Open Journal of
Clinical & Medical
Case Reports

Volume 5 (2019)
Issue 9

ISSN: 2379-1039

Dual manifestations of thrombocytopenia in Plasmodium vivax malaria

Christie Becu; Anand Gourishankar*

***Anand Gourishankar**

Department of Pediatrics at John P. and Katherine G. McGovern Medical school/UT Health, 6431 Fannin street, Rm. JJL480 Houston, Texas, 77030, USA

Phone: 713-5005-586; Email: anand.gourishankar@uth.tmc.edu

Abstract

We describe a patient who was infected with Plasmodium vivax and presented with Immune Thrombocytopenia (ITP) without malaria symptoms or signs of active infection. Thrombocytopenias in malaria and ITP have different symptoms, labs, and pathogenesis. Though rare, there are other cases where patients developed severe ITP following malaria infection.

Keywords

pediatric; immune thrombocytopenia; ITP; autoimmune; parasitemia; malaria

Abbreviations

P. vivax: Plasmodium vivax; ITP: immune thrombocytopenia; WBC: white blood count; M-CSF: macrophage colony-stimulating factor; PAIgG: platelet-associated IgG

Introduction

While malaria is a proficiently studied disease with a well-known natural history, atypical presentations can lead to misdiagnosis of a separate disease or perhaps even expose a separate disease process that developed as a consequence of malaria. Particularly, in this case, Plasmodium vivax is known to infect through the Anopheles mosquito. Sporozoites will then infect hepatocytes and enter a dormant state called the hypnozoite, which can remain dormant for weeks or years. When the dormant state reactivates, typical malaria symptoms can be divided into uncomplicated or severe presentations. Typical mild symptoms of uncomplicated malaria may include a 48-hour cycle fever (because of the reproductive cycle of the species), chills, diaphoresis, headache, fatigue, malaise, myalgia, arthralgia, anorexia, nausea, vomiting, abdominal pain, and diarrhea. Severe symptoms in children consist of severe anemia with hemolysis, disseminated intravascular coagulation, thrombocytopenia, acute lung injury leading to respiratory distress, metabolic acidosis, altered mental status, and coma. In this case, we shall examine how a pediatric patient with a

known diagnosis of malaria Plasmodium vivax (P. vivax) infection presented to the hospital on multiple occasions, once with symptoms of more severe thrombocytopenia without expecting severe malarial symptoms and again with a more classic uncomplicated malaria picture with only mild thrombocytopenia. This case draws attention to how one patient can present with thrombocytopenia of multiple etiologies or how malaria can trigger the development of another form of thrombocytopenia.

Clinical Course

When the 20 months-old-infant first presented at the hospital, he had just emigrated from Afghanistan three months prior. During the most recent hospitalization, his father (the only family member who spoke English) reported that the patient, as well as two of his siblings, were diagnosed and treated for malaria the previous year. However, this history was not elicited when he was first hospitalized for epistaxis that progressed to mucosal bleeding from his gums over 5 hours. When his epistaxis began, his parents noted the patient was more somnolent than usual describing his speech as if he had just woken up from sleep. He did have two episodes of non-bloody diarrhea two days before bleeding. The family denied the recent history of fever, cough, hemoptysis, night-sweats, acute changes in weight, congestion, rhinorrhea, vomiting, myalgias, or arthralgia. He never experienced symptoms of bleeding like this before. On physical exam, it was noted he had dried blood on his nares, gums, and rectum, as well as diffuse petechiae and purpura on his abdomen, arms, and head. No lymphadenopathy, hepatosplenomegaly, jaundice or bone pain. Labs were drawn and demonstrated hemoglobin of 11.2 gm%, hematocrit 33, WBC $10.5x10^3/mm^3$, and platelet count of $18,000/mm^3$. A peripheral blood smear exam showed severe thrombocytopenia and normocytic anemia without schistocytes. He was subsequently diagnosed with Immune Thrombocytopenia (ITP) and treated with methylprednisolone and followed by IVIG twice for persistent platelets $<20,000/mm^3$. Following the second dose of IVIG, his platelets rose to $29,000/ mm^3$, and he was discharged after two days with aminocaproic acid as needed for epistaxis.

Immediately the next day the following discharge, the patient presented to the emergency department again for vomiting and fever in 100.7^0 F. During this visit his white blood count (WBC) was $15.6x10^3/mm^3$ and platelet count measured $79,000/mm^3$. He was treated with IV fluids and ondansetron until his vitals were stabilized and was discharged the same day. The patient followed by his primary care physician in 2 weeks and his platelet count rose to $277,000/mm^3$.

The patient presented to the emergency department again approximately two months later, this time complaining of worsening two days of fever that rose to 105.5^0 F, vomiting, decreased oral intake, headache, arm, and leg pain, fever, chills, and diaphoresis. At this admission, the patient's father reported that he suspects malaria to be the cause of the patient's current symptoms since his siblings had similar symptoms, which the father then divulged their family history. During this admission his WBC was $5.2 x10^3/ mm^3$, platelet count was $99,000 /mm^3$, hemoglobin 10.1gm%, hematocrit 30.2, and a peripheral smear demonstrated P. vivax with a parasitemia of 2.40. Liver enzymes were unremarkable, and coagulation studies were slightly elevated but within the normal range (PT 15.7, INR 1.22). An ultrasound was performed for concern of splenomegaly, which there was no abnormality. The CDC was consulted which reported his level

of thrombocytopenia was not atypical nor did he have severe disease. He was prescribed three days of atovaquone-proguanil (G6PD level was pending), and he was discharged the following day as he appeared clinically stable and his normal disease process of malaria was deemed not concerning (being discharged with a platelet count of 75,000 mm^3, malarial parasitemia of 0.5).

At the follow-up appointment two weeks later, G6PD labs resulted as normal, so he was prescribed primaquine, but was unable to obtain it due to denial of insurance coverage. He had been afebrile from his last hospitalization. No new laboratory tests were obtained at that visit. The patient's hospitalization and clinic visits, presentations are summarized in Table 1.

Table 1: Hospitalization Summaries

Time line: MM/DD	2/18 - 2/20	2/21	3/9	5/8-5/9
Chief complaint	Severe hrombocytopenia symptoms: epistaxis, mucosal bleeding	ED - fever and vomiting	Follow-up	malaria symptoms: body aches, fever, vomiting, hills
Temperature (^0F)	97	100.7		105.5
Hemoglobin (gm%)/ hematocrit	11.2/33	10.5/31.5	11.5/35.1	10.1/30.2
Red cell distribution width	14.8 – 14.9	15.1	14.7	14.0-14.1
WBC ($10^3/mm^3$)	10.5	15.6	8.7	5.2
Platelets/mm^3	18,000 →29,000 (following treatment)	79,000	277,000	99,000 →75,000
peripheral smear	severe thrombocytopenia, normocytic anemia without schistocytes	Not available	Not available	Plasmodium vivax with a parasitemia of 2.40 →0.5 (following treatment)
Treatment	methylprednisolone IVIG x2 Aminocaproic acid	IV fluids Ondansetron		Atovaquone-proguanil

Discussion

Thrombocytopenia is one of the most prominent laboratory findings, occurring in 75-80% of patients infected with P. Vivacious [2]. According to one study with 90 patients with P. vivax infection vs 52 healthy controls, patients with P. vivax demonstrated a statistically significant difference in means of hemoglobin, leukocyte count, red cell distribution width, and platelet count (for platelet count, 133,200/ mm^3 vs 265,000/mm^3 in infected vs healthy subjects respectively; $p<0.0001$) [3]. Severe thrombocytopenia (50,000 /mm^3) is rare for patients with isolated P. vivax infection. Even when P. vivax infected patients have platelet counts as low as 10,000mm^3, they do not show signs of bleeding [1,4]. Various proposed mechanisms for thrombocytopenia secondary to P. vivax infection exist. A clinical trial studying recombinant macrophage colony-stimulating factor (M-CSF) in 24 patients with P. vivax malaria observed that elevated levels of M-CSF were inversely related to platelet number, and suggested that M-CSF enhances macrophage-mediated platelet destruction activity [5]. Another proposed pathogenesis for malarial thrombocytopenia is an immune mechanism where platelet-associated IgG (PAIgG) binds platelet-bound malarial antigens, leading to platelet destruction seen in 16/17 patients infected with P. vivax [2]. According to this study, the targeted PAIgG would not bind directly to the platelet surface if malarial antigen was not present and additional malarial antigen could competitively displace platelet-bound antibodies. The association of elevated PAIgG with thrombocytopenia was again demonstrated in another case report where two patients

presented with thrombocytopenia (22,000/mm^3 and 53,000/mm^3) and elevated PAIgG levels (308 ng/10^7 cells and 431.7 ng/10^7 cells, normal 9-25 ng/10^7 cells) [6]. In all studies, thrombocytopenia, as well as abnormal lab values of M-CSF and PAIgG (both not measured in our patient), resolved with antimalarial treatment of the active infection without immunosuppressive therapy such as a corticosteroid.

In contrast, thrombocytopenia from ITP is characterized by platelet counts below 100,000/mm^3 and other blood components such as red and white blood cells are within the normal range [7]. Primary ITP is an idiopathic autoimmune disease where both autoimmune destruction of platelets, as well as impaired thrombopoiesis due to failed thrombopoietin response and megakaryocyte apoptosis leads to thrombocytopenia. Secondary ITP results from other etiologies such as a respiratory virus, rubella, rubeola, varicella, hepatitis, HIV, lymphoproliferative disorders, live virus vaccination, or drugs such as trimethoprim/sulfamethoxazole, quinine, quinidine, and chloroquine [8,9]. 75% of ITP patients were found to have an anti-platelet immunoglobulin G against glycoprotein IIb/IIIa and Ib/IX, resulting in phagocytosis of platelets or lysis secondary to complement activation. Other studies suggested that patients who did not possess antiplatelet IgG had thrombocytopenia caused by T-cell mediated cytotoxicity [10]. Symptoms such as purpura on the skin or mucous membranes, petechiae, hematomas, epistaxis or bleeding from the gums, and blood in urine or stool may be present, but obvious bleeding may only occur when platelets are <20,000/mm^3) [8]. Beyond bleeding symptoms, constitutional symptoms such as fever or weight loss and clinically significant lymphadenopathy or hepatosplenomegaly are atypical [7]. ITP is a diagnosis of exclusion, and the only lab that is mandatory for diagnosis is a peripheral blood smear to confirm thrombocytopenia in the absence of red or white blood cell abnormalities [7] since auto-antibody labs lack both sensitivity and specificity [11]. In most cases, it is safe to simply observe patients with ITP unless they are suffering from symptomatic bleeding, which in that case standard treatment consists of corticosteroids, IVIG, or monoclonal antibodies like Anti-CD20 or Anti-(Rh)D, which have a 75-95% rate of response. Clinical and lab comparisons between ITP vs. Malaria are made in Table 2.

Table 2: ITP vs. Malaria: Clinical Presentation and Lab Expectations

	ITP	**Malaria**	
Symptoms	purpura on the skin or mucous membranes, etechiae, hematomas, epistaxis or bleeding from the gums, and blood in urine or stool	**MILD** Fever/chills, diaphoresis, headache, fatigue, malaise, myalgia, arthralgia, anorexia, nausea, vomiting, abdominal pain, and diarrhea	**SEVERE** severe anemia with hemolysis, disseminated intravascular coagulation, thrombocytopenia, acute lung injury leading to respiratory distress, metabolic acidosis, altered mental status, and coma
Red Blood Cell Changes	None	Anemia ↓H/H ↑Red Cell distribution width	
White Blood Cell Changes	None	↑WBC	
Platelet changes	<100 x10^9/L (1)	133,200/mm^3 (2)	
Peripheral smear changes	Thrombocytopenia without red or white blood cell changes	Parasitemia evident	
Proposed Platelet Associated IgG	Targets platelet glycoprotein IIb/IIIa and Ib/IX (1)	Target platelet-bound malarial antigen (3)	

The patient's first presentation to the hospital with severe thrombocytopenia (18,000/mm^3) resulting in mucosal bleeding, diffuse petechiae, and purpura did not present typically like mild malaria with symptoms of fever, chills, diaphoresis, nausea or vomiting. Nor did it present like severe thrombocytopenia of severe malaria, since other severe malaria symptoms such as anemia (hemoglobin <5gm%) with hemolysis, lung injury, or metabolic acidosis were absent. Most significantly, he had the pertinent negative finding where his peripheral smear did not show evidence of red cell morphological changes or malaria. However, we cannot concretely identify a pure ITP picture either, considering his slightly low-normal hemoglobin/hematocrit and slightly increased fever and white count the day the following discharge. In general, the patient's separate hospitalizations for bleeding due to severe thrombocytopenia vs. mild malaria symptoms had inconsistent labs and very little overlap of symptoms. The first hospitalization with the most severe thrombocytopenia, lacking clear malarial symptoms or laboratory evidence, presented more like ITP possibly secondary to malaria. His response to IVIG during his first hospitalization also indicated pathogenesis more likely to be ITP than malaria since the thrombocytopenia began to resolve without malarial treatment. Though not widely reported, other cases of possible malaria-induced ITP have been noted. One case report describes a 20-year-old man in Amazonas, Brazil with no history of bleeding diatheses and a confirmed diagnosis of P. vivax who experienced three separate episodes of severe thrombocytopenia (ranging 1,000/mm^3 to 3,000/mm^3) that improved (ranging 38 ,000/mm^3 to 66,000/mm^3) after being treated with prednisone 1 mg/kg/day for one week [9]. He experienced severe thrombocytopenia and oral bleeding symptoms again whenever his oral corticosteroid dose was reduced. Another case report describes a 61-year-old Italian man diagnosed with infection with Plasmodium falciparum who presented to the hospital for cerebral malaria and was found to have a platelet count of 9,000/mm^3. His platelet count recovered to 257,000/mm^3 following 1 week of erythrocyte exchanges and high-dose chloroquine therapy, but in a modified antibody-specific Immobilization of platelet antigens (MAIPA) assay, he was found to have antibodies that reacted with glycoprotein IIb-IIIa and gpIa-IIa despite having no previous history of thrombocytopenic disorders [12]. To our knowledge, there are no reports of pediatric patients who developed autoimmune thrombocytopenia secondary to malaria.

Conclusion

Clinicians should be aware that while thrombocytopenia is a well-known symptom of severe malaria, patients with malaria can develop thrombocytopenia separate from malaria symptoms in the form of secondary ITP. Conversely, though not a commonly known cause of secondary ITP, it is important that patients with ITP and risk factors for malaria exposure, such as travel and immigration should be closely followed for possible underlying infection with malaria.

References

1. Song HH, O SO, Kim SH, Moon SH, Kim JB, Yoon JW, et al. Clinical features of Plasmodium vivax malaria. Korean J Intern Med. 2003; 18: 220-224.

2. Kelton JG, Keystone J, Moore J, Denomme G, Tozman E, Glynn M, et al. Immune-mediated thrombocytopenia of malaria. J Clin Invest. 1983; 71: 832-836.

3. Koltas IS, Demirhindi H, Hazar S, Ozcan K. Supportive presumptive diagnosis of Plasmodium vivax malaria. Thrombocytopenia and red cell distribution width. Saudi Med J. 2007; 28: 535-539.

4. Makkar RP, Mukhopadhyay S, Monga A, Monga A, Gupta AK. Plasmodium vivax malaria presenting with severe thrombocytopenia. Braz J Infect Dis. 2002; 6: 263-265.

5. Lee SH, Looareesuwan S, Chan J, Wilairatana P, Vanijanonta S, Chong SM, et al. Plasma macrophage colony-stimulating factor and P-selectin levels in malaria-associated thrombocytopenia. Thromb Haemost. 1997; 77: 289-293.

6. Yamaguchi S, Kubota T, Yamagishi T, Okamoto K, Izumi T, Takada M, et al. Severe thrombocytopenia suggesting immunological mechanisms in two cases of vivax malaria. Am J Hematol. 1997; 56: 183-186.

7. Labarque V, Van Geet C. Clinical practice: immune thrombocytopenia in paediatrics. Eur J Pediatr. 2014; 173: 163-172.

8. Imbach P. Guide to Understanding ITP (Immune thrombocytopenia). 2011.

9. Lacerda MV, Alexandre MA, Santos PD, Arcanjo AR, Alecrim WD, Alecrim MG. Idiopathic thrombocytopenic purpura due to vivax malaria in the Brazilian Amazon. Acta Trop. 2004; 90: 187-190.

10. Jernås M, Carlsson LMS, Wadenvik H, Jacobsson S, Carlsson B, Olsson B, et al. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. Nat Med. 2003; 9: 1123-1124.

11. Berchtold P, Muller D, Beardsley D, Fujisawa K, Kaplan C, Kekomaki R, et al. International study to compare antigen-specific methods used for the measurement of antiplatelet autoantibodies. Br J Haematol. 1997; 96: 477-483.

12. Conte R, Tassi C, Belletti D, Ricci F, Tazzari PL. Autoimmune Thrombocytopenia in malaria. Vox Sang. 2003; 85: 221.

Manuscript Information: Received: May 05, 2019; Accepted: June 14, 2019; Published: June 28, 2019

Authors Infomation: Christie Becu[1]; Anand Gourishankar[2]*

[1]Doctor of Medicine Candidate, Department of Pediatrics at John P. and Katherine G. McGovern Medical school/UT Health, Houston, Texas, USA

[2]Associate Professor, Department of Pediatrics at John P. and Katherine G. McGovern Medical school/UT Health, Houston, Texas, USA

Citation: Becu C, Gourishankar A. Dual manifestations of thrombocytopenia in Plasmodium vivax malaria. Open J Clin Med Case Rep. 2019; 1554.