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Acute Orbitopathy Manifesting as Periorbital Cellulitis in Sickle Cell Disease

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Abstract

Sickle cell disease is a hemoglobinopathy that results in paroxysmal vascular occlusion and tissue infarction that can manifest in a plurality of tissues. Vasoocclusive crises in sickle cell disease commonly involve bone marrow of the long bones and vertebrae. Involvement of bones with less marrow space, including the bones of the orbit, is reported rarely in the literature and can closely mimic orbital cellulitis, both clinically and radiologically. The present case is a 3 years old boy, a known case of sickle cell disease, who presented with what was thought to be orbital cellulitis and was treated accordingly. Subtle radiologic features of sickle cell orbitopathy were initially overlooked, resulting in an incorrect diagnosis and a treatment delay for the patient. Correctly treated most cases resolve with no adverse effects. This case highlights the importance of maintaining a high index of suspicion in patients with known sickle cell disease, even when the presentation is not classic.

Keywords

Sickle Cell Disease, Orbital Cellulitis, Orbital Infarction, Sickle Cell Orbitopathy

1. Introduction

Sickle cell disease (SCD) is a hemoglobinopathy characterized by chronic hemolytic anemia and vaso-occlusive crises. It is due to a single amino acid mutation on the β chain of hemoglobin. The disorder is inherited in autosomal fashion, and the patients that typically experience clinical manifestations are homozygous for the sickle cell β globin mutation (HbSS) or compound heterozygotes with 1 sickle cell allele and an abnormality in the other allele that disallows adequate transcription of normal β chain. In either case, the relative amount of hemoglobin with sickle mutation (HbS) is enough to allow red blood cells to assume a

sickled shape when the plasma oxygen content or pH decreases. The sickled red blood cells can occlude microcirculation and cause infarction to tissues downstream or vaso-occlusive crisis [1]. The most frequent complications requiring hospital admissions for patients with sickle cell disease are painful vaso-occlusive crises (**Table 1**) [2].

Vaso-occlusive crises affect virtually all patients with sickle cell disease, often beginning in late infancy and recurring throughout life. The pathogenesis of the microvascular occlusion, the hallmark of the painful sickle cell crisis, is complex involving activation and adhesion of leucocytes, platelets and endothelial cells as well as hemoglobin S-containing erythrocytes. While this process can occur in virtually any organ, it is particularly common in the bone marrow, resulting in bone marrow infarction typically in the medullary cavity or epiphyses. The reasons for the vulnerability of the bone marrow to microvascular occlusion are unclear but may be partly because of marrow hypercellularity leading to impaired blood flow and regional hypoxia. Clinically, patients complain of intense pain localized to one or more areas of their skeleton. This may be accompanied by localized tenderness, swelling and erythema over the site of infarction; fever and leukocytosis are also common. Most patients recover from vaso-occlusive crises with no further complications. However, when marrow infarction involves the epiphyses, this may give rise to joint effusions that are clinically similar to septic arthritis [2]. Involvement of the orbital bones in an acute vaso-occlusive crisis is an uncommon manifestation but has been reported in various case reports [3] (**Figure 1**).

There can often be great difficulty in differentiating orbital bone infarction from osteomyelitis/orbital cellulitis clinically as well as radiologically, which was the case with our patient. Orbital infarction usually presents with acute onset of periorbital tenderness, swelling, erythema, and pain to the orbit. Soft tissue swelling of the orbit can result in proptosis and attenuation of extraocular movements [4] [5].

Expedient diagnosis of sickle cell orbital infarction is crucial to avoid potentially irreversible visual loss through an orbital compartment syndrome. Although CT is readily accessible in an acute setting, the changes shown may be subtle and misinterpreted leading to an incorrect diagnosis and treatment plan. Magnetic resonance imaging is thought to be superior to CT (often not available acutely, however) as it can show bone marrow infarction, which helps confirm the diagnosis of sickle cell orbitopathy [2] [3] (**Figure 2**).

Table1. Acute bone problems in sickle cell disease.

- Painful (vaso-occlusive) crisis
- Osteomyelitis
- Stress fracture
- Orbital compression
- Dental complications
- Vertebral collapse
- Bone marrow necrosis

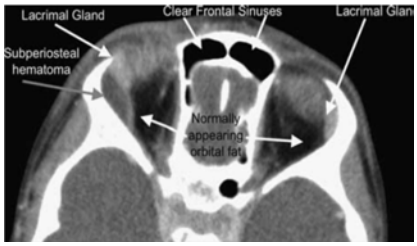

Figure 1. Axial computed tomographic soft tissue windows showing the subperiosteal hematoma, located on the lateral wall. This is an unusual location for a subperiosteal abscess. The adjacent orbital fat is not inflamed, and the frontal sinuses are clear. The right lacrimal gland has been displaced anteriorly.

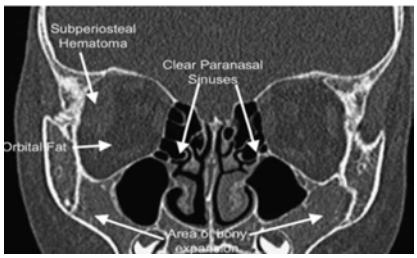

Figure 2. Coronal computed tomographic bony windows showing clear paranasal sinuses. The abnormal bony expansion of the maxillary bones is clearly seen. The marrow cavities are a similar density to orbital fat, indicating abnormally active bone marrow. These bony findings are typically seen in children with sickle cell. The subperiosteal hematoma is difficult to appreciate when the bony windows are examined.

Authors are herewith presenting such a case of orbital bone infarction and osteomyelitis in a 3-year-old boy with sickle cell disease, managed successfully with blood transfusion and intravenous antibiotics only, without steroid or surgical intervention.

2. Case Presentation

In October 2019, a 4-year and 7-months old Saudi boy known with homozygous sickle cell disease, presented at King Fahd Armed Forces Hospital after 2 days of progressive swelling of his upper and lower eyelids. He had no pain or mucopurulent discharge. Vision remained unchanged. He had no systemic symptoms, such as fever, rash, fatigue, or weight loss. Parents denied recent history of infection, chalazion, bug bite, or ocular or head trauma. Parents acknowledged a similar presentation in his left eye in July 2018, and he was diagnosed with bilateral preseptal collections by Computed Tomography (CT). He was treated with a blood transfusion, and eye symptoms resolved after 2 weeks. He had a history of multiple food allergies to (Wheat, Soya, and Eggs), that was confirmed using a radioallergosorbent (RAST) test, in-addition to Cow-milk-protein allergy. He had laparoscopic cholecystectomy (in 2017) and multiple times of hospitalization for vaso-occlusive pain crises in the head, chest, abdomen, and hip. Multiple

emergency room visits for left supracondylar fracture and right proximal humerus fracture. He was taking folate daily to maximize hematopoiesis and penicillin to prevent encapsulated bacteria.

On examination, his visual acuity was 20/30 OD and 20/25 OS. His external exam revealed mild proptosis OD and prominent right upper and lower eyelid swelling without erythema extending to the right cheek. He could not open his right eye without manual manipulation. He had no pulsation, tenderness, nodularity, or induration upon palpation. His left eye was normal. His pupils measured 4 mm in the dark and 2 mm in the light OU with no relative afferent papillary defect. His motility exam was full, and he was orthophoric. His intraocular pressures were normal. Anterior segment exam was normal. Ophthalmoscopy revealed normal discs, macula, and vessels OU. Cup-to-disc ratio was within normal. The patient was admitted given his complicated sickle cell history, high risk for infection, and concerning his previous similar orbital manifestations.

His complete blood count showed elevated white blood cells (17.3), reticulocytosis (17%), neutrophilia (88%), and thrombocytosis (388). His hemoglobin and hematocrit were low (8.4 and 28 respectively). Abnormal red blood cell morphology was noted on the peripheral smear, including sickled red blood cells. Computed tomography scan of the orbits and sinuses were performed two days following his admission and revealed a 1.5 cm × 0.5 cm × 1.6 cm thin rim-enhancing fluid collection in the inferiolateral aspect of the extraconal space (right orbit), without evidence of periosteal reaction. Also, about 1.7 cm × 0.6 cm × 1.7 cm thin rim-enhancing fluid collection in the inferiolateral aspect of the extraconal space (left orbit). No evidence of thrombosis in the vessels, sinuses, or lacrimal gland in both sides. No evidence of intracranial extension. Preserved and symmetrical appearance of the recti muscles. Unremarkable appearance of both globes (**Figure 3**).

Based on the fluid collection with rim enhancement on computed tomography (CT), he was diagnosed with orbital cellulitis with subperiosteal effusion, which can occur secondary to an orbital wall infarction in SCD. Despite being treated with broad spectrum intravenous antibiotics (ceftriaxone and vancomycin) for 72 hours, the periorbital edema was progressing, the patient continued to have intermittent spikes of fever, and his inflammatory markers were rising. On-top of his orbital presentation, the patient developed Acute Chest Syndrome by his fourth day of admission, which was complicated with left-side pleural effusion. Considering the clinical status of the patient, he was shifted to the Pediatric intensive care unit for close monitoring, and an urgent Manual Exchange Transfusion was performed. Two days after starting him on triple-antibiotics-regimen (Vancomycin, Metronidazole, and Ceftriaxone), the patient showed clinical improvement and decline in his inflammatory markers. An MRI of the orbits revealed bilateral orbital bone osteolytic changes with soft tissue accommodation of fluid, suggestive of orbital wall osteomyelitis (**Figure 4**). However, the child showed significant improvement in upcoming days with decrease in swelling

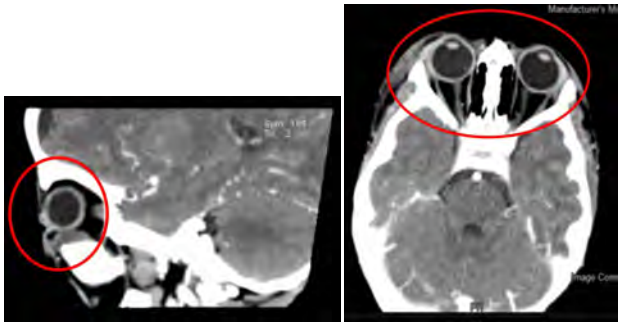

Figure 3. Computed tomography scan of the orbits and sinuses. The red circle points to a 1.5 cm × 0.5 cm × 1.6 cm thin rim-enhancing fluid collection in the inferiolateral aspect of the extraconal space (right orbit), and about 1.7 cm × 0.6 cm × 1.7 cm thin rim-enhancing fluid collection in the inferiolateral aspect of the extraconal space (left orbit).

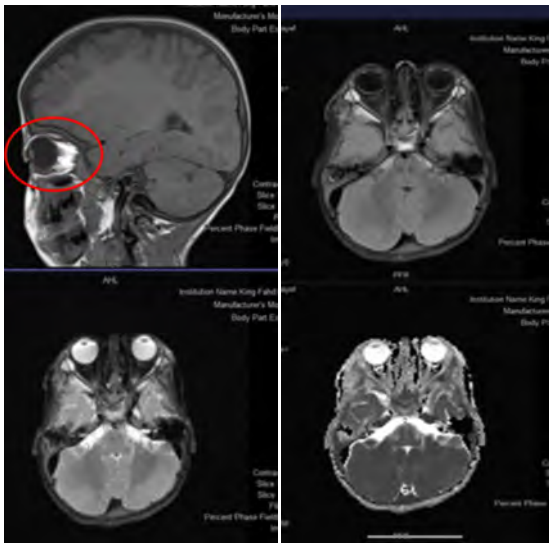

Figure 4. An MRI of the orbits revealed bilateral orbital bone osteolytic changes with soft tissue accommodation of fluid (red circle), suggestive of orbital wall osteomyelitis.

and erythema of eyelids, and improvement in eye opening. So, further imaging, surgical intervention or steroid was deferred. He was discharged after completing 21 days course of IV antibiotics with normal vision and no residual eyelid swelling. He was advised to continue on oral antibiotics for another three weeks, while being seen at the outpatient clinics weekly.

3. Discussion

Facial bone involvement is rare in SCD patients, and mainly seen in pediatric patients, who have a greater marrow space compared to older individuals. Bilateral orbital involvement is reported in 42% of cases of SCD with orbital infarction [6]. Patients with SCD are relatively immunocompromised and therefore more susceptible to infections. Orbital imaging and correct interpretation in SCD patients presenting with orbital swelling is paramount for differentiation

between hematoma and infection. Most of these cases, if timely diagnosed, can be managed successfully with exchange transfusion. A subperiosteal orbital hematoma (SOH) can be managed with supportive corticosteroid therapy, which is contraindicated with infection. Surgical decompression is indicated when SOH is associated by impaired ocular movement and deteriorating vision, termed orbital compression syndrome. Infection needs to be tackled with aggressive antibiotic treatment, and abscess may require drainage. Among the causes in the differential diagnosis of periorbital edema, the etiological factors that can be taken into consideration as causes of periorbital swelling in patients with sickle cell anemia are cavernous sinus thrombosis and periorbital bone infarctions. Normal results of fundus examination with no signs of papilledema may exclude the diagnosis of cavernous sinus thrombosis. The diagnosis of bone infarction is made by demonstration of activity-deficient area appearing in the infarcted regions by technetium Tc 99m medronate bone scintigraphy. Diagnosis of osteomyelitis is made by demonstration of hyperactive areas on technetium Tc 99m medronate and gallium citrate Ga 67 bone scans. Orbital cellulitis will show diffuse infiltration of orbital and/or periorbital tissue with enhancement. Periosteal abscesses will present as a hypodense biconcave mass with peripheral enhancement, in which gas inclusions can be present. Periosteal abscesses are often associated with sinusitis. Differentiation between facial bone infarction and osteomyelitis is a diagnostic challenge. Both can present with bone oedema, soft tissue enhancement, and collections. When cortical defects are present diagnosis of osteomyelitis is more likely.

4. Conclusion

This case report highlights the importance of maintaining a high index of suspicion in patients with known sickle cell disease presenting with pain, orbital swelling and restriction of ocular movement. Red blood cell transfusion immediately on clinical suspicion only may be sufficient for uneventful recovery, without steroids or surgical intervention. Expedient diagnosis of orbital bone infarction and orbital compression syndrome in children with sickle cell disease is crucial because this is a potentially sight-threatening entity.

Consent

An informed consent was obtained from patient's family to report the case.

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Conflicts of Interest

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

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Do Antineoplastic Drugs Play an Additional Role in the Progression of Non-Compaction Cardiomyopathy? A Case Report

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Abstract

Non-compaction cardiomyopathy is a rare form of cardiomyopathy; its most common clinical manifestations are heart failure (HF), ventricular arrhythmia, thromboembolism, and sudden cardiac death. We report a rare case of a 63-year-old man with chest tightness, worsening lower leg edema, dyspnea, and decreased exercise tolerance. He had a medical history of gastric cancer treated with subtotal gastrectomy and post-operative chemotherapy with paclitaxel and fluorouracil three years ago. At that time, he was diagnosed with non-compaction cardiomyopathy, and the thickened and reticulated trabecular muscle was exclusively confined to left ventricular apex. Five months ago, he was admitted to our hospital with heart failure and treated for dilated cardiomyopathy, echocardiography revealed severe trabecular noncompact myocardium in both ventricles, which was confirmed by cardiac magnetic resonance imaging (CMR). It is generally accepted that non-compacted myocardium forms in the early embryonic stage, which raises a question in our case whether acquired factors, such as antineoplastic drugs, potentially accelerate the pathological progression of non-compaction cardiomyopathy. Considering there are disparities between current screening tools such as echocardiography and CMR regarding diagnostic criteria, multi-detector CT may be an alternative examination method that could provide a new perspective for diagnosis.

Keywords

Non-Compaction Cardiomyopathy, Antineoplastic Drugs, Heart Failure, Diagnosis

1. Introduction

Non-compaction cardiomyopathy is a congenital cardiomyopathy characterized

by a distinctive ("spongy") morphological appearance of the ventricular myocardium. Non-compaction predominantly involves the distal (apical) portion of the left ventricle (LV) with deep intertrabecular recesses (sinusoids) in communication with the ventricular cavity, resulting from an arrest in normal embryogenesis [1]. Feldt *et al.* first described non-compaction of the ventricular myocardium on autopsy in 1969 [2]. The gross anatomical appearance is characterized by numerous, excessively prominent trabeculations and deep intertrabecular recesses [3]. Non-compaction cardiomyopathy can be familial. In one study, 6 of 34 patients (18%) had a family history of left ventricular non-compaction (LVNC) [4]. The most common clinical manifestations are heart failure (HF), ventricular arrhythmia, thromboembolism, and sudden cardiac death. The condition is diagnosed by two-dimensional echocardiography or magnetic resonance imaging [5]. We report a rare case of a patient who was admitted to our hospital with clinical symptoms of HF and a history of gastric cancer treated with subtotal gastrectomy and post-operative chemotherapy with paclitaxel and fluorouracil. After further examination, he was diagnosed with biventricular non-compaction cardiomyopathy with biventricular thrombosis.

2. Case Presentation

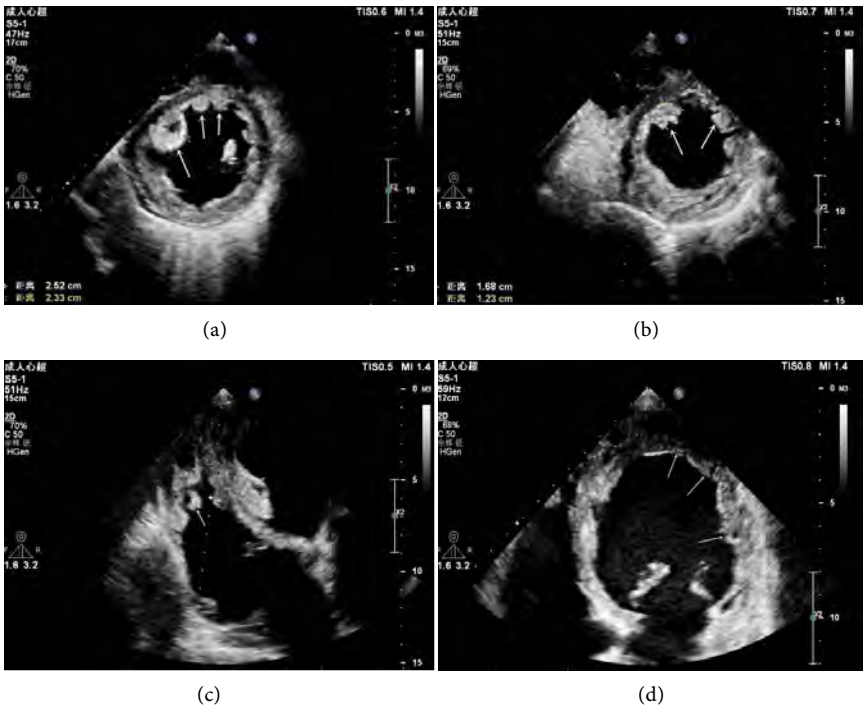
A 63-year-old man was admitted to the hospital with chest tightness, worsening lower leg edema, dyspnea, and decreased exercise tolerance. The patient complained that he had these symptoms for 1 year and was getting worse, during which there was no regular treatment. He had no family history of sudden cardiac death, and he denied any history of drinking or smoking. The patient had gastric cancer treated with subtotal gastrectomy and a month-interval of post-operative chemotherapy with 4 cycles of paclitaxel (150 mg on day 1) and fluorouracil (50 mg on day 1 - 14) 3 years ago. Echocardiography before the surgery suggested the left ventricular apical trabecular muscle became thickened and reticulated but cardiac function was normal, but he did not take it seriously and refused to do further cardiac examination and treatment. Five months ago, he was admitted to our hospital with dyspnea and abdominal distension. According to his medical records at our hospital, physical examination showed a remarkable systolic murmur of grade 4/6 over the left second intercostal area without radiation to the carotids and a pansystolic murmur of grade 3/6 at the apex without radiation, as well as jugular venous distention. The chest examination revealed decreased thorax movement, vocal tremor, and a decrease in breath sounds bilaterally. The 12-lead electrocardiogram showed sinus rhythm with 2nd degree type 1 atrioventricular block. The echocardiogram revealed whole heart enlargement and systolic dysfunction characterized by a left ventricular ejection fraction (LVEF) as low as 26%, but his sonographer did not notice the presence of trabeculae in the ventricular myocardium. Moreover, the results of the coronary computed tomographic angiography (CTA) were normal. Thus, the patient was initially diagnosed as dilated cardiomyopathy (DCM) and benefited from the treatment.

Despite standard treatment for DCM, he was admitted again to our hospital with worsening symptoms of heart failure (HF). The echocardiogram revealed that an enlarged heart with mitral and aortic valve insufficiency, severe systolic dysfunction characterized by an left ventricular ejection fraction (LVEF) as low as 23%, restrictive diastolic dysfunction, including peak E (early diastolic)/A (late diastolic) velocity > 1.5, shortened deceleration time of the E-wave, and slightly hyperechoic masses in the left and right ventricular chambers, the biggest of which measured 2.52 × 2.33 cm (**Figure 1(a)**). The 12-lead electrocardiogram showed non-persistent ventricular tachycardia and 2nd degree type 1 atrioventricular block. The D-dimer and tumor biomarkers were normal. The patient's medical history, symptoms, and examination (especially the presence of biventricular mobile masses) were strongly suggestive of thrombus. As the patient was willing to undergo repeated blood tests for anticoagulant treatment and undertake bleeding risks, we tentatively used warfarin at alternate dosages of 1.875 mg/day and 1.25 mg/day, aiming for an international normalized ratio (INR) level of 2.0 - 3.0. Echocardiographic reexaminations 2 days later showed that the volume of the masses in the left and right ventricular cavities decreased significantly, which confirmed that the mobile masses were thrombi (**Figure 1(b)** and **Figure 1(c)**). Considering the thrombus could mobilize at any time, we continued to use warfarin for anticoagulation, administered diuretics, and administered the calcium sensitizer, levosimendan at dosage of 12.5 mg, to improve cardiac function. After 6 days of comprehensive treatment, the patient's condition improved significantly.

To further clarify the thrombus situation, echocardiography was performed again, the results of which revealed that the area of left ventricular thrombus significantly decreased and the right ventricular thrombus disappeared. Furthermore, we found a severely thin myocardial wall and the appearance of prominent trabeculations in the left ventricle (**Figure 1(d)**). Two-dimensional CMR in the axial and sagittal planes showed highly trabeculated non-compacted myocardium involving the apical and lateral segments and a thin compact epicardial layer with massive thrombus formation between the trabeculae; the ratio of the thickness of the non-compact to compact myocardium was 3.7, more than 2.3 (**Figure 2(a)** and **Figure 2(b)**). According to the results of the echocardiography and CMR, the patient was diagnosed with non-compaction cardiomyopathy. Since there are no proposed guidelines for the management of patients with LVNC and the patient have evidence of severe LV dysfunction, the therapeutic treatment for this patient was basically limited to pharmacotherapy for heart failure and thrombosis.

In view of the above results, we believed that the patient received a clinical misdiagnosis five months ago. Moreover, we found that a large amount of non-compacted myocardium were present in the ventricular wall, mainly in the left ventricular wall, and a large number of thrombus were present in the ventricular cavity when we conducted multiplanar reformation based on the results of the coronary CTA performed five months ago (**Figure 3(a)** and **Figure 3(b)**).

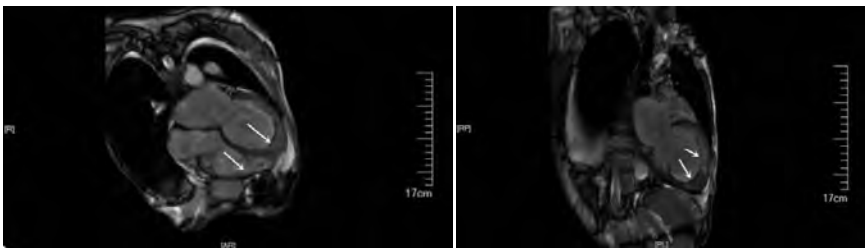
Non-compaction cardiomyopathy is a genetically heterogenous disorder, with both X-linked as well as autosomal dominant inheritance. Because of the potential genetic influence, we performed a series of examinations for the patient's 38- and 31-year-old daughters; neither showed signs of heart failure and the electrocardiogram was normal. In order to clarify the situation of their hearts, transthoracic echocardiography was performed, the results of both revealed a thickened and reticulated left ventricular apical trabecular muscle (Figure 4(a) and Figure 4(b)). Sadly, the two daughters refused further CMR.



(a) (b)

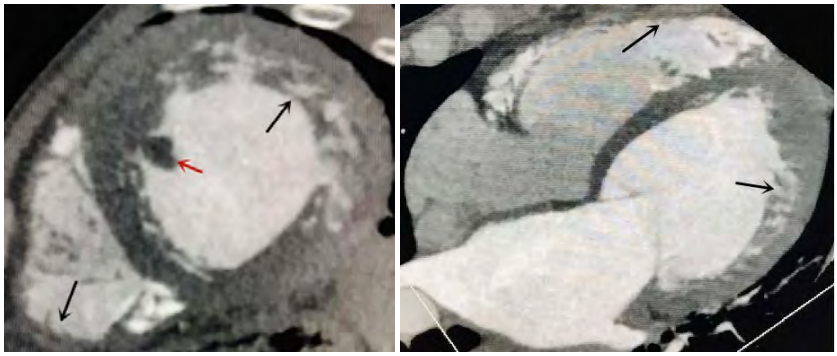
(c) (d)

Figure 1. Transthoracic echocardiography demonstrated massive thrombus formation (arrow) within left ventricular cavity (a), significantly reduced thrombotic masses after two days of anticoagulation therapy in left and right ventricular cavity (b and c), and delayed revealed severe non-compacted myocardium with excessive trabeculae and deep recesses after six days of anticoagulation therapy (d).



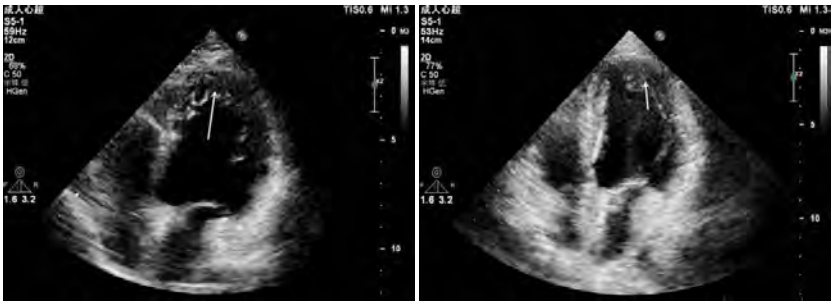
(a) (b)

Figure 2. Cardiac four chamber cine MRI image demonstrated a thick non compact endocardial layer with excessive trabeculae and deep recesses (arrow) in the apical and lateral segments (a); Two chambers view showed a non-compacted hypertrabeculated spongy layer (arrows) was identified, with a ratio greater than 2.3:1 of the compacted layer at the end of diastole (b).



(a) (b)

Figure 3. Retrospective coronary computed tomography angiography showed massive thrombus formation (red arrow) and non-compacted myocardium (black arrows) in left ventricle (a); Numerous prominent trabeculations and deep intertrabecular recesses (arrows) in left and right ventricle (b).



(a) (b)

Figure 4. Echocardiography of the patient's 38- and 31-year-old daughters demonstrated a thickened and reticulated trabecular muscle (arrows) in the apex of left ventricle (a and b).

The patient recovered and was discharged seven days later on the following medications: angiotensin-converting enzyme inhibitor, coenzyme Q10, furosemide, spironolactone, betabloc, and warfarin. Yet, after repeated admitted to the heart failure unit for aggravating heart failure, he passed away four months later.

3. Discussion

Non-compaction cardiomyopathy is a rare form of cardiomyopathy characterised by spongy hypertrabeculation of the ventricular myocardium resulting from failure or arrested compaction of the myocardium in utero, with uncertain etiology and mechanism but is generally considered autosomal dominant inheritance. However, it can also be sporadic [6]. Although LVNC mainly affects the left ventricle, isolated right ventricular and biventricular non-compaction may also occur. In the early embryo, the heart is a loose, interwoven mesh of muscle fibers. The developing myocardium gradually condenses, and the large spaces within the trabecular meshwork disappear, resulting in condensing and compaction of the ventricular myocardium and solidification of the endocardial surfaces [7]. These changes mainly occur between 5 and 8 weeks of embryonic life, pro-

ceeding from the epicardium to endocardium and from the base of the heart to the apex [8]. But recently, it has been proposed that acquired triggers are associated with the formation of non-compacted myocardium. A case report published in 2019 indicated that LVNC could be a myocardial response to acquired triggers, such as drug toxicity, rather than a primary cardiomyopathy [9].

In this perspective, our case raises a relevant hypothesis that the application of paclitaxel and fluorouracil potentially exacerbated deterioration of cardiac intrinsic anomaly structure formation in a patient with non-compaction cardiomyopathy. Therefore, the role of antineoplastic drugs play in progression of non-compaction cardiomyopathy may suggest more considerable treatment protocols applied in those patient, which provides a new idea in future prognostic improvement.

Our patient had heart failure since he received post-operative chemotherapy with paclitaxel and fluorouracil. Fluorouracil-related cardiotoxicity is incompletely understood and may be related to coronary thrombosis, arterial inflammation, spasm or contraction, and direct damage to the myocardium [10]. Cardiac toxic effects from paclitaxel associated with hypotension and myocardial damage, manifesting as grade 3 or 4 left ventricular end systolic diameter (LVSD) or asymptomatic LVEF decline, was low [11]. In addition, fluorouracil and paclitaxel related cardiotoxicity are mostly reversible after drug withdrawal. However, their effect on the trabeculae of the myocardium remains unclear and requires further investigation. In our case, considering the patient received no cardiotoxic drugs or other cardiac risk factors after chemotherapy, his fundamental myocardial disease may be more susceptible to the rapid increase of non-compacted myocardium caused by fluorouracil and paclitaxel related cardiotoxicity. Our patient's non-compacted myocardium occurred in the left and right ventricles, especially in the apex and lateral walls of left ventricle. Combined with the echocardiographic results performed 3 years ago, these facts strongly suggest that antineoplastic drugs may cause the deterioration of cardiac functions of non-compaction cardiomyopathy by promoting trabecular formation in the myocardium. More clinical evidence is required to clarify whether the effect of antineoplastic drugs on the myocardium of patients with non-compaction cardiomyopathy is an accidental case or a common phenomenon.

Traditionally, diagnosis is heavily reliant on advanced imaging with echocardiography or CMR. As the first-line tool for diagnosing non-compaction cardiomyopathy, echocardiography is low-cost, convenient, non-invasive, and has high sensitivity to monitor and evaluate the status of blood flow in the ventricular cavity in real time. The most commonly used echocardiographic standard was proposed by Jenni *et al.* [12]. Compared with echocardiography, CMR is a more accurate means of characterizing non-compacted myocardial tissue. The diagnostic criterion for CMR is end-diastolic non-compression/compression > ratio 2.3. CMR is not only the most accurate method for diagnosing non-compaction cardiomyopathy, it can also predict the prognosis of these patients, and identify myocardial fibrosis using advanced gadolinium enhancement (LGE) technology [5]. In our

case, the structure of the non-compaction of the ventricular myocardium did not appear in the initial echocardiography, which may result from not only the presence of a large number of biventricular thrombus affecting the imaging of the biventricular wall, but also from poor image quality and operator inexperience. Similarly, significant reduction of intracardiac thrombi may have ultimately revealed biventricular trabeculae on the subsequent echocardiograph. Therefore, uncertainties in ultrasonic evaluations may lead to delays in non-compaction cardiomyopathy diagnoses. We are attempting to draw lessons from the identification of multitudinous myocardium by imagological examination. Although non-compaction cardiomyopathy has symptoms similar to DCM, we should make full use of imaging to identify cardiac structural and functional changes to differentiate between DCM and non-compaction cardiomyopathy. To explore the type of cardiomyopathy, we usually use echocardiography and computed tomography in medical practice. Notably, visualization of the left ventricular apex and right ventricle can be limited on echocardiography; for example, apical hypertrophic cardiomyopathy may not be identified [13]. Instead, evidence of ventricular dilatation, increased wall thickness, or subclinical myocardial infarction may be observed on multiplanar reformation (MPR) of coronary CTA. In general, hospitals, especially for those not eligible for MRI and echocardiographic results, cannot adapt to clinical demand. For these patients, we may be able to take a more convenient approach—multi-detector CT (MDCT).

There are no specific treatment guidelines for this type of cardiomyopathy, and no evidence that patients with non-compaction cardiomyopathy have different outcomes and should be treated differently from HF patients [14]. Notably, prevention from thromboembolic events is an important management goal for non-compaction cardiomyopathy. However, limited evidence exists to determine the correct course of antithrombotic medication options partly due to the low prevalence LVNC. Anticoagulation is generally recommended for those presenting with ventricular systolic dysfunction, antecedent systemic embolism, cardiac thrombus, and atrial fibrillation [15]. In our case, the patient was treated with warfarin instead of new oral anticoagulants (NOACs) and showed no significant biventricular thrombus during the two follow-ups after discharge. However, there is still insufficient evidence to support the efficacy of the new oral anticoagulant over vitamin K antagonists in patients with non-compaction cardiomyopathy combined with thrombus. It is obvious that further studies should address a comprehensive anticoagulation strategy for a reduced risk of bleeding, thromboembolic events, and mortality in this patient population.

4. Limitations

There are some limitations in our case report. We have not performed genetic testing for patients before and after taking antineoplastic drugs, nor have we investigated the mechanism by which antineoplastic drugs aggravate cardiac functional insufficiency, so we cannot pinpoint the specific role antineoplastic drugs

played in the process of trabecular formation in patients with non-compaction cardiomyopathy from a pathological perspective. In addition, we failed to do genetic testing for the patient's daughters, so we could not analyze the genotype of non-compaction cardiomyopathy among those family members.

5. Conclusion

Our case report presents a patient with primary non-compaction cardiomyopathy showed a rapid deterioration of cardiac function combined with a thin myocardial wall, prominent biventricular trabeculations, and thrombogenesis following treatment with antineoplastic drugs, which indicates that antineoplastic drugs may potentially accelerate the progression of non-compaction of the ventricular myocardium. In addition, we discuss the process of diagnosis and identification of cardiomyopathy and propose multi-detector CT, as an alternative imagological examination, may provide us a new perspective to diagnose non-compaction cardiomyopathy. However, more studies are required to clarify the pathogeny of non-compaction cardiomyopathy.

Ethics Approval and Consent to Participate

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Authors' Contributions

Dr. Gang Tian: diagnosed the case and instructed the patient's treatment. Mr. Chaodi Luo and Dr. Yanjie Yang: collected the primary data and drafted the initial manuscript. Dr. Chun Yang: Helped process echocardiographic images. Dr. Xiang Hao and Ms. Zhenzhen Duan: assisted with the treatment of the patient. Dr. Guoliang Li: Assisted with the analyzation of the case characteristics and gave writing suggestions. All authors contributed to discussions and critically appraised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare that they have no competing interests.

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List of Abbreviations

CMR	Cardiac magnetic resonance imaging
CT	Computed tomography
CTA	Computed tomographic angiography
DCM	Dilated cardiomyopathy
HF	Heart failure
INR	International normalized ratio
LGE	Gadolinium enhancement
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVNC	Left ventricular non-compaction
LVSD	Left ventricular end systolic diameter
MDCT	Multi-detector computed tomography
MPR	Multiplanar reformation
NOACs	New oral anticoagulants

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Successful Management of Wound Dehiscence after Total Knee Arthroplasty by Topically Using Recombinant Basic Fibroblast Growth Factor

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Abstract

Wound complications are estimated to be affected in about 9% of TKA patients, which may increase the risk of deep periprosthetic infection and results in re-operation, joint fusion, or amputation. Here we have reported a female patient who suffered wound rupture due to early post-operation mobilization and weight-bearing. The wound dehiscence was successfully managed by applying recombinant basic fibroblast growth factor-2 and anti-infective treatment without removing prosthetic joint.

Keywords

Wound Dehiscence, Total Knee Arthroplasty, Recombinant Basic Fibroblast Growth Factor

1. Introduction

Early weight bearing is a high risk for wound rupture post-orthopedic surgery, especially after the lower extremity surgery. Here, we have reported a 66-year old female patient who was diagnosed as osteoarthritis for the right knee and has developed a total knee arthroplasty. She has also suffered wound rupture due to early post-operation mobilization and weight bearing. The wound dehiscence can be successfully managed by applying recombinant basic fibroblast growth factor-2 and anti-infective treatment without removing prosthetic joint. The work has been reported in line with the SCARE criteria [1].

2. Presentation of Case

Our case was reviewed and approved by Review Board of our institute. A

66-year-old Chinese female presented with a progressive pain on right knee for 2 years, which aggravated after 2 weeks and have shown difficulty in walking. The pain was localized to the right knee with limited range of motion at the knee joint. The patient did not show any other health related symptoms. The physical examination revealed significant effusion, moderate swelling of right knee, and a normal but painful range of motion and instability in both knees. Plain radiographs of the knees displayed severe degenerative changes with narrowing of the joint spaces in her right knee (**Figure 1(a)**, **Figure 1(b)**). Total knee anthropology was performed in right knee. A posterior stabilizer prosthesis was also implanted. There were no intraoperative complications and the alignment as well as stability of the prosthesis was satisfactory.

On postoperative day 19, the surgical wound on the right knee was partially dehiscence (**Figure 2(a)**) due to early weight bearing and passive maximum flexion for 80˚ of the knee joint. Under sterile technique, the wound was attended by debridement and followed by irrigation. During this process, we have taken discharges for examination multiple times. The first cultured results showed *Enterococcus faecium* whereas other secretions cultured of wound were negative. The patient did not show any symptoms or signs of active infection or loosening of the prosthesis three days post procedure. The laboratory data for white blood cell (WBC) count and a CRP level were normal. The antibiotics were given for 2 weeks based on drug sensitivity results. The implanted prosthesis was not removed based on the appearance of the wound and weak inflammatory response in a blood examination. The wound was re-sutured on postoperative day 22 and again on day 25 (**Figure 2(b)**). Even the debridement and dressing were performed every day, the healing of subcutaneous tissue and skin was poor. To promote wound healing, the patient was prescribed to use recombinant human basic fibroblast growth factor (bFGF) solution (SHUANGLU Pharmaceutical, Beijing, China) in wet dressing every other day following sterilizing the wound. On postoperative day 28, healthy granulation tissue was seen in the subcutaneous layer (**Figure 2(c)**). The patient continued dressing and the administration with rh-bFGF which resulted in gradual improvement in healing of skin. The wound completely closed on postoperative day 57 (**Figure 2(d)**). The latest follow up visit, 1.5 years postoperatively, has shown that patient had no infection, or instability of the prosthesis in her knee and her range of motion is 0˚ - 100˚.

3. Discussion

Wound complications are estimated to be affected in about 9% of TKA patients, which may increase the risk of a deep periprosthetic infection and results in re-operation, joint fusion, or amputation [2]. About 71% of patients subsequently diagnosed with prosthetic joint infection had preceding superficial wound complications [3]. Surgical wound dehiscence significantly impacts on mortality and morbidity rates post-operation that results in prolonged hospital

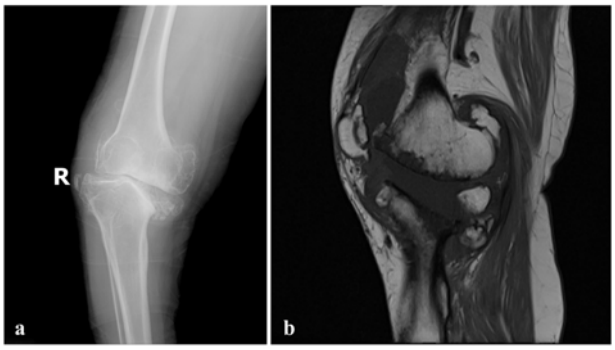

Figure 1. Anteroposterior radiographs and magnetic resonance imaging scans of the patient. Radiograph shows degenerative change and osteophytes in the left knee joint (a) and narrowing the joint space and severe joint destruction (b).

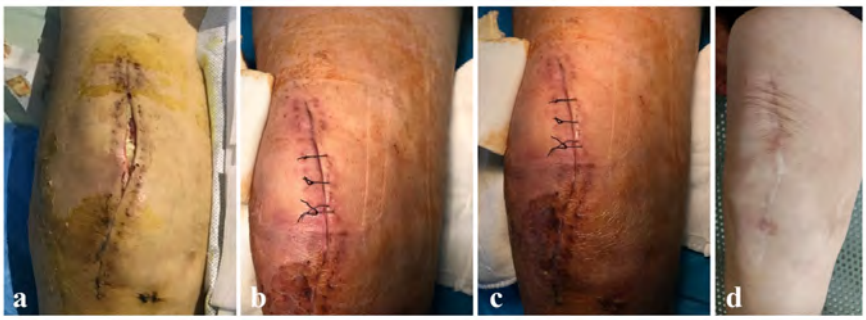

Figure 2. Photographs of the surgical wound at the right knee on postoperative day (POD)-19 (a), POD-25 (b), POD-28 (c), and POD-57 (d).

stays. Rheumatoid arthritis, diabetes mellitus, impertinently joint motion and early weight bearing could be a risk factor for wound dehiscence in TKA [4]. In our study, patient suffered wound dehiscent for trying to walk or for trying to perform passive flexion without any assistant before the superficial wound healing. Furthermore, her body weight was 61 kg and BMI 26.4 kg/cm^2, which indicated over-weight. Another risk factor in our case study was the wound dehiscent had happened outside the ward that had large possibility of wound infection. Therefore, we had chosen a conservative method through debridement and dressing to avoid closed wound infection. Delayed sutured could be performed when infection excluded preliminary.

Wound healing is a complex, evolutionarily conserved, multi-cellular process [5]. FGF-2 or bFGF have been shown to be integral in cutaneous wound healing, specifically stimulates the growth of normal human epidermal keratinocytes and fibroblast. bFGF could regulate the synthesis and deposition of various extracellular matrix components, also promote keratinocyte motility during the process of re-epithelialization, stimulates the migration of fibroblasts and induce them to produce collagenase in vitro [6]. Currently, recombinant human or bovine basic FGF has been widely used in chronic wound treatment resulted in an improvement in incisional wound healing by an increase in breaking strength, collagen content, and epidermal thickness [7].

4. Conclusion

This is the first case report using bFGF for TKA surgical wound dehiscence. Our therapeutic regimens of rh-bFGF treatment for wound dehiscent started in early stage after determining the opened wound had no infection and instability of the prosthesis. Wound healing was completed at 21 days for the rh-bFGF treated compared to traditional method of debridement. The healing of surgical wound was previously shown to be accelerated by bFGF. In addition, the application of rh-bFGF to superficial wound dehiscence in TKA patients is considered to be reasonable and has the potential to become a promising strategy. Furthermore, it is economically affordable method which will reduce the infection rates and will result in shorter hospital stay.

Conflicts of Interest

The authors declared that they have no conflicts of interest to this work.

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Bariatric Surgery Impact on Sickle Cell Disease Pain Crisis: A Case Report

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Abstract

Sickle cell disease (SCD) is an autosomal genetic blood disorder resulting in multiple end-organ complications. Malnutrition is a stress factor that can cause a SCD crisis. Bariatric surgery is a weight reduction surgery that involves the binding or removing a part of the stomach or resecting and re-routing the small intestine to a small stomach pouch. It is known to cause malnutrition and stress. Malnutrition affects more than two billion people of all ages worldwide due to different causes. Long-term deficiency of micronutrients leads to reduced immunity, leukopenia, and diseases affecting the psychological, skeletal, and central nervous system. We here present the case of a 20-year-old woman with SCD and class III obesity. She underwent sleeve gastrectomy in 2018 following psychological distress caused by being severely overweight. She had mild SCD pain, but after the bariatric surgery, it became severe, requiring morphine treatment and monthly exchange transfusion beside the NSAID which become not much effective as before bariatric surgery. Our findings show that bariatric surgery, which leads to a stressful condition, can aggravate the SCD pain crisis, thereby highlighting the need for alternative methods of weight reduction in these patients. Controlled studies are required for the proper assessment of bariatric surgery in SCD.

Keywords

Sickle Cell Disease, Bariatric Surgery, Pain Crisis

1. Introduction

Sickle cell disease (SCD) is an autosomal genetic blood disorder leading to severe anemia and impaired tissue perfusion, resulting in multiple end-organ compli-

cations. Pain is the most common complication of SCD. Some SCD patients have mild to moderate pain, while others have severe vaso-occlusive complications, which lead to a pain crisis. Poor hydration increases blood viscosity. Even mild dehydration can have a significant impact on hemoglobin concentration [1]. Stress factors that affect the SCD pain crisis are fever, loss of fluids due to excessive sweating, vomiting, diarrhea, malnutrition, high temperature, and humidity. The renal complications in SCD can impact the urine concentration resulting in higher urine loss and dehydration due to tubular damage [2].

Bariatric surgery (BS) is a weight reduction surgery that involves binding or removing part of the stomach or resecting and re-routing the small intestine to a stomach pouch. The United States National Institutes of Health recommends BS for individuals with a body mass index (BMI) ≥ 40 and those with a BMI of ≥35 with comorbidities such as diabetes and other obesity-related severe disorders [3]. All forms of BS reduce food intake and the quality of micronutrients absorption. Following BS, appropriate incorporation of vitamins and minerals can help maintain normal metabolic functions, energy production, hormone synthesis, and decrease the risk of nutrient-related health problems [4]. In bodyweight calculations, a BMI of <18.5 falls within the underweight range, between 18.5 and <25 is the normal range, between 25.0 and <30 is the overweight range, and <30.0 falls within the obese range. Obesity is frequently subdivided into categories: Class 1: BMI of 30 to <35, Class 2: BMI of 35 to <40, Class 3: BMI of 40 or higher. Class 3 obesity is sometimes categorized as "extreme" or "severe" obesity [5].

Micronutrient deficiencies cause several diseases while exacerbating many others and affect more than two billion people of all ages. It is associated with 10% of all deaths in children and child welfare. Lack of one or several micronutrients is caused by its inadequate intake, malabsorption, increased requirements, and drug-nutrient interactions. In about 70% of the children and 40% of the adults, these deficiencies cause complications [6]. In many cases, the response to a nutrient deficiency also seems to be genotype-specific. Gene-nutrient interactions are thus a fascinating example of physiological reactions to the environment and diet at the molecular level [7]. Long-term deficiency of micronutrients could cause many disorders, including reduced immunity and leukopenia. Gastrointestinal, central nervous system, psychological, skeletal, and reproductive systems are most affected by these deficiencies [8]. This study aimed to highlight that bariatric surgery is not suitable for all morbidity obese people, and more diseases should be added to the contraindications list of BS.

2. Case Study

The patient was a 20-year-old woman with SCD. She weighed 104 kilograms, was 156 cm tall, and had a BMI of 42. She had neither hypertension nor any metabolic and other chronic disorders. The indication for this surgery was the severe psychological distress from being grade III overweight, and the failure to

reduce weight with many other measures. Although she had SCD, she was never under follow up with a hematologist as she only had mild chronic SCD pain, which was controlled with nonsteroidal anti-inflammatory drugs (NSAIDs). She underwent lap sleeve gastrectomy in 2018, after she signed a consent form. On two weeks post the BS, she was admitted with vomiting and abdominal pain; subsequently, she required several admissions because of dehydration and severe body pain. The SCD pain crisis became severe, requiring morphine to control the pain. She was given intravenous fluids on several occasions. Lately, she has been on a monthly exchange transfusion to control the SCD pain and to reduce the morphine requirement. Her lab findings before and after the BS are as follows:

Before the BS, complete blood count (CBC) on 29-08-2017: White blood cells (WBCs): 17.5 (4 - 10) × 10^9/L, red blood cells (RBC): 3.89 (3.8 - 4.8) × 10^{12}/L, hemoglobin: 111 (120 - 150) g/L, hematocrit: 0.384 (0.36 - 0.46) L/L, platelet count: 523 (150 - 410) × 10^9/, MCV: 90 (83 - 101) fl, MCH: 29 (27 - 32) pg, MCHC: 348 (315 - 345) g/L, and reticulocytes: 11.6 (0.5 - 2.5)%. Coagulation profile: INR: 1.35 and APTT: 35.2 (27 - 38.3) sec. Serum ferritin: 95.1 (11 - 306) ng/L. Hb electrophoresis: Hb A = 0%, Hb F = 26.1% Hb A2 = 1.3%, and Hb S = 72.6%. G6PD: normal. Liver function test: Total protein: 73 (61 - 79) g/L, albumin: 40 (35 - 48) g/L, total bilirubin: 82 (3 - 25) Umol/L, direct biluribin: 26.2 (1.7 - 8.6) Umol/L, LDH: 528 IU/L, ALT: 79 (10 - 60) IU/L, AST: 85 (10 - 42) IU/L, glucose: 5.0 (3.9 - 6.1) mmol/L, and Ca: 2.17 (2.1 - 2.6) mmol/L. Renal function test: BUN: 0.9 (2.5 - 7.1) mmol/L, creatinine: 56 (26 - 77) umol/L, Na: 138 (134 - 144) mmol/L, K: 4.03 (3.6 - 5.1) mmol/L, alkaline phoshatase: 142 (42 - 98) IU/L, corrected Ca: 2.17 mmol/L.

Abdominal ultrasound before the BS was not available.

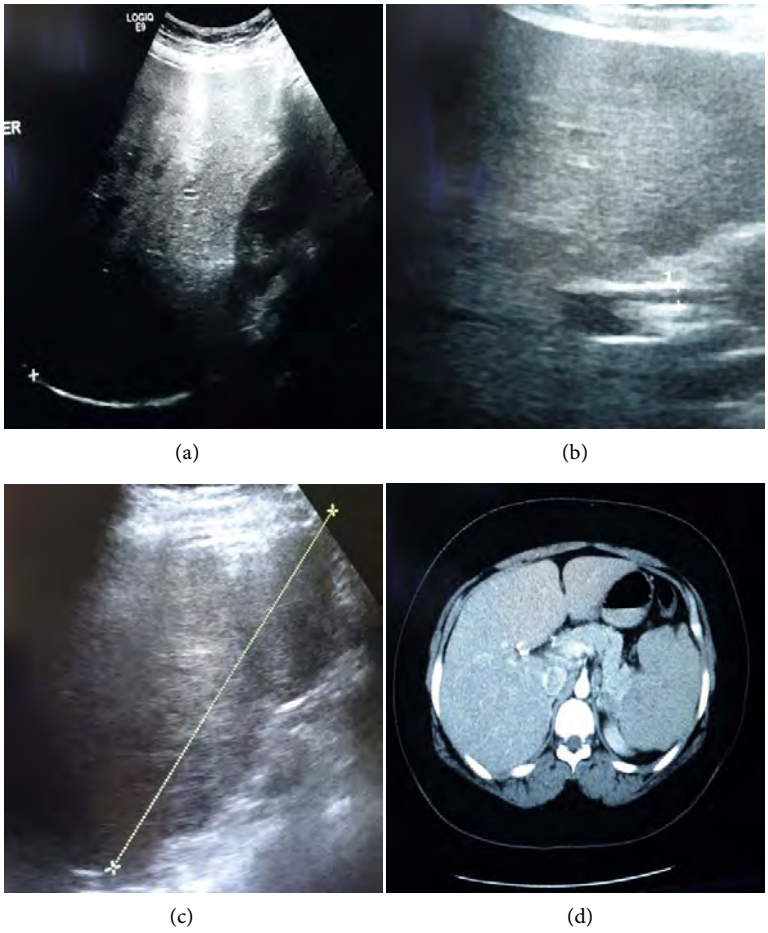
Eighteen months after the BS, her body weight, height and BMI were 65 kg, 155 cm, and 26.7, respectively. Other lab findings were as follows:

WBC: 12.2 (3.8 - 4.8) × 10^{12}/L, RBC: 3.08 × 10^{12}/L, hemoglobin: 93 (120 - 150) g/L, hematocrit: 0.271 (0.36 - 0.46) L/L, platelet count: 322 (150 - 410) × 10^9/, MCV: 88 (83 - 101) fl, MCH: 30 (27 - 32) pg, MCHC: 343 (315 - 345) g/L, and reticylocytes: 6.67 (0.5 - 2.5)%. Coagulation profile: INR: 1.22 and APTT: 30.7 (27 - 38.3) sec. Serum ferritin: 269.5 ng/L (11 - 306) ng/L.

Liver function test: Total protein: 58 (61 - 79) g/L, albumin: 33 (35 - 48) g/L, total bilirubin: 91 (3 - 25) Umol/L, direct biluribin: 10.6 (1.7 - 8.6) Umol/L, ALT: 17 (10 - 60) IU/L, AST: 36 (10 - 42) IU/L, glucose: 4.6 (3.9 - 6.1) mmol/L, and Ca: 2.08 (2.1 - 2.6) mmol/L.

Renal function test: BUN: <0.4 (2.5 - 7.1) mmol/L, creatinine: 48 (26 - 77) umol/L, Na: 142 (134 - 144) mmol/L, K: 3.35 (3.6 - 5.1) mmol/L, alkaline phosphatase: 67 (42 - 98) IU/L, and corrected Ca: 2.22 mmol/L.

An abdominal ultrasound after the BS revealed mild hepatomegaly, mild splenomegaly, and cholecystectomy. The enlarged spleen indicated suspected old splenic infarctions due to SCD. There were no indications of intra-abdominal abscess or collections (**Figure 1**).



(a) (b)

(c) (d)

Figure 1. Abdominal ultrasound & CT. (a) Mildly enlarged bright liver measuring about 20 cm in the mid-clavicular craniocaudal dimension; (b) Removed gall bladder with normal diameter of CBD measuring about 5 mm; (c) Enlarged spleen measuring about 14 cm in craniocaudal dimension with irregular outline due to old infarcts; (d) Axial CT image showing hepatosplenomegaly surgical clips of cholecystectomy irregular outline of the.

The patient currently weighs 65 kg, but she has frequent episodes of severe SCD pain, which require morphine and monthly exchange transfusion.

3. Discussion

A SCD patient is a fragile person who needs to stay well hydrated and away from any stress, including psychological, to avoid a painful vaso-occlusive crisis. Common complaints following BS include lethargy, easy fatigue, headaches, and muscle wasting. Reduced food intake is a stressor and contributes to SCD pain and other SCD-related complications [9]. BS deprives the body of water, which increases the blood viscosity resulting in more frequent and severe episodes of SCD crisis.

The aberrant migration of potassium and chloride ions across the RBC membrane causes RBC dehydration, which consequently increases the tendency of hemoglobin to polymerize and sickle [10]. After BS, patients usually develop

dumping syndrome, characterized by abdominal pain, nausea, vomiting, diarrhea, and diaphoresis [11]. A few months or few years after BS, the patients become deficient in micronutrients and trace elements including water, fat-soluble elements such as iron, calcium, phosphorus, copper, magnesium, selenium, chromium, and zinc [12], as well as vitamins such as thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, cobalamin and vitamins B, D, C, E, K. These nutrients and elements work as enzymatic cofactors in several metabolic processes and biochemical reactions. Therefore, BS can cause a wide range of nutritional, systemic, and psychiatric complications [13]. Arginine and L-glutamine, which are essential micronutrients in SCD, can get severely depleted and influence both the pain intensity and general health of the SCD patients [14]. Proteins are key regulators of metabolism and DNA replication. They also aid in digestion as well as combating infections by strengthening the immune system [15]. The specific risk for developing micronutrient and protein deficiencies cannot be predicted as there is no consensus on the amount of vitamin and mineral supplementation required after BS. However, it is clear that micronutrient deficiencies are relatively common in patients after all types of BS, and so, it is important to screen them before and periodically after the surgery for micronutrients and trace elements [12]. For any type of surgery, SCD patients need special hematological recommendations for maintaining adequate blood level, oxygen saturation, and proper hydration before and after the surgery [16]. Surgical clearance is required from a hematologist before the surgery to avoid any unexpected complications. Pre-operative assessment must include a careful review of the patient's known crisis triggers, baseline hematological profile, transfusion requirements, pre-existing organ dysfunctions, pain degree, and opioid consumption.

4. Conclusion

Compared to healthy individuals, those with SCD have a much lower tolerance for stress. Bariatric surgery puts these patients in a severely stressful condition. This case is significant for both areas of hematology and bariatric surgery. In this study, the SCD pain crisis worsened following the sleeve gastrectomy surgery, indicating that SCD could be a contraindication for such surgery. This case emphasized that bariatric surgery is not suitable for all obese overweight people. Controlled studies are required to assess and define the guideline to improve the outcomes of bariatric surgery, which is now a standard procedure in many countries.

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Conflicts of Interest

The authors have no conflict of interest in this study.

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Unpredictable Placental Abruption: Case Series

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Abstract

Background: The diagnosis of placental abruption is primarily clinical, but findings from imaging, laboratory, and postpartum pathologic studies can be used to support the clinical diagnosis. In patients with classic symptoms, fetal heart rate abnormalities, intrauterine fetal demise, and/or disseminated intravascular coagulation strongly support the clinical diagnosis and indicate extensive placental separation. In a few cases, placental separation has not been recognized and was only identified upon cesarean section as an incidental finding. *Objectives*: To describe the clinical presentations and pregnancy outcomes of placental abruption cases that are not diagnosed before cesarean delivery, termed "unpredictable placental abruption" and also cases diagnosed before cesarean delivery, termed "predictable placental abruption". *Methods*: A retrospective analysis of 100 cases of placental abruption was identified by cesarean delivery at Tu Du hospital from September 2018 to May 2019. Clinical variables were compared between the unpredictable and predictable groups. The unpredictable group consists of cases that are not diagnosed before cesarean delivery, while the predictable cases were identified placental separation before cesarean delivery. The maternal and fetal outcomes were also studied. *Results*: In 100 cases of placental, abruption by gross clinical examination of the placenta at the time operation revealed that, 33% were unpredictable. Placental abruption attributed to maternal complications included one case of total hysterectomy (1%) with no cases of disseminated intravascular coagulation (DIC), shock or maternal death; specifically, this case of total hysterectomy appeared with predictable one. There were two cases of stillbirths. Among the 98 live neonates, 15 cases (14.7%) experienced severe birth asphyxia resulting in eight neonatal deaths; two of which were caused by heart disease and necrotizing enterocolitis. Sixty-three neonates were delivered prematurely (61.74%), with mean gestational age of 34.64 ± 3.32 weeks. Among the 33 unpredictable cases, there were no stillbirths but 60.6% and 12.1% experienced moderate and severe asphyxia, respectively. All unpredictable cases had obvious indications of cesarean section but the basic

symptoms and signs of acute placental abruption included the onset of preterm labor, unspecified intrapartum hemorrhage, hypertonic uterine contractions and fetal distress for emergency caesarian section; however there were also cases where there were no symptoms and signs. *Conclusions*: Unpredictable placental abruption cases—not suspected of having abruption, termed—"concealed" or "chronic" placental abruption, may have variable clinical manifestations and better pregnancy outcomes.

Keywords

Placental Abruption, Pregnancy Outcomes, Concealed Placental Abruption, Chronic Placental Abruption

1. Introduction

Placental abruption, defined as the complete or partial separation of the placenta before delivery, is a major cause of poor pregnancy outcome that often requires an emergency cesarean section and intensive care of the newborn. Placental abruption complicates approximately 1% of pregnancies (Ananth *et al*., 2015) [1] but the perinatal mortality rate is 20-fold higher in comparison to pregnancies without abruption (12% versus 0.6%, respectively) (Tikkanen *et al*., 2013) [2]. For the mother, complications include hemorrhagic shock (19.4%), Couvelaire uterus (16.5%) and disseminated intravascular coagulation (DIC) (5.8%) (Pitaphrom and Sukcharoen, 2006) [3]. The perinatal outcomes include low birth weight (65.0%), preterm (56.3%), severe birth asphyxia (16.5%) and perinatal death (16.5%) (Pitaphrom and Sukcharoen, 2006) [3]. A case-control study has also shown a greater risk for adverse long-term neurobehavioral outcomes for infants delivered after placental. Specifically, hypoxia-associated periventricular leukomalacia and sudden infant death syndrome are more common in newborns delivered after placental abruption (Ananth *et al*., 2017) [4].

While some placental abruptions may occur acutely after a sudden mechanical event (e.g., blunt trauma, sudden uterine decompression, or motor vehicle accident), more cases result from more chronic processes that are related to the abnormal development of spinal arteries and the thrombin initiating-cycle pathway of vascular disruption, hemorrhage, inflammation, as well as contractions and ruptures of membranes. The classic signs and symptoms of placental abruption are vaginal bleeding, abdominal pain, fetal distress and hypertonic uterus or tetanic contractions. The diagnosis of abruption is clinical, with ultrasonography and other tests being of limited value.

Tu Du Hospital is the leading center in obstetrics and newborns with 2000 beds in South Vietnam. It also administrates the Minister of Health's protocols in Vietnam Women's Reproductive Health. However, in clinical practice, some cases that have poor perinatal outcomes in pregnancies are due to the discovery placental abruption after cesarean delivery. In the present study, we designed a

retrospective, descriptive study to evaluate the clinical characteristics of cases with or without predictable placental abruptions before cesarean delivery.

2. Methods

The present study consisted of a retrospective review of the medical records of all patients with a diagnosis of placental abruption from September 2018 to May 2019 at Tu Du Hospital. All electronic medical records were searched for the diagnosis of placental abruption according to code O45 of the International Classification of Diseases 10 (ICD 10). Diagnoses were based on gross clinical examination of the placenta at the time of operation. The criterion for inclusion was a single pregnancy with more than 28 weeks of gestation. Cases of placenta previa and multiple gestation were excluded. Records of cases consisting of maternal and neonatal data were reviewed and collected in the data collecting form. All cased, termed "predictable" placental abruption if they were suspected before the time of operation. While, the "unpredictable" cases were not thinking of placental abruption before operation.

We collected maternal characteristics including demographic data, smoking history, past obstetric history, presenting symptoms, pertinent physical examination results, investigations performed, and complications. Neonatal data collected were gestational age at delivery, birth weight, Apgar score at 1 minute and 5 minutes, fetal death (delivery of a dead fetus at or after 28 weeks of gestation) and neonatal death.

Our research was observational study. Before going research, we were accepted by Medical Committee of University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam and Tu Du Hospital. We used Stata software for describing and analyzing data.

3. Results

From September 2018 to May 2019, we collected 100 cases were single births with diagnoses of placental abruption. Fourteen cases were excluded due to placental previa, gestational age being less than 28 weeks, or missing data.

Demographic characteristics of placental abruption patients are shown in Table 1. The mean maternal age of cases was 30.7 ± 5.88 years. Sixty percent had one or more deliveries with 27% having a history of a cesarean section. Although all cases of women reported no smoking, 27% of their partners smoked.

Maternal and neonatal data are shown in Table 2. All study cases chosen involved cesarean sections in which the amount of blood loss was estimated to be 293.5 ± 117.9 ml. Maternal complications only included one case of total hysterectomy with no cases of DIC, shock, and maternal death. The mean birth weight was 2274.4 ± 117.9 g with 59.18% of neonates were born less than 2500 g. There were two cases of stillbirths. Among the 98 live neonates, 15 cases (14.7%) experienced severe birth asphyxia resulting in eight neonatal deaths; two of which were caused by heart disease and necrotizing enterocolitis. Sixty-three

neonates were delivered prematurely (61.74%), with mean gestational age of 34.64 ± 3.32 weeks. There were 58 neonates (59.18%) that were admitted to ICU and 40 (40.82%) were healthy. The length of ICU stay for neonates was approximately 9 days (9 ± 6.7 days) with a healthy recovery of 52 neonates.

Some study cases of placental abruption were identified during cesarean delivery, but there were some cases where diagnoses made before operation. Thus, we classified the former as unpredictable in 33 cases (33%) and the latter as predictable in 67 cases (67%) to analyze clinical presentation. Table 3 presents clinical manifestation in predictable and unpredictable placental abruption before cesarean section.

Table 1. Demographic characteristics of studying cases.

Characteristics	Cases (n = 100)
Maternal age (y)	
<20	1 (1%)
20 - 34	71 (71%)
≥35	28 (28%)
Parity	
0	40 (40%)
1 - 3	60 (60%)
Maternal history	
Previous cesarean section	27 (27%)
Premature delivery	10 (10%)
Chronic hypertension or pregnancy induced hypertension	6 (6%)
Smoking by	
Woman	0 (0%)
Partner	27 (27%)

Table 2. Maternal and neonatal data.

Characteristics	Cases (n = 100)
Pregnancy status	
Gestational age at delivery (weeks)	34.64 ± 3.32
28 - <32	21 (21%)
32 - <34	19 (19%)
34 - <37	33 (33%)
≥37	37 (37%)
Preeclampsia	24 (24%)
Maternal outcome	
Estimated blood loss (ml)	293.5 ± 117.9
Length of maternal hospital stay (days)	5.1 ± 0.7
Maternal complications	1 (total hysterectomy)
Perinatal outcome	
Birth weight (grams)	2274.4 ± 764.4
Stillbirth	2 (2%)
Live newborn	98
Severe birth asphyxia	15
ICU	56
Neonatal death	8
LBW	58

LBW: live born weight.

Table 3. Clinical manifestation in predictable and unpredictable placental abruption before cesarean section.

Characteristic	Predictable placental abruption (n = 67)	Unpredictable placental abruption (n = 33)	PR
Vaginal bleeding	35 (52.24%)	5 (15.15%)	P < 0.005
Abdominal pain	14 (20.90%)	14 (42.42%)	
Uterine tenderness, uterine tetanic contractions, or hypertonic uterus	5 (7.46%)	4 (12.12%)	
Bloody amniotic fluid	12 (17.91%)	6 (18.18%)	P > 0.05
Fetal heart rate abnormalities	13 (19.40%)	15 (45.45%)	
Retroplacental blood clot by ultrasound	54 (80.60%)	0 (0.00%)	
Extent of abruption			
<30%	2 (2.98%)	22 (66.67%)	
30 - <50%	4 (5.97%)	8 (24.24%)	
50 - <80%	27 (40.30%)	2 (6.06%)	
80 - 100%	34 (50.75%)	1 (3.03%)	

Vaginal bleeding, which ranges from moderate to severe, related significantly to cases of predictable placental abruption before operating (P < 0.005). More than 50% of patients in the predictable group experienced vaginal bleeding compared to only 15% of patients in the unpredictable group. However, abnormal pain, uterine tenderness, uterine tetanic contractions, or hypertonic uterus in the unpredictable group was roughly twice as high as the predictive group. Fetal heart rate abnormalities were the second most prevalent symptom in the unpredictable cases with 45.45%, which is more than double that of the predictable cases. Bloody amniotic fluid was similar between the two groups with 17.91% in the predictable group and 18.18% in the unpredictable group.

The prominence of a retroplacental blood clot by ultrasound was striking. In the predictable group, 80.6% of patients had retroplacental blood clots compared to no cases in the unpredictable group.

Table 4 displays pre-operative diagnoses of 33 unpredictable placental abruptions in our study. All cases had consistent reasons for a caesarean section such as obstructed labor due to shoulder or breech presentation, and incomplete rotation of fetal head. These cases all had at least one of the basic symptoms and signs of acute placental abruption, such as vaginal bleeding, uterine contractions, and possibly a nonreassuring fetal heart rate. However, their symptoms and signs were evaluated at the onset of preterm labor, unspecified intrapartum hemorrhage, hypertonic uterine contractions, and fetal distress during emergency caesarian section. Some abruptions were asymptomatic; for instance, Case *25405*, and Case *89563* with obstructed labor due to breech presentation or Case *17891* with failed medical induction of labor. Prior of operation, there were nine cases (27.3%) of fetal stress by electrocardiograph, resulting in one severe and six moderate birth asphyxia, while there were 24 cases without fetal heart abnormal-

ity that had three severe and fourteen moderate asphyxia. Fetal stress by electrocardiograph is not related to the worse fetal outcome or severe asphyxia in unpredictable placental abruption.

Table 5 shows the pregnancy outcome of unpredictable placental abruption cases. The mean birth weight was 2465.15 ± 837.17 which ranges from 1000 to 4300 g and 45.45% neonates were born less than 2500 g. Among the 33 unpredictable cases, there were no stillbirths but 60.6% neonates experienced moderate asphyxia, while 12.12% experienced severe asphyxia. Six cases were less than 32 weeks of gestation with four severe and two moderate asphyxia. Thus, that there appear to be a significant correlation between premature birth and asphyxia. However, there seems to be no relationship between asphyxia and extent of placental abruption. In the unpredictable cases, there is only one case with 80% abruption, but the neonate had moderate asphyxia.

Table 4. Preoperative diagnosis (ICD-10 version) and outcomes of thirty-three cases of unpredictable placental abruption.

	Case	Preoperative diagnosis	Maternal outcome			Neonatal outcome		
			Extra-c/s (*)	Extent of abruption	Blood lost	Age	Asphyxia (**)	Weight
1	70100	Labour and delivery complicated by fetal stress, unspecified (068.9)	No	20%	500	36w	M	2500 g
2	*72873*	Obstructed labour due to breech presentation (064.1)	Yes (UA)	50%	500	36w3d	M	3000 g
3	*74585*	Failed medical induction of labour (061.0)	No	20%	500	40w1d	No	2900 g
4	*74754*	Labour and delivery complicated by other evidence of fetal stress (068.8)	No	20%	250	37w	M	1800 g
5	*75265*	Severe pre-eclampsia (014.1)—cesarean scar-onset of labour	Yes (UA)	80%	300	38w	M	3400 g
6	*75399*	Obstructed labour due to shoulder presentation (064.4)—cesarean section	No	30%	300	37w3d	M	3000 g
7	*83573*	Severe pre-eclampsia (014.1)—cesarean scar due to breech presentation	No	30%	200	28w6d	M	1000g
8	*87198*	Labour and delivery complicated by other evidence of fetal stress (068.8)	Yes (US)	10%	300	36w6d	No	3900 g
9	*89612*	Labour and delivery complicated by other evidence of fetal stress (068.8)	Yes (UA)	10%	200	39w	M	2700 g
10	*89910*	Obstructed labour due to incomplete rotation of fetal head (064.0)	Yes (UA)	30%	200 ml	38w4d	M	2700 g
11	*89563*	Obstructed labour due to breech presentation (064.1); IUGR	Yes (UA)	15%	200	36w6d	M	2200 g
12	*91330*	Labour and delivery complicated by other evidence of fetal stress (068.8)—Severe pre-eclampsia (014.1)	Yes (UA)	20%	200	33w5d	M	2000 g
13	*94317*	Labour and delivery complicated by other evidence of fetal stress (068.8)—caesarean scar	Yes (UA)	15%	200	32w1d	M	2200 g

Continued

14	*94799*	Delivery by emergency caesarean section (082.1) by uterine contractions	Yes (UA)	10%	200	39w1d	No	3000 g
15	*97193*	Delivery by elective caesarean section (082.0). PROM	No	10%	300	38 w	M	3300 g
16	*97295*	Obstructed labour due to shoulder presentation (064.4)—PROM	No	10%	200	30w	S	1350 g
17	*100044*	Labour and delivery complicated by other evidence of fetal stress (068.8)—traffic accidence	No	20%	200	35w	M	1900 g
18	*104490*	Delivery by elective caesarean section (082.0) due to shoulder presentation	Yes (UA)	15%	200	30w6d	M	1400 g
19	*106584*	Labour and delivery complicated by other evidence of fetal stress (068.8)	Yes (UA)	20%	500	37w6ds	No	1900 g
20	*916*	Hypertonic, incoordinate, and prolonged uterine contractions (062.4)—caesarean section	No	10%	200	39w3ds	No	2700 g
21	*1860*	Pre-eclampsia superimposed on chronic hypertension (011)—Caesarean section (082.0) due to breech presentation	Yes (UA)	30%	200	28w6ds	S	1000 g
22	*3815*	Labour and delivery complicated by other evidence of fetal stress (068.8)—Caesarean section (082.0)	Yes (UA)	30%	200	32w1d	M	1350 g
23	*9400*	Labour and delivery complicated by other evidence of fetal stress (068.8)	No	40%	200	30w5d	S	1500 g
24	*10455*	Delivery by emergency caesarean section (082.1) due to Intrapartum haemorrhage, unspecified (067.9)	Yes	10%	800	37w3ds	No	2800 g
25	*13190*	Obstructed labour due to breech presentation (064.1)	Yes (UA)	50%	500	35w3ds	M	2200 g
26	*16297*	Delivery by emergency caesarean section (082.1) due to uterine contraction	No	10%	300	38w5ds	No	4300 g
27	*17891*	Failed medical induction of labour (061.0)	No	20%	200	38w 4ds	No	3200 g
28	*22202*	Obstructed labour due to breech presentation (064.1)—caerarean section	Yes (B-Lynch+ UA)	20%	600	35w5ds	M	2500 g
29	*22465*	Labour and delivery complicated by other evidence of fetal stress (068.8)—Severe pre-eclampsia (014.1)—cesarean scar	No	10%	300	31w4ds	S	1450 g
30	*22536*	Hypertonic, incoordinate, and prolonged uterine contractions (062.4)	Yes (UA)	10%	300	38w4ds	M	3400 g
31	*22617*	Delivery by emergency caesarean section (082.1) due to pain in scar	Yes (UA)	30%	200	33 w	M	2300 g
32	*25405*	Obstructed labour due to breech presentation (064.1)—PROM	Yes (UA)	10%	400	35w5ds	No	3100 g
33	*29322*	Labour and delivery complicated by other evidence of fetal stress (068.8)—breech presentation	No	30%	400	38w	M	3400 g

*Extra-c/s: caesarian section with some special procedures; **Birth asphyxia: M (moderate) = Apgar at 1 minute ≤ 6, S (severe) = Apgar at 1 minute ≤ 4. IUGR: Intrauterine growth restriction, PROM: Prelabor Rupture of Membranes, UA: uterine artery ligation.

Table 5. Perinatal outcome of the unpredictable group.

Characteristics	Cases (n = 33)
Birth weight (grams)	2465.15 ± 837.17 g
Stillbirth	0
Live newborn	33 (100%)
Moderate birth asphyxia	20 (60.6%)
Severe birth asphyxia	4 (12.12%)
Low birth weight	14 (45.45%)

4. Discussion

The primary etiology for placental abruption is still unclear, but several possibilities have been identified, including pre-eclampsia, chronic hypertension, previous history of placental abruption, increased maternal age, cigarette smoking, and cocaine use (Tikkanen *et al.*, 2006; Ananth, Smulian and Vintzileos, 1999) [2] [5]. In the present study, only six patients had chronic hypertension and/or pregnancy induced hypertension in the past but 24% had it during pregnancy. This finding supports other studies that have proved the strong relationship between hypertensive disorders and placental abruption. The risk for placental abruption was 4.8-fold (95% CI 2, 2 - 10) if both women and partners were smokers. Maternal smoking (OR 1.8; 95% CI 1.1, 2.9) and paternal smoking (OR 2.2, 95% CI 1.3, 3.6) were found to be independently associated with placental abruption (Tikkanen *et al.*, 2006) [6]. In our study, 27% of partners smoked, and the case of women passive smoking should be. Our study was too small to evaluate whether passive smoking is a risk factor for placental abruption. Studied based on cotinine assessments can better evaluate the effects of passive smoking on placental abruption.

Placental abruption is associated with an increased incidence of preterm as well as maternal and perinatal morbidity. It has various presentations and severities; therefore, the maternal and perinatal outcomes are different. In our study, maternal complications involved only one case with hysterectomy, none of them expressed DIC or hemorrhagic shock that ended in death. For the mother, the potential consequence of abruption is primarily related to the severity of placental separation. The degree of abruption in our case study was mild or moderate, which was similar to the frequency of serious complications to another retrospective cohort study (33 per 10,000 women). However, serious complications were less than a study with severe abruptions (DIC: 5.8%; hemorrhage shock: 2.9%) (Pitaphrom and Sukcharoen, 2006) [3].

Compared to studies by Chang and Cheng (2001) [7] and Sheiner *et al.* [8] our study data was higher. Our incidence of preterm birth and birth asphyxia were 63% and 15.3%, respectively, while 40% to 60% of abruptions occurred before 37 weeks of gestation and 14% occurred before 32 weeks (Chang and Cheng, 2001; Sheiner *et al.*, 2002) [7] [8]. The risks to the fetus are related to both the severity of separation and the gestation age at which delivery occurs. This explains the lower incidence of birth asphyxia in our study, while it is up to 47.6% in a study

of severe cases (Pitaphrom and Sukcharoen, 2006) [3]. Abruption causes more severe and prolonged hypoxia than cord prolapse and is a major cause of fetal stress. Fetal asphyxia, preterm and growth restriction can contribute to poor fetal outcome. Briefly, the perinatal mortality in the present study is 8%, the same as a population-based study which ranges from 3% to 12% (Ananth and VanderWeele, 2011) [9].

In our study, nearly all cases had vaginal bleeding, abdominal pain and/or uterine tenderness, hypertonic contractions, and possibly fetal heart rate abnormalities as well as presentation of acute abruption rather than chronic abruption. The unpredictable patients presented more abdominal pain, uterine contractions, and fetal heart rate abnormalities than vaginal bleeding; perhaps they had symptoms of a "concealed abruption", where all or most of the blood is trapped between the fetal membrane and decidua, rather than escaping through the cervix and vagina. Some cases may be asymptomatic and only recognized as an incidental finding during caesarean section. Almost all unsuspected placental abruption cases had one or more risk factors for pregnancy, such as preeclampsia, hypertensive disorders, malpresentation, pre-labor rupture of membranes and intrauterine growth restriction prior to caesarean section. Therefore, chronic abruption may go unsuspected because symptoms involve relatively light, intermittent bleeding and clinical manifestations of ischemic placental disease that may develop over time. Three of the unpredictable cases had intrauterine growth restriction (*106584*, *100044*, *70100*) and were at risk of chronic abruption, but ultrasound examination could not identify a placental hematoma.

All cases, termed "predictable", were identified placental abruption by sonographic retroplacental hematoma and indicated emergency cesarean delivery. In contrast to the predictable cases, a retroplacental hematomas could not be found in the unpredictable placental abruption cases. Whether a hematoma is identified depends on the extent of hemorrhage, chronicity of the bleeding, and the amount of blood escaped through the cervix. Sonographic findings consistent with placental abruption are associated with worse maternal and perinatal outcomes. Our study may prove that unpredictable cases may be concealed or chronic abruption. In addition, almost all unpredictable cases have immediate indications of cesarean section through signs of a nonreassuring fetal heart rate, labor arrest or active labor, so that there is insufficient time to find sonographic evidence of a retroplacental hematoma. Furthermore, if an emergency cesarean delivery is required, placental abruption will be an inevitable finding.

The lack of severe pregnant outcomes in our study correlates to the degree of abruption. The extent of abruption is larger in predictable than in unpredictable cases and in most cases is smaller than 50%. When placental separation exceeds 50%, acute disseminated intravascular coagulation and fetal death are common. Therefore, unpredictable cases are not associated with worse maternal and fetal outcome. Moreover, optimal outcomes were more likely from treatment by a team of experienced obstetricians, anesthetists, and neonatologists. Cases recruited in our study were delivered by cesarean section, which is the best option

when vaginal delivery is not imminent and rapid control of bleeding is required to prevent and manage maternal hemodynamic instability or significant coagulopathy. In the same way, cesarean section is safe choose for neonates, especially for live fetus with nonreassuring fetal status.

5. Conclusion

In conclusion, placental abruption with a severe degree of separation is often suspected because obvious symptoms and signs, such as vaginal bleeding, abdominal pain, fetal distress and sonographic retroplacental hematomas, which should be followed by prompt evaluation of maternal and fetal status and appropriate management. The worse pregnancy outcomes are related to severe degree of abruption. In contrast, cases not suspected of having abruption (*i.e.* "concealed" or "chronic" placental abruption) may have variable clinical manifestations and better pregnancy outcomes. Fetal outcomes are associated with gestational age at delivery.

Limitation of the Study

The research did not cover a long enough period of time so that strong evidence of unpredictable placental abruption was built.

Conflicts of Interest

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

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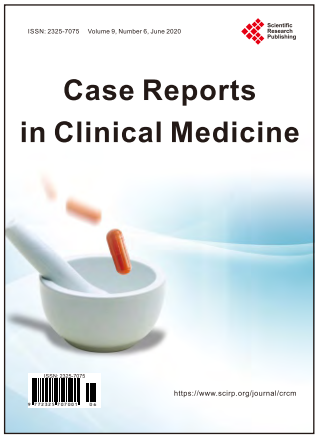

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