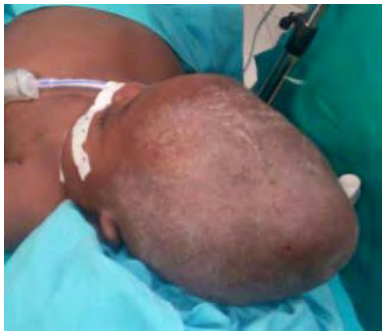


Figure 1. Clinical photograph showing the swelling in the right parietal region.

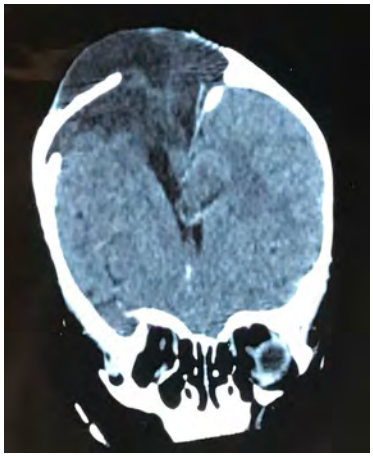
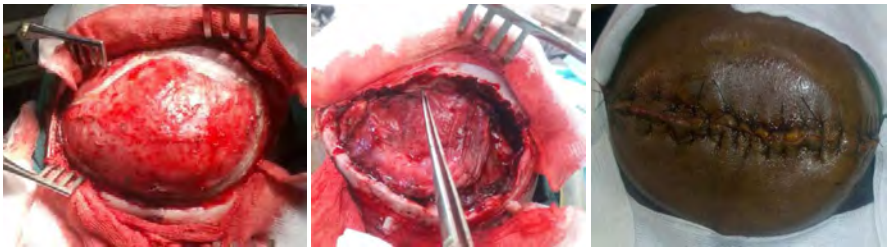


Figure 2. CT scan showing type 3 GSF including parietal bone diastasis with leptomeningeal and porencephalic cyst.



(a) (b) (c)

Figure 3. Operative photograph showing (a) Exposure after skin incision; (b) Bone defect and duraplasty and (c) Skin closure.

was uneventful and the child was discharged home five days after surgical intervention. Good cosmetic outcome as well as good functional outcome was obtained at 6 months follow-up.

3. Discussion

The first description of growing skull fracture (GSF) was reported by Howship in 1816 [8]. GSF is an unusual complication of pediatric head trauma occurring mainly in children under the age of 30 months [1] [2] [9] [10]. It can also occur following craniosynostosis repair [11], or as a complication of traumatic assisted delivery using obstetrical forceps or vacuum. Other terms used to describe GSF includes leptomeningeal cyst, traumatic leptomeningeal cyst, and craniocerebral erosion [12]. GSF are more common in young children, particulary those under 3 years of age due to the thinner calvarium increased malleabililty of the skull and rapid cranial in this age group. In our case, the trauma occurred when the girl was 3 months old and the diagnosis was made 9 months later. The pathogenesis of GSF is not completely understood but many hypotheses have been described in the literature. GSF requires a skull fracture, rupture of the dura which occurred at the time of initial fracture, immature membranous bone formation, and the presence of an outward driving force like growing brain, hydrocephalus,

or edema. Swelling or a defect of the scalp is usually the main clinical presentation [13] [14]. This swelling is very often the reason for consultation with the doctor. The delay in treatment can lead to progression of a GSF with neurological deficits, such as seizures, hemiparesis, mental retardation, and headaches [15] [16]. In addition to the swelling of head, our patient had left hemiparesis due to the long delay of nine months before the diagnosis. CT scan is the most common imaging modality used to confirm the diagnosis of GSF. MRI also is one of the imaging modality but there is no consensus about it superiority to CT scan. In our case, CT scan was sufficient to confirm the diagnosis of GSF. According to the natural history described by Naim-Ur-Rahman *et al.* [17], GSF was classified in 3 types. Type 1 lesions comprising of GSF with leptomeningeal cyst, whereas type 2 lesions contain gliotic brain, and type 3 are associated with a porencephalic cyst. Our patient was been classified as type 3. Surgical technique in GSF includes duraplasty, cranioplasty or combined dura-cranioplasty. In our case, duraplasty alone using autologous tissue with pericranium was the surgical technique. According to the literature, cranioplasty is not essential for the surgical treatment of GSF. Surgical repair of GCF is often associated with complications like infection. No complications were found in our case and Good cosmetic outcome as well as good functional outcome was obtained at 6 months follow-up.

4. Conclusion

GSF can lead to serious neurologic complications. Therefore educating parents on this potential outcome and close follow-up with clinical and imaging screening is recommended to screen children at risk for the development of the disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Subacute Chorea Induced by Organic Solvents

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Abstract

Introduction: Chronic exposure to organic solvents may result in a variety of neurologic complications like dementia, cerebellar dysfunction, pyramidal syndrome, cranial nerve abnormalities, and neuropathy. **Clinical Presentation:** We report an unusual case of subacute chorea induced by occupational exposure. Brain magnetic resonance imaging showed diffuse white matter T2 hyperintensity. The screening of basic blood tests, and CSF studies to eliminate alternate diagnoses, were normal. The patient received 1000 mg/day of intravenous methylprednisolone for 3 days, with cessation of professional activity. We observed a regression of neurological symptoms after 3 months of follow-up. **Conclusion:** This case highlights the diversity of acute or chronic neurological complications of solvents.

Keywords

Acute Chorea, Diffuse White Matter T2 Hyperintensity, Organic Solvent Exposure

1. Introduction

Chorea is a hyperkinetic abnormal movement characterized by involuntary brief, random, and irregular movements, giving it a dancelike appearance. The etiology of adult-onset sporadic chorea is diverse and can be categorized into acquired and genetic causes. It is crucial to identify acquired causes, as many of them are treatable. However, the toxic causes are uncommon and evidence is mostly based on case reports or series. The organic solvent exposition is rarely reported as a cause of chorea. We describe a case of acute chorea after the organic solvent exposition.

2. Case Report

A 54-year-old man was admitted to the emergency department for the subacute

onset of generalized abnormal movements associated with the behavioral disorder and personality changes, 2 weeks before admission. He had no medical history and no remarkable family history. He worked as a professional painter for 15 years, with recently overexposure to solvents in a confined workspace without protection.

His general medical examination findings are body temperature of 36.6˚C, blood pressure of 122/77 mmHg, and regular pulse rate (75 bpm). The neurological examination revealed mutism with frontal lobe syndrome and generalized spontaneous movements that are irregularly timed, randomly distributed, abrupt, and predominantly proximal and making walking impossible, suggestive of chorea. His cranial nerves were unremarkably normal. The deep tendon reflexes were also normal.

Brain magnetic resonance imaging (MRI) showed diffuse symmetric hyperintensities in periventricular white matter sparing U-fibers, involving internal capsules, on T2-weighted and diffusion-weighted sequences. There were also more marked hyperintensities T2-weighted and hypointense T1-weighted on bilateral globus pallidus (Figure 1).

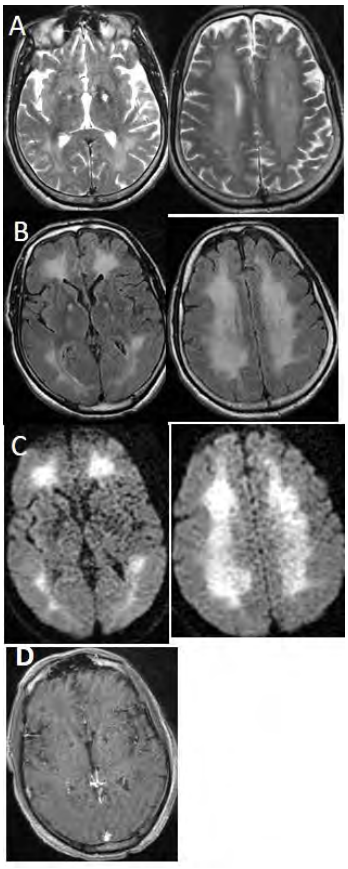

Figure 1. Brain MRI (A) axial T2-weighted, (B) axial fluid attenuation inversion recovery (FLAIR) images, and (C) proton density-weighted show bilateral symmetric extensive hyperintensities in the periventricular white matter, in the posterior limb of the internal capsule, in the centrum semiovale and the globus pallidus. Axial T1-weighted image with contrast (D) shows hypointense bipallidal lesion.

Inflammatory markers were not elevated (erythrocyte sedimentation rate 6 mm/hr and C-reactive protein 2 mg/L). Cerebrospinal fluid (CSF) analysis showed albuminocytologic dissociation with hyperproteinorachia at 1100 mg/L and normal white cell count (1Element /mm^3). Oligoclonal bands were absent.

The EEG showed a diffuse slowing down of the cerebral activity without any epileptic pattern.

Nerve conduction studies in Electromyography are normal

A computed tomography (CT) of the chest, abdomen, and pelvis, and a panel of tumor markers (anti-Hu, anti-Ri, anti-Yo, and anti-Ma antibodies) in the serum and CSE were negative. The Whole-body positron emission tomography (PET) was not done.

Given the radiological imaging, the normality of the blood test, and knowledge of the patient's overexposure to solvents in a confined workspace during 10 days, with no protective measures, preceding the neurological symptoms by 5 days, subacute solvent encephalopathy was the most probable diagnosis.

The patient received 1000 mg/day intravenous methylprednisolone for 3 days, in addition to a daily dose of 10 mg of Memantine with cessation of professional exposure.

Gradual improvement with complete regression of chorea after 2 weeks, progressive resolution of the frontal syndrome was noticed after 6 weeks. At 3 months follow-up, he had a normal neurological examination.

Control MRI showed mild regression of white matter abnormalities with moderate brain atrophy (Figure 2).

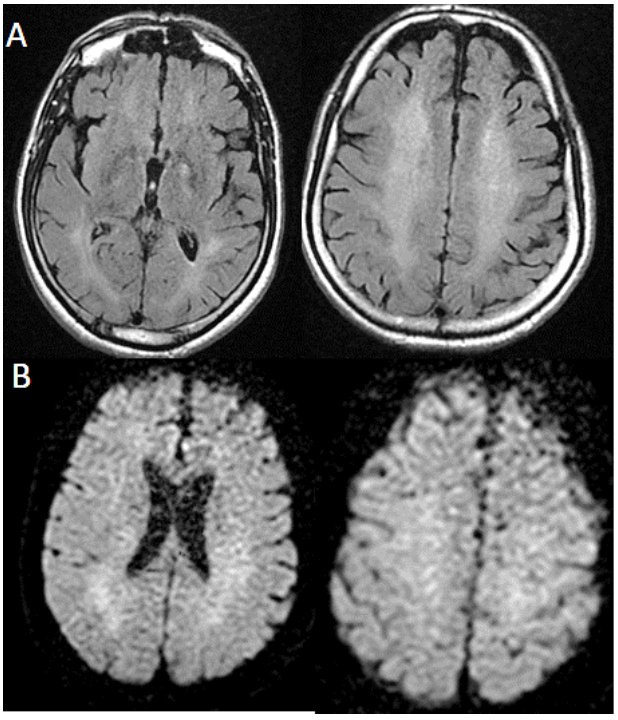

Figure 2. Brain MRI showing mild regression of hyperintensities and apparition of brain atrophy on the axial FLAIR (A) and proton density-weighted images (B).

3. Discussion

Organic solvents are volatile and lipophilic substances with low molecular weight. They are contained in many paint adhesives, inks, and cleaning products. The chemical properties of organic solvents rapidly penetrate the central nervous system (CNS) after inhalation [1]. The myelin of the enter ral and peripheral nervous system is rich in lipids, making it sensitive to damage by lipophilic substances such as volatile solvents [2].

In many countries, organic solvents are the most abused substances and are a public health problem in young people. Neurological complications due to illicit or occupational exposure to solvents are poorly defined. Chronic exposure to solvents can induce neurological toxicities such as demyelinating neuropathy, seizures, progressive encephalopathy, pyramidal syndrome, cerebellar syndrome, parkinsonism, and cranial nerve abnormalities [1] [2] [3]. The risk of experiencing acute neurological effects is also possible, in cases of high exposure (consumer overdose; confined workplace, or no personal protective equipment) [2] [3]. However, subacute movement disorders due to solvent exposure are uncommon, are rarely reported in the literature.

The most common causes of sporadic chorea are vascular disease, infectious diseases (AIDS, borreliosis…), metabolic disorders (non-ketotic hyperglycaemia or hyponatremia), autoimmune disease (systemic lupus erythematosus, Gougerot-Sjögren syndrome…), and genetic causes [4] [5].

The occurrence of Chorea is not rare after exposure to drugs such as neuroleptics, anticonvulsants, psychostimulants, and substance abuse (Heroin, Cocaine…) [1] [6] [7] [8]. However, chorea is an exceptional manifestation of organic solvent neurotoxicity unlike the parkinsonian syndrome [8].

The possible explanation for its occurrence in cases of solvent exposure is the increased dopamine concentrations in rat striatum and NMDA antagonism [8].

CT scan findings of the chronic solvent-exposed subject show cerebral atrophy correlated to long-term exposure [1] [10]. The MRI findings were mainly brain atrophy and the focal or extensive white matter hyperintensity on T2-weighted, and proton density-weighted (DW) sequences [10]. T2 hypointensity of the thalami and basal ganglia commonly attributed to the accumulation of iron, have also been reported [10]. Brain MRI is essential to exclude differentials diagnosis before concluding solvent-induced encephalopathy [1] [9].

Certain similarities between the lesions seen in brain MRIs of solvent abusers and reported findings of multiple sclerosis may suggest that demyelination is a neuropathological element in solvent neurotoxicity [10]. Therefore, white matter change is considered to represent damage in myelin similar to the demyelination reported in solvent abusers' autopsy reports [3].

Electroencephalogram (EEG) is abnormal in about fifty percent of the patients. EEG abnormalities that have been reported are slow activity and excessive beta activity, but there is no specific pattern to solvent toxicity [1].

Cerebrospinal Fluid Protein (CSF) analysis is necessary to exclude differential

causes. The albuminocytologic dissociation in CSF was frequently reported in the literature supporting the demyelination hypothesis [2].

Electromyography abnormalities that were observed in individuals exposed to solvents include a mixed sensory/motor neuropathy or inflammatory demyelinating polyradiculoneuropathy [2].

There are no specific treatments. Early diagnosis and cessation of exposure to solvents is the most effective therapy [1]. The hypothesis evoked in the literature, that the solvents caused the demyelinating lesions of the nervous system, explains the use of high doses of methylprednisolone in some cases [3].

Avoiding solvent abuse and preventing occupational exposure through the use of protective equipment and better ventilation of workplaces are the most effective way to prevent the neurotoxicity of solvent.

4. Conclusion

Solvent neurotoxicity in adults is well known with diverse clinical features. However, chorea is rarely described. Solvent neurotoxicity might not be apparent from routine toxicology tests and the diagnosis requires an exposure history, neurological symptoms, MRI findings, screening of basic blood tests, and CSF studies to discard alternate diagnoses. Improvement or stabilization of neurological symptoms after removal from exposure is another diagnosis support [1] [4].

Consent for Publication

Written informed consent was obtained from the patient's legal guardian(s). A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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Severe Anaemia during Natalizumab Treatment: Case Presentation with Literature Review

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Abstract

Progressive multifocal leukoencephalopathy is the most common serious complication related to natalizumab. However, serious haematological complications are very uncommon during treatment with natalizumab. Here we reported the case of an 18-year-old man with a 4-year history of relapsing-remitting multiple sclerosis. He was treated firstly by Teriflunomide for 1 year, but he presented relapses and his MRI shows new contrast-enhancing lesions. Therefore, we decided to switch from Teriflunomide to Natalizumab. The patient presented with profound anaemia after the 16th infusions treatment with Natalizumab. The patient's hemoglobin was 3.2 g/dL with a lower blood reticulocyte value. After red cell transfusions and cessation of Natalizumab, anaemia resolved. Natalizumab was changed by an anti-CD20 monoclonal antibody. The patient had a stable course of multiple sclerosis at 13 months after initiation of Rituximab. We should alert clinicians to be aware of the possibility of anaemia during treatment by Natalizumab.

Keywords

Anaemia, Erythroblasts, Haematological Monitoring, Multiple Sclerosis, Natalizumab

1. Background

Natalizumab (NTZ) is the first efficacious monoclonal antibody approved for relapsing-remitting multiple sclerosis (RRMS) in 2010, likely in highly active forms [1]. It is also used in active inflammatory bowel disease [2] [3]. The overall incidence of adverse events associated with NTZ is low. This treatment's known serious adverse effect is progressive multifocal leukoencephalopathy caused by John

Cunningham Virus (JCV) [1]. Severe anaemia may not be recognized as an adverse effect of NTZ treatment, and its cause remains unclear. In this case report, we describe this rare complication of NTZ treatment, with a literature review.

2. Case Report

Mr. T. A is an 18-year-old man with a 4-years history of RRMS, but no other notable medical history. He was treated firstly by Teriflunomide for 1 year, which was switched to monthly Natalizumab infusion, due to lack of efficacy since April 2019. The patient remained clinically and radiographically stable during NTZ treatment. In July 2020, 3 weeks after the 16th NTZ infusions, the patient developed severe fatigue, shortness of breath, palpitation, and vertigo with no haemorrhagic syndrome and no fever. Physical examination revealed pallor and tachycardia (110 bpm).

Laboratory testing revealed profound normocytic normochromic anaemia with hemoglobin at 3.2 g/dL and a lower blood reticulocyte value (1785/mm^3), with no abnormalities in lymphocytes (6840/mm^3) or in platelet counts (324,000/mm^3). Erythroblasts precursors were absent. Sternal puncture revealed hypercellular marrow with the presence of many signs of dyserythropoiesis, megaloblasts with pearl chromatin, multinucleated erythrocytes, interchromatin bridges, images of cells in mitosis and karyorrhexis. Vitamin B12, folic acid, and iron levels were normal. Parvovirus serology was negative. The erythrocyte sedimentation rate, Reactive C Protein (RCP), serum bilirubin, and serum lactate dehydrogenase (LDH) were normal. There were no splenomegaly or mass lesions in total body CT scans. Bone marrow aspirate was not done.

We, therefore, ruled out myeloproliferative disease and diagnosed severe anaemia from possible drug toxicity (NTZ). We discontinued NTZ treatment and the patient was treated by blood transfusions. Haemoglobin was at 9.7 g/dL five days after transfusion. The patient had complete recovery of all clinical symptoms of anaemia.

We switched from NTZ to an anti-CD20 monoclonal antibody (Rituximab) considered as another second-line therapy in MS, with rapid action delay, to avoid the risk of rebound effect at 7 weeks to the last infusion of NTZ. Anaemia resolved and haemoglobin was 14 g/dL after 2 months NTZ discontinuation. The patient had a stable course of RRMS 18 months after initiation of Rituximab, without the appearance of a new episode of anaemia.

3. Discussion

Multiple sclerosis (MS) is one of the most frequent neurological diseases and it is a cause of disability among the young population [1]. The therapeutic arsenal in the disease-modifying therapy of MS, especially in its relapsing-remitting form, is becoming richer. The news drugs are characterized by the varying mechanisms of action and the potentially higher efficacy on the inflammatory component of the disease.

NTZ is a humanized monoclonal antibody that is used for the treatment of highly active MS since 20 years, with better control of disease activity. Except for PML, the pivotal studies of NTZ did not demonstrate severe adverse events with haematological safety profile and do not recommend any haematological monitoring [1]. A post-marketing prospective study assessing of incidence of hematologic side effects during NTZ treatment, included 66 patients, revealed a high occurrence of hyperlymphocytosis (48%) and hypereosinophilia and low risk of anaemia 6% (4 patients) [4]. Some case reports of severe anaemia during NTZ treatment have been also described, but it is extremely rare, we found only 3 cases in the literature [5] [6] [7].

The physiopathology of aneamia with NTZ is unknown. NTZ is a humanized monoclonal antibody directed against α-4 β1-integrin expressed by leucocytes (VLA-4). NTZ thus inhibits the adhesion of lymphocytes to endothelial vascular cell adhesion molecules and prevents their migration into the central nervous system.

VLA-4 is also known expressed on erythroblasts, hence NTZ may inhibit erythropoiesis and maturation of erythroblast and lead to the appearance of erythroblast in peripheral blood (PB) [8]. The erythroblast appearance in PB, may explain a previous case of severe anemia, and it has been described as a reversible adverse effect of NTZ treatment [8] [9].

The immune-mediated acute haemolytic anaemia is another reported possible mechanism of anaemia during NTZ treatment [4]. Hemolytic anemia was ruled out in our patient.

To our knowledge, this is the 4th case of Natalizumab-induced severe anaemia reported so far in the literature (**Table 1**) [5] [6] [7]. The age of the 3 patients was around 50, whereas our patient was younger. In the first case reported in 2012, the anemia had appeared after the first infusion [5], whereas in the 2 following cases with ours the anemia had appeared beyond the fifteenth infusion. The hemoglobin level was variable in the 3 cases and the lowest in our case.

Table 1. Cases of severe aneamia during NTZ treatment in the literature with our case.

	Gender/ Age (years)	Number of infusions of NTZ	Hemoglobin	Management	Treatment switch
Midaglia 2012 [5]	F/50	1	5.4 g/dL	Transfusions, Intravenous immunoglobulin and steroids	NA
Simone 2014 [6]	F/51	34	7.3 g/dL	Transfusions, Discontinued NTZ	NA
Seibert 2015 [7]	F/49	15	7.4 g/dL	3 monthly blood transfusions Discontinued NTZ	NA
Our Case	M/18	16	3.2 g/dL	Transfusions, Discontinued NTZ	Rituximab

Management of anemia in all cases was based on blood transfusion and discontinuation of NTZ therapy. The evolution was favorable in all 4 cases.

4. Conclusion

Fatigue is a frequent symptom of MS but it can also be related to anaemia secondary to DMTs. Despite the rarity of this haematological complication with NTZ, it seems feasible to regularly monitor blood cell count to optimize treatment safety in an individualized approach.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Prostate Cancer and Low Back Ache—Evidenced Role of Physiotherapy

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Abstract

Low back pain remains a most common clinical entity among musculoskeletal disorders. Pain reducing modalities, Manual therapy various specific techniques were widely used physiotherapeutic means as part of treatment for subjects with low back pain. An emerging trend with Independent physiotherapy practice, knowing red flags, conditions requiring investigations and experts treatment were to be recognized and adhered for maximizing patients care and benefits. Prostate cancer among men above 50 years were more found to be linked with Low back pain. This original research presentation where a subject having chronic low back pain found to have prostate cancer were analyzed and discussed with scientific evidence on clinical manifestations, investigations and medical management. Underlines the importance of recognizing, directing and getting treated of the root cause of subjects suffering with Low back pain due to prostate cancer and not just keep treating the symptoms alone were major purpose of this study.

Keywords

PC—Prostate Cancer, QOL—Quality of Life, LBA—Low Back Ache, PA—Physical Activity, PSA—Prostate Specific Antigen, CAD—Coronary Artery Disease, DRE—Digital Rectal Examination, WHO—World Health Organization

1. Introduction

Prostate Cancer (PC) is the most common non-cutaneous cancer in men and second leading cause of cancer related mortality in men [1]. Cao and Ma 2011 [2], conducted a meta-analysis of 26 studies found 12% - 20% of deaths from PC are related to obesity, where every 5 Kg/m^2, there was a concomitant increase in biochemical recurrence by 21% and the risk of death from PC increases by 15%.

Scher *et al.*, 2016 [3] in a survey among 109 men, 25% had family history of

prostate cancer, 26% had an elevated Prostate specific antigen (PSA), 22% were prostate cancer survivors, 94% were white, non-Hispanic, 84% were married, 81% were urban had a mean Body mass index (BMI) of 29.5 Kg/m^2 (80% were obese), 29% vigorous Physical activity (PA), 52% moderate, 18% sedentary, Diet 26% meat daily, 64% dairy daily [4].

Physiotherapist, recognized as first contact health care expert for musculoskeletal disorders by World health organisation (WHO), a big boon for physio practice globally. At the same time, an updated clinical knowledge of various conditions associated with age related clinical situations, investigations needed, physical examinations, medical history related issues, lifestyle changes, when to refer to medical experts with due clinical reasoning skills are paramount.

Low back pain, most common condition to be treated by physiotherapist, where not to treat the symptom alone; but physiotherapist should have analytical ability to find relative pathological origin. In an era of patient centered therapy, advanced communication technology based information prompt diagnosis and reference remains key components. Many associated clinical conditions such as tuberculosis of spine, prostate cancer should be treated medically prior to physiotherapy. Hence with a middle aged man complaining of low back ache with obesity, sedentary lifestyle, alcoholism, urinary disturbances should be initially referred for PSA screening and Digital rectal examination (DRE).

Various risk factors, investigations, clinical course, treatment and complications of prostate cancer were discussed with evidence. Role of physiotherapy with critical analysis on a patient with LBA and prostate cancer were provided. Importance of being first contact health expert a thorough knowledge of various clinical conditions related to musculoskeletal disorders mainly low back ache are highlighted.

1.1. Low Back Pain and Prostate Cancer

Among younger patients, the PC is usually very aggressive and requires treatment [5], with one of the late manifestations is bone pain by way of skeletal metastasis [6] may present with low back pain, thus knowledge of middle aged man with low back, sacro iliac and hip pain should be referred for medical management [7]. A patient with metastatic disease may complain of night pain, intense pain at rest with unexplained weight loss [8]. Patients with Prostate cancer (PC) may have decreased urine stream, increased frequency and urgency [5]. Johnson 1994 [9] had a patient with one month abdominal and back pain has referred to physical and laboratory examination, later was diagnosed and treated for PC.

1.2. Investigations

Routine screening of PC includes PSA and DRE at the age of 50 years [10], men at higher risk for PC should screen for PC at 40 years [11].

1.3. Management of Prostate Cancer

Metz *et al.* 2016 [12], have recorded men after PC diagnosis wanted to improve

their health with diet, Le masters *et al.* 2014 [13] have insisted on lifestyle changes as less likely to occur as more time passes after any cancer diagnosis. Physical activity appeals to mean as effective weight management strategy [9] and PC as it is empowering [14]. Compared with female cancer survivors male cancer survivors are 30% more likely to meet American cancer society's recommendations at 150 moderate to vigorous PA per week [15].

1.4. Complications

While data of PA on PC are not conclusive [16] men with PC are more likely to die of CVD [17]. Advanced PC commonly spreads to the bones which cause pain in the hips, spine, ribs and impotence was considered to be an important and early marker for PC [18]. Ketch and Ji *et al.* 2018 [19] have recorded that 2/3rd of early stage of PC death from Cardio vascular diseases (CVD) was more common than from PC. 65% to 80% of men with metastatic disease have bone metastasis and is common with PC with skeletal related events cause pain and Quality of life (QOL). Prostate gland is divided into different zones, peripheral zone is the most common site of malignancy and is palpable [20].

2. Aims and Objectives of This Research Were

1) To evaluate low back pain among prostate cancer.

2) To be familiar with prevalence, prognosis, treatment and complications of prostate cancer.

3) To analyse the role of physiotherapy among patients with prostate cancer.

Preview and Purpose of Presentation:

55 year old endomorph male with sedentary lifestyle with chronic low back pain for more than a year. He was treated by orthopaedic surgeon with Non-steroidal anti-inflammatory drug (NSAID), Short wave diathermy (SWD), Light amplification stimulation with emission & radiation (LASER) therapy and exercises during this period (June 2018-December 2018). He was diagnosed with prostate cancer later and was treated with due medication has recovered clinically and with laboratory reports in 3 months period (July 2019-September 2019).

Other Related Findings of the Subject:

Body Mass Index—32 Kg/m^2, Waist Circumference (WC)—115 cm, Vegetarian, was an alcoholic till last year, Non-smoker, with long hours of sitting for more than 10 hours daily. Father of two adult, was regular with walking for 45 minutes of 5 days per week.

History of father with Coronary artery disease (CAD), Stroke twice, mother with Parkinsons, CAD, diabetic, both parents are endomorph.

3. Results & Discussion

The results and clinical prognosis of the subjects condition prior to prostate cancer with LBA is shown in **Table 1** below.

Table 1. Results and clinical prognosis of the subjects condition prior to prostate cancer with LBA.

PARAMETERS	PRE	POST	SE	Tests of Significance	P-Value
BMI	38 kg/m^2	32 kg/m^2	0.71	8.45	>0.01
Waist Circumference	130 cm	115 cm	2.23	6.73	>0.01
Oswestry Disability Score	76	48	6.48	4.32	>0.05
Incentive Spirometry	2400 cc	3600 cc		-	

Critical Research Analysis

1) Is there a need for physiotherapists to know about prostate cancer
2) What is the role of physiotherapist among prostate cancer subjects and
3) How outcome of this research will be helpful for physiotherapists?

Knowing physiotherapy, developing advanced skills are good equally learned on clinical conditions such as obesity, lifestyle related diseases, habits, influence of gender, age, genetic influence, family history, behaviour and nature of pain should be gathered and their relevant clinical implications are to be considered prior to specific physiotherapy evaluations.

As shown in Introduction, Review of Literature prostate cancer is related to obesity, family history, urinary disturbances, low back pain, and pain in the night, radicular symptoms to abdomen, sedentary lifestyle, consumption of alcohol, dairy habits, and male above 40 years. Screening the prostate specific antigen and digital rectal examination are highly recommended above 40 years especially by American Cancer Society. As low back pain manifest among prostate cancer subject, may be due to skeletal metastasis, with known rapid progression.

Being a common clinical condition physiotherapists treat, not only to be familiar with prostate cancer, directing or referring a subject with these history, symptom can rise standard of physio practice and maximise patient care. Practice of manual therapy, short wave diathermy, ultrasound therapy, resisted exercises with undiagnosed prostate cancer subjects with low back pain can prove catastrophically. Hence this critical research upholds higher physio standard.

Among prostate cancer subjects medically treated with chemotherapy, with care as decreased bone mineral density, lower vitamin D3, as part of low back ache due to skeletal metastasis, mechanical low back due to obesity.

4. Key Findings

Heaviness, Stiff joints, Painful low back, low VD3, obesity, physical inactivity, previous history of alcoholism, sedentary lifestyle, both parents having CAD are predisposing and risk factors for PC. Clinical findings with excessive sweating, moderate exercise tolerance, Polyarthralgia with pain radiating to groin, adductor tightness, bilateral hamstring tightness, above all hard, solid, rocky on palpation of spinal muscles with partial relief with every session of exercise as subjective reporting by the patient.

If low back pain continues with radicular symptoms for more than 3 months physiotherapist should refer for physician or to screening for other causes including prostate cancer, ankylosing spondylitis, VD3, osteoporosis, kidney stone, tuberculosis of hip or spine. Deep heat modalities such as Short wave diathermy, Manual therapy should be judiciously applied on these subjects.

Severe forms of resisted exercises again a physiotherapist should wisely use his clinical knowledge, with following guideline can be adhered:

1) Stretching and Strengthening exercises should be careful with low load.

2) Deep heat modalities to be cautiously used.

3) Weight reduction exercises

4) Aerobic exercises, Lifestyle modification.

5) Physical exercises among prostate cancer subjects are not evidenced.

6) Depends on the level of staging in cancer, exercise tolerance to be gradually increased. As fatigue among these subjects are high.

7) Resisted exercises needs to be planned carefully.

8) Gym related activities should be monitored.

9) Manual therapy should adhere to basic guidelines and avoid high thrust techniques.

10) Core Strengthening can be useful for waist reduction, mobilising joints as well strengthening means of lower back, lumbo pelvic region.

11) Incentive Spirometry can be used to improve vital capacity.

As non-availability of Randomised controlled trial (RCT) on the role of physiotherapy among prostate cancer were available findings of this research subject with prostate cancer gets more significant.

5. Executive Summary

Low back pain, a common clinical condition, physiotherapists are involved. Middle aged subject, complaining of Low back ache (LBA), Sacroiliac pain should be asked for screening of PSA and Digital Rectal examination. Family History of prostate cancer, obesity, lifestyle, changes in urine frequency to be recorded and to be investigated and treated by physician/urologist prior to physiotherapy. As prostate cancer, an aggressive in nature low back ache not responding to physiotherapy exercises in few sessions other probable causes should be considered. Deep heat modalities such as short wave diathermy, ultrasound therapy should be judiciously used among young middle aged subjects with undiagnosed pathology in mind. Role of physiotherapy among PC not evidenced but weight reduction exercises, stretching, lifestyle modification are productive. Knowledge of risk factors for PC, Investigations, clinical prognosis, and physiotherapists should be more familiar.

6. Conclusions

When treating low back ache subjects, if pain persists, or inadequate positive results are seen clinically and by functional means, physiotherapist should use their

clinical reasoning skills, discuss with senior therapists, refer from evidences for obvious other causes of low back ache than musculoskeletal. Thereby developing an attitude of scientific practice by referring to concerned medical professional as part of integrated healthcare of patients were not researched here.

Further studies involving larger sample size, more physiotherapy variables and a control group are recommended.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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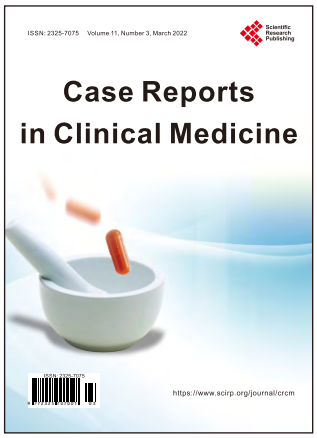

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