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The Uncommon Association between Typhoid Fever and Immune Thrombocytopenic Purpura

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MAPG and RZV gathered patient information and wrote the manuscript. Authors SVK, RTA, LSA and HSV made the cared the patient, reviewed the manuscript and provided expert suggestions. All authors reviewed and accepted the final manuscript for submission.

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Case Study

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ABSTRACT

Aims: To report an uncommon and underreported association between immune thrombocytopenic purpura and typhoid fever and review the available literature.
Presentation of Case: We present a 19 year-old female with two weeks of vaginal and gastrointestinal bleeding. At the time of presentation, fever, pallor, petechial lesions, ecchymosis and hepatosplenomegaly were noted. Initial workup for associated secondary viral infections were negative, hematologic studies were undertaken. Immune thrombocytopenic purpura was diagnosed and treatment with prednisone initiated. Nonetheless, after initial improvement, fever recurred and *Salmonella typhi* was isolated on blood culture, after treatment with ciprofloxacin symptoms disappeared with good evolution after outpatient follow-up.
Discussion: Immune thrombocytopenic purpura is commonly associated to several viral and

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some bacterial infections, yet *Salmonella typhi* has not been consistently proved to be associated. A growing body of literature shows that a diverse variety *Salmonella sp.* presentation can be associated to immune thrombocytopenic purpura. Both diseases reverse after antibiotic treatment.

Conclusion: Typhoid fever should be included in the differential diagnosis when other causes of immune thrombocytopenic purpura have been discarded and clinical presentation is suggestive.

Keywords: Immune thrombocytopenic purpura; typhoid fever; thrombocytopenia; Salmonella typhi.

1. INTRODUCTION

Typhoid fever is a severe systemic disease, caused by *Salmonella typhi.* The natural history is well describe due to studies done in the pre-antibiotic era. On the first week there is usually rising fever and bacteremia; pulse-temperature dissociation can be seen. During the second week patients develop abdominal pain and a distinctive rash of salmon colored, blanching macules usually in the abdomen and thorax. If the disease is not treated, hepatomegaly and splenomegaly, along with gastrointestinal bleeding, ileocecal perforation and subsequent peritonitis can present on the third week. If the patient does not receive treatment and complications do not ensue, disease will become self-limited by the end of the fourth week [1]. Since *Salmonella typhi* is transmitted through contact with poorly hygienic food, sanitary conditions predispose countries such as Peru to have endemic infection [2].

The most common hematologic manifestations are anemia and leukopenia, complete absence of eosinophils on peripheral blood is relatively common. Low platelet count is not commonly seen. In a pediatric case series [3], thrombocytopenia was found on 24% of pre-school aged children, with a minimum count of 120 000 x 10^9/L.

Due to poorly recognized hematologic manifestation, we present a case of typhoid fever associated to immune thrombocytopenic purpura in an adult woman.

2. PRESENTATION OF CASE

A 19-year old female presented to the emergency room of the “Cayetano Heredia” hospital with fever, gum bleeding, epistaxis and melena for 13 days. At first she presented fever and chills that did not respond to over the counter medication, associated to stabbing headache of 3/10 intensity, general malaise, nausea and bilious vomits.

Ten days before admission the patient presented intermittent, malodorous and abundant diarrhea three times a day, along with occasional melena. Later petechial lesions in thorax and abdomen developed, along with red-wine depositions. Eight days before admission gum bleeding, epistaxis, vaginal bleeding, coluric urine presented and petechial lesions expanded to the upper and lower extremities. Due to persistence of symptoms the patient went to the emergency room.

On biological functions, patient referred low appetite, weight loss of approximately 6 kg, hypersomnia and malaise. Past medical history was negative for previous diseases, previous surgeries, allergies, and alcohol and tobacco abuse. She denied travels within the last year and recent immunizations. Last menstrual period started 20 days before admission, with regular characteristics and had given birth one year earlier without complications. She denied use of birth control methods, risk factors for sexually transmitted diseases.

The patient lives in the province of Chimbote, in a precarious house, without potable water and breeds chickens. She sells newspapers and usually eats in a market near her working place. Family history was unremarkable.

Physical examination showed blood pressure: 100/60 mmHg without orthostatic changes, heart rate 100 bpm, respiratory rate of 20 per minute and temperature 37.5℃.

Skin was pale, with petechial lesions and hematomas in tights and abdomen. No jaundice, nor lymphadenopathies were found. On the abdomen, hepatomegaly and splenomegaly were found. Gynecologic examination revealed active bleeding. Rectal examination was delated due to evident melena. Cardiovascular, respiratory and neurological examination where unremarkable.

Laboratory exams showed hemoglobin 5.38 g/dL, MCV 89.9 fl, MCH 30.3 g/dL, 7 900 WBC

× 10^3/microL (0% bands, 50% segmented, 0% eosinophils, 0% basophils, 9% monocytes and 41% lymphocytes) and 16 x 10^9/L platelets. The peripheral smear showed anisocytosis and macrocytosis, scarce lobulated neutrophils and severe thrombocytopenia. Urinalysis showed 80-100 red blood cell per high powered field, without white blood cells. ALT 110 U/mL, AST 128 U/mL, LDH 1331 U/mL.

Serology for HIV, VDRL, hepatitis C, HBsAg, HBcAg, Rose Bengal, 2-mercaptoethanol, anti-nuclear antibodies and parasitological exam on feces were negative. Tube agglutinations for Brucella where 1/20 were negative. Typhoid fever O antigen agglutination was 1/80 and H antigen was 1/80.

An abdominal ultrasonography was obtained that showed mild splenomegaly. Chest X- ray was unremarkable. Bone marrow aspirate showed 70% cellularity, with 3 hematopoietic series and mild megakaryocytic and erythroid hyperplasia. Bone marrow biopsy showed scarce hematopoietic tissue with 3 adequately matured series.

On the day of admission 6 platelet packets were transfused and the following day more platelet transfusion was needed due to persistent bleeding. Based on the isolated thrombocytopenia (other than normochromic normocytic anemia, likely due to bleeding), and lack of other more likely possibilities, the diagnosis of immune thrombocytopenic purpura (ITP) was made and treatment with Prednisone 60 mg per day was started. On the sixth day of hospitalization fever recurred, a complete blood count and blood cultures were taken. Exams showed hemoglobin 9.8 g/dL, 7800 WBC x 10^3/microL, 0% bands and 42 x10^9/L platelets.

Fever persisted until the eleventh day of hospitalization, when blood culture revealed *Salmonella typhi* sensitive to all the tested antibiotics, thereby treatment with ciprofloxacin 500 mg PO twice a day was started and fever ceased.

The patient was discharged 4 days later, the last platelet study showed 211 x10^9/L platelets, (Table 1) antibiotic treatment was indicated until the third day after discharge and the prednisone dosage was diminished progressively.

On out-patient follow up 2 weeks later she showed improvement, afebrile and with a platelet control within normal ranges, thereby prednisone was finally suspended.

3. DISCUSSION

ITP is a common acquired hematologic disorder without clear etiology. Incidence is higher in children than in adults, with an estimated rate of 22 cases per million persons per year [4]. Many reports suggest a female predominance and 72% of patients under 40 years old.

Some cases are associated to previous viral infection, most commonly reported viral infections include HIV, Cytomegalovirus, Herpes zoster virus and Hepatitis C virus are the most commonly identified [1]. Brucellosis has also been described as a possible cause [5]. Another predisposing factor to ITP is the presence immune system abnormalities such as antiphospholipid syndrome, systemic lupus erythematosus, Evan's syndrome or sarcoidosis [6].

There are several theories regarding the pathophysiology of ITP [7,8]. The first proposes that antibodies against certain virus cross react and increase platelet elimination; for example HIV proteins can be similar to platelet's glycoprotein IIb/IIIa. Regarding ITP associated to bacteria, *Helicobacter pylori* produces platelet aggregation and cross reaction between platelet associated IgG and *H. pylori* cytotoxin-associated gene A. Other bacteria produce lipopolysaccharides that attach to platelet surface and increase the phagocytosis.

Clinical presentation of ITP is variable, presentation is most commonly insidious, but abrupt and acute presentation is not uncommon. Platelet dysfunction manifestations can vary from mild severity such as petechial lesions and hematomas, to life-threatening hemorrhagic diathesis. Typical bleeding is described as mucocutaneous, such as epistaxis, gum bleeding and menorrhagia. Gastrointestinal and intracranial bleeding are uncommon, as well as hematuria [8]. In this patient the reason for gastrointestinal bleeding is possibly not only related to ITP, but a concomitant gastrointestinal infection by *Salmonella typhi* may play a role.

It is widely accepted that *Salmonella* family produce hematologic disease such as leukopenia and anemia. Nonetheless a case report describes the occurrence of neutropenia, thrombocytopenia and acute renal failure in a patient with carotid arteritis caused by *Salmonella enterica*, [9] and also fever and thrombocytopenia were described during *Salmonella enteritidis* infection [10].

Table 1. Progression of complete blood count

	Hospitalization day		
	1st	6th	15th
Hemoglobin (g/dL)	5.38	9.8	-
MCV (fL)	89.9	-	-
MCH (g/dL)	30.3	-	-
WBC (x 10^3/microL)	7.9	7.8	-
Platelets (x 10^9/microL)	16	42	211

Salmonella typhi is not yet recognized as a known cause of ITP in any age group, [11] yet a report published by Gétaz et al. [12] in 1977 where they describe a 13 year old female with epistaxis and gum bleeding, with 8.2 g/dL, 6000 WBC x10^3/microL with left deviation and 8 x10^9/L platelets on admission. After obtaining blood cultures ITP was diagnosed and ampicillin treatment was started. Similarly, a recent case report has also reported this association in a 10-year-old boy, whose symptoms resolved after antibiotic and corticosteroid treatment [13].

On the sixth day of hospitalization blood culture was positive to *Salmonella typhi* and tiamfenicol is started, finally platelet count returned to normal after 10 days of antibiotic treatment. Mittal et al. [14] reported three children with infection by *Salmonella typhi* that presented fever, urticarial, thrombocytopenic purpura and meningitis.

Another case series in pediatric patients [3] showed hematologic manifestations of typhoid fever in 89 patients. These patients presented changes in all three hematologic series, for example in pre-school aged children anemia was found on 76%, leukopenia in 47%, along with zero eosinophils in 83% of them, and thrombocytopenia in 24%, of whom 7% persisted thrombocytopenic until finishing treatment, with all of them normalizing 15 days after treatment. In school aged children, 61% presented anemia, 65% presented leukopenia and 98% had zero eosinophils, and thrombocytopenia in 42%. Authors concluded that the cause of this alteration is platelet destruction in the spleen and liver.

In this case the patient had 16 x10^9/L platelets and gastrointestinal bleeding. On admission the diagnosis of ITP is made, and the most common causes for secondary ITP were discarded. On the second day 60 mg per day prednisone was started, on the sixth day platelet count increased, but fever ensued. This delay in the appearance of fever might be due to immunosuppressive therapy [15]. Platelet count remained stable and fever persisted until ciprofloxacin therapy was started due to blood cultures results, positive for *Salmonella typhi,* when fever decreased platelet count increased at the same time, suggesting the cause of the thrombocytopenia was the infection.

Similar management has been previously reported, [16] were upon recognition of isolated thrombocytopenia in a patient with fever, diarrhea and abdominal pain an infectious cause was suspected and antibiotic started promptly. ITP has also been previously reported after non-gastrointestinal presentations, such as septic arthritis, again antibiotic were successfully used to treat these patients [17].

4. CONCLUSION

It is important to add infection by *Salmonella typhi* in the differential diagnosis of secondary ITP associated to fever and other signs of infection, especially when common secondary causes have been ruled out. The present case and other reports on the literature show a rapid response to antibiotic therapy.

CONSENT

Written informed consent was obtained from the patient for the publication of this case report.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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