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Case Report

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Brucellosis masquerading as ITP in an Omani child with thrombocytopenia

Abstract

Immune thrombocytopenic purpura (ITP) is considered as the most common diagnosis in children who are otherwise well, and present clinically with isolated thrombocytopenia. Hereby, we report on a child who presented with isolated thrombocytopenia that proved to be secondary to brucellosis. She had no history of fever or other clinical manifestation of brucellosis. Initially, the child was labeled as having ITP, but she did not respond to treatment with oral steroids, pulse methylprednisolone or IVIg. Diagnosis was suspected based on her residence in an area endemic for brucellosis. Blood culture grew gram negative bacilli suggestive of brucellosis and serologic testing proved infection with Brucella Melitensis and Brucella Abortus. Thrombocytopenia improved promptly after starting specific antibiotic therapy for Brucellosis.

Keywords: ITP, thrombocytopenia, IVIg, SQUH, ecchymotic

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Case summary

A 5 year-old Omani girl, who had been previously healthy, was referred from a local hospital in Salalah, Dhofar to Sultan Qaboos University Hospital (SQUH) for further evaluation and management of thrombocytopenia. She presented to the local hospital complaining of gum bleeding, multiple petechial spots on the lower limbs and trunk, and epistaxis for the preceding 10 days. There was no history of fever, pallor, bony aches, arthralgia/ arthritis, headache, or other skin rashes. She had history of recurrent epistaxis, and foul smelling nasal discharge for 3 months before presentation. Family history was negative for low platelets or easy bruising. Her clinical examination was unremarkable apart from multiple ecchymotic lesions on both legs, few petechiae on anterior chest wall and face. There was no other active bleeding, no hepatosplenomegaly, and no lymphadenopathy. Right sided nasal foreign body was suspected, but surgical removal was postponed because of her low platelet count.

Initial complete blood count revealed Hb of 11.4g/dl, Platelets $4x10^3/mm^3$, WBC $10.2x10^3/mm^3$, with normal differential counts, and blood smear did not show abnormal cells. Provisional diagnosis was ITP, and she was treated with oral prednisolone (2mg/kg/day) for 3 days. Follow up CBC did not show response, with a platelet count of 5, then $3x10^3/mm^3$. IV methylprednisolone was initiated at 10mg/kg for 3 days with no response (platelet count of $6x10^3/mm^3$). As she was scheduled for surgical removal of a nasal foreign body, one dose of IVIg at 800mg/kg was given in an attempt to obtain a safe platelet count for the procedure. The response to IVIg was not optimal as well. The patient was referred to SQUH for further assessment and management. At our hospital, clinical examination was unremarkable apart from few ecchymotic lesions on the legs and mild cellulitis on the dorsum of left hand, for which she received oral amoxicillin-clavulenic acid for 5 days.

Repeat CBC at SQUH showed bi-cytopenia with Hb of 7.5 g/dl (microcytic hypochromic, reticulocytes: 3.5%, absolute reticulocytic count: 112, RDW 17.8%), and platelet count of $17x10^3/mm^3$. WBCs ($13.4\ x10^3/mm^3$) and differential counts were normal. Her blood group was O +ve and there was no atypical antibodies detected. Blood film showed neutrophils containing toxic granules, with shift to the left (myelocytes +). Reactive lymphocytes, atypical lymphocytes and reactive monocytes were noted. EBV, CMV and adenovirus PCR were negative. ANA was also negative and coagulation screening (PT, aPTT, fibrinogen, TT) was normal. Thrombocytopenia was confirmed on blood film, and occasional large platelets were seen, suggestive of peripheral destruction. LDH was slightly elevated (351u/ml), and she had normal liver and kidney function tests. Because of bi-cytopenia, bone marrow aspiration was performed. Trilineage hematopoiesis was present with a normal myeloid/erythroid ratio. Erythroid precursors were normoblastic and orderly in maturation with no dysplasia. Myeloid component was non–dysplastic and sequential, and blast cells were <1%. Megakaryocytes were plentiful and lymphoplasmacytic component was unremarkable. Bone marrow trephine biopsy showed normal cellularity, and trilineage hematopoiesis with normal maturation. Megakaryocytes were increased in number, with rare hypolobated and mononucleated forms. There was no evidence of abnormal infiltrates, granulomas, hemophagocytosis or fibrosis (reticulin was 1+). The findings were compatible with ITP. Based on the blood film that suggested possible sepsis, septic workup was requested. CRP was moderately elevated (19), blood culture grew gram negative bacilli, positive for oxidase and urease suggestive of Brucella species. Brucella serology was positive for Brucella Melitensis (1: 10240), and Brucella Abortus (1: 10240), confirming the diagnosis of brucellosis. Treatment was initiated using cotrimoxazole (5mg/kg/12hours)+ rifampicin (15mg/kg/day)+ IV gentamycin (5mg/kg/day). Prompt response was noted, with rising of platelet counts from 17 to $43x10^3/mm^3$ at day 3, and 57 at day 5 of treatment. A repeat blood culture after 1 week of antibiotic treatment was reported as negative. The child was discharged home, with a plan to continue antibiotics (cotrimoxazole and rifampicin) for a total of 6 weeks. Platelet count upon discharge was $121\ x10^3/mm^3$, and Hb was 9.2gm/dl.

Discussion

ITP is the most frequent diagnosis in children presenting with isolated thrombocytopenia. As per ASH guidelines, therapeutic intervention is not necessary, unless the patient has active bleeding. Bone marrow assessment is also not required in children with no atypical features.[1] In the current case, the clinical scenario of isolated thrombocytopenia in an otherwise well child was in favor of ITP.

Because she had clinical bleeding (epistaxis and gum bleeding), first line therapy with short course of steroids was initiated. Her bleeding stopped, but she remained severely thrombocytopenic, unfit for invasive surgical procedure. She received one dose of IVIg, still with partial response. Her poor response to specific treatment of ITP, together with involvement of a second cell line (development of DAT negative anemia), warranted a marrow examination, that ruled out a marrow pathology. Surprisingly, diagnosis of brucellosis was revealed on obtaining a blood culture and was confirmed by serological testing. Although the child was referred from an area endemic for brucellosis (Salalah, Dhofar), absence of fever and other classical clinical manifestations delayed the clinical suspicion, and caused delayed diagnosis and treatment.

Brucellosis is considered a major health problem in certain areas around the world, mainly in the Middle East and Mediterranean countries. In 2015, Al-Rawahi,[2] studied the epidemiology of brucellosis in the Sultanate of Oman. He reported that 2.4% of animals were seropositive for brucellosis. The southern governorate (Dhofar) had significantly more seropositive holdings than did the northern governorates (8.6% versus 0.97%) ($p<0.001$) highlighting the endemic nature of the disease in Dhofar. A retrospective analysis of human brucellosis in Oman between 1995-2012, reported 2737 cases, 96.7% of them were from Dhofar. Young individuals below 10 years of age were more at risk.[2]

Ingestion of raw infected milk and dairy products, as well as contact with infected animals is the main sources of human brucellosis. Aerial transmission through contaminated environmental soil is less implicated. In a study conducted by EL-Amin et al.[3] in children infected with brucellosis in Dhofar, fever was the main clinical manifestations of brucellosis (91%), followed by musculoskeletal manifestations like arthritis in 70% of children >7years of age. Both clinical manifestations were absent in the current case. Younger children had more severe systemic illness, with leukopenia and thrombocytopenia.[3] Basically, Brucella can affect any organ system, and its clinical manifestations can be confused with many systemic illnesses.

As early as the forties of last century, thrombocytopenic purpura in association with brucellosis had been reported.[4] In 1984, Crosby et al.,[5] studied the hematological manifestations of brucellosis in a cohort of 34 patients. Anemia, lymphopenia, leukopenia, thrombocytopenia, neutropenia, pancytopenia and splenomegaly were reported (in 74-20% of patients respectively). Bleeding complications were encountered in 24% of patients, who had also clotting abnormalities (low platelets, low fibrinogen and prolonged TT).[5]

Several reports stated that brucellosis is frequently associated with hematological abnormalities, mainly mild anemia and leukopenia. On his review, Young et al.[6] reported that thrombocytopenia is relatively less common, (1-8%) and rarely severe enough to be associated with clinical bleeding.[6]

Multiple possible mechanisms have been proposed for hematological abnormalities associated with acute brucellosis.[7] Bone marrow suppression leading to pancytopenia is attributed to the affinity of Brucella species to the reticuloendothelial system. Such a mechanism is excluded in our patient, based on her normal bone marrow cellularity. Hypersplenism is reported in some cases to cause severe pancytopenia that responded only to splenectomy. Although our patient did not have clinical splenomegaly, the possibility of hypersplenism cannot be ruled out, in view of her associated anemia with reticulocytosis and negative direct antiglobulin test (DAT). Other mechanisms that can lead to thrombocytopenia with brucellosis is hemaophagocytosis (Not evident in the current case, in view of absent clinical and laboratory criteria), and DIC (no evidence on blood film). Microangiopathic hemolytic anemia was reported in association with brucellosis by Young et al.[6] Immune thrombocytopenia had been postulated as another pathophysiological mechanism. Some reported a severe course of Brucella–induced immune thrombocytopenia with significant bleeding, requiring treatment with IVIg.[7] Others reported milder thrombocytopenia that was reversible after initiation of antibiotic therapy. Direct platelet damage by bacterial endotoxin, causing endothelial damage, platelet adhesion and/or removal from the blood stream might also be implicated.

Different approaches had been practiced for management of Brucellosis- associated thrombocytopenia.[8] Similar to our case, Akbayram et al.,[8] emphasized on isolated thrombocytopenia, mimicking ITP as the sole hematological abnormalities in children with Brucellosis, that resolved after antimicrobial treatment of Brucella.[9] Farah et al.,[10] also reported isolated thrombocytopenia as the sole manifestations of brucellosis in an 8 year-old boy, that developed mucosal bleeding and splenomegaly. In contrast to our patient, their patient responded well to IVIg and steroids.[10] Sevinc et al.,[11] reported good response to short term standard steroids in addition to anti-brucellosis treatment,[11] while Gürkan et al.[12] used high dose methylprednisolone at 30mg/kg to control epistaxis in a patient with severe Brucella induced thrombocytopenia. In the extreme case of brucella– induced microangiopathic hemolytic anemia complicated by intracranial hemorrhage, Young et al.[6] used a combination of platelet transfusion, fresh-frozen plasma, tranexamic acid, dexamethasone in addition to antibacterial drugs.[6]

We assume that Brucella-induced immune–mediated thrombocytopenia and direct platelet damage by the bacteria are the most probable pathophysiologic mechanisms in our patient. Large platelets on blood smear, and increase number of megakaryocytes with hypolobated forms in bone marrow examination support the immune mechanism. Lack of response to steroids and IVIg does not exclude the immune mechanism, as cases of steroid/IVIg–refractory ITP requiring second line therapy are well known among ITP patients. Fortunately, our patient showed good prompt response to anti–Brucellosis treatment and did not require further specific treatment for thrombocytopenia, supporting the direct platelet damage theory.

Conclusion

Brucellosis should be considered as a possible diagnosis in children from endemic areas presenting with hematologic abnormalities. Thrombocytopenia could be the only manifestation of Brucellosis and should be suspected, even in the absence of fever and other classic clinical manifestations. Prompt diagnosis and specific treatment is needed to reverse thrombocytopenia and prevent possible serious bleeding.

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Conflict of interest

The author declares that there is no conflict of interest.

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