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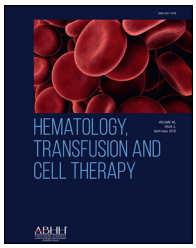

Case Report

Immune thrombocytopenia associated with *Helicobacter pylori* – unclear associative mechanisms

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Introduction

Primary immune thrombocytopenia (ITP) is an immune-mediated acquired disease characterized by a transient or persistent isolated decrease in the platelet count (peripheral blood platelet count $<100 \times 10^9$/L) and, depending upon the degree of thrombocytopenia, an increased risk of bleeding. Secondary ITP includes all forms of immune-mediated thrombocytopenia except primary ITP.[1] Secondary ITP may be triggered by inherited or acquired predisposing diseases such as chronic infections or autoimmune diseases.[2] Various chronic infections have been implicated in the disease, such as hepatitis C (HCV), human immunodeficiency virus (HIV) and *Helicobacter pylori* (*H. pylori*). The relationship between *H. pylori* infection and ITP was first described in 1998, when an Italian group reported an increase in the platelet count in 8 of 11 ITP patients treated with eradication therapy.[3] Since then, multiple studies have reported cases of eradication of *H. pylori*.[4–10]

Several theories have been proposed to explain the role of *H. pylori* in ITP development, including molecular mimicry between platelets and *H. pylori* antigens, platelet aggregation, down-regulation of the reticuloendothelial system and induction of a Th1 phenotype, which presumably favors the onset and/or persistence of ITP, but until today no proven mechanism exists, regarding the possible pathogenesis.[11,12] Currently, molecular mimicry between antigens and homology of *H. pylori* Urease B with platelet surface glycoprotein IIIa, leading to platelet destruction, is the most commonly accepted, but the exact mechanism is not completely understood.[4,8,13]

Despite this apparent association, the response of the platelet count to *H. pylori* eradication therapy has somewhat shown discrepancy between studies, and various factors, such as strains of *H. pylori*, prevalence of *H. pylori* infection and genetic and environmental factors may influence the outcomes.[9]

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The *H. pylori* infection in patients with ITP varies greatly from one country to another, being higher in developing countries and lower in industrialized countries. Most studies report higher platelet response rates to eradication therapy in series with higher prevalence of *H. pylori* infection.[6] Given that *H. pylori*-associated ITP prevalence was not found different from that reported in the general healthy population matched for age and geographical area, it would stand to reason that the prevalence of *H. pylori* infection in ITP mirrors the prevalence of *H. pylori* infection in the general population. This may explain why the probability of response appears to be consistently higher in patients from Italy and Japan, where the reported general prevalence is 50% and 70%, respectively, when compared with American studies, in which the general prevalence of *H. pylori* infection in North American patients is 22%. One possible explanation for this association may relate to the CagA-positive strains of *H. pylori*, since most strains in Japan express it, whereas the proportion of the CagA-positive strains in Western Countries is much lower.[11]

Nevertheless, irrespective of all contributing factors, what seems to be a common denominator is that *H. pylori* eradication appears to have a limited but valuable effect, particularly in young patients who have a relatively mild disease of short duration.[10]

Case report

A 57-year-old male, with no previously known medical history, no use of medication and an irrelevant epidemiologic context, was admitted to our institution with an evolving petechial rash and gingivorrhagia within the previous month. No other symptoms where referred. On physical examination, he presented an extensive hematoma on the left lower leg, ecchymosis on the back and along the arms and legs and cutaneous petechiae restricted to the lower limbs. No other abnormalities where found. The first bloodwork showed an abnormal platelet count of $<10 \times 10^9$/L and he was admitted for further study.

The initial workup showed no abnormalities besides persistent thrombocytopenia ($<10 \times 10^9$/L). The peripheral blood smear was normal. Serologies for HIV, HCV, hepatitis B (HBV), Parvovirus B19, Epstein Barr virus (EBV) and Herpes simplex 1 and 2 viruses (HSV 1 and 2) where negative. The iron kinetics were normal, as were vitamin B12, folic acid and copper. The protein electrophoresis was also normal. The auto immunity, including the antiphospholipid syndrome study, was negative. The chest X-ray was normal and the abdominal ultrasound showed no splenomegaly.

Despite no new mucocutaneous bleeding lesions having been found, and the initial manifestations being in the process of disappearing, the patient maintained persistent thrombocytopenia ($<10 \times 10^9$/L) in the first week after admission.

To continue the exclusion of secondary causes of ITP, the patient was then tested for *H. pylori* infection by means of an *H. pylori* stool antigen test, which was positive. Eradication therapy was immediately started (Amoxycillin 1000 mg bid, Clarithromycin 500 mg bid, Metronidazole 500 mg bid and Pantoprazole 40 mg bid, for 14 days), accompanied by a gradual increase in platelet count, 12×10^9/L within 3 days of eradication therapy and 59×10^9/L at the time of discharge. One month after treatment completion, he was reevaluated in consultation, showing full recovery with platelet counts of 139×10^9/L and no recurrence of bleeding symptoms. Six months later, he repeated the *H. pylori* stool antigen test, confirming successful eradication and during that time he had remained asymptomatic, with a normal platelet count (148×10^9/L).

Discussion

In an effort to standardize terminology, Rodeghiero et al. defined primary ITP as an autoimmune disorder characterized by isolated thrombocytopenia ($<100 \times 10^9$/L) in the absence of other causes or disorders that might be associated with thrombocytopenia. Secondary ITP was defined as all forms of immune-mediated thrombocytopenia, except primary ITP.[1]

Although primary ITP diagnosis was clinically feasible, we conducted a thorough investigation to exclude potential secondary causes. The initial study showed no abnormalities, supporting our suspicion and, given the absence of systemic symptoms and no other abnormalities in blood lines, no bone marrow examination was performed, as the American's Society of Hematology Clinical Practice Guideline on the Evaluation and Management of ITP recommends, irrespective of the patient's age.[14]

Throughout the initial workup, the patient maintained clinical stability and no recurrence of bleeding symptoms, but there was no increase in the platelet count. Despite this, no therapy was initiated, based on the consensus that the majority of patients with no bleeding or mild bleeding (defined as skin manifestations only, such as petechiae and bruising) can be treated with observation alone, regardless of platelet count, as recommended in the guidelines referred to above. As all results came back negative, we considered screening for *H. pylori* infection. The *H. pylori* can be detected at endoscopy by histology, culture or urease tests. Non-invasive methods include the ^{13}C-urea breath test, antigen detection in stools and serum antibody assays, and these methods are generally reserved for patients in whom the obtaining of biopsies may be associated with complications (e.g., anticoagulation therapy, severe thrombocytopenia). The first two non-invasive methods are considered to be more accurate, with both sensitivity and specificity in the range of 90–95%. The serum antibody assay, although less expensive, lacks accuracy. It is not a specific indicator of active infection and therefore, since antibody titers fall slowly after successful eradication, it cannot be used to determine the *H. pylori* infection eradication or to detect reinfection.[11] In our patient's case, given his low platelet count and the bleeding risk associated with the biopsy, the diagnosis was made by antigen detection in stool. Once the diagnosis was confirmed, we started the *H. pylori* eradication therapy. As observed in similar case reports, there was an increase in the platelet count after the *H. pylori* eradication therapy and no recurrence after 6 months of follow-up. According to Rodeghiero et al, for cases associated with *H. pylori* infection, a diagnosis of secondary ITP (*H. pylori*-associated), would require the demonstration of complete resolution of ITP after proven eradication of the bacteria,[1] as was done in our patient's case.

Individual characteristics that predict platelet response to the *H. pylori* eradication therapy have been extensively analyzed in the *H. pylori*-associated ITP patients. The most consistently reported feature that predicts a favorable response is a shorter duration of ITP.[6,10,13] Other clinical characteristics, including age less than 65 when diagnosed with ITP, higher baseline platelet count, no prior corticosteroid therapy, no concomitant corticosteroid therapy and no prior therapy for ITP, have inconsistently been reported.[7,13] According to that which was previously stated, our patient exhibited the best profile to presumably benefit from screening and treatment and, as reported, showed an excellent and consistent response to eradication therapy.

Conclusion

Although the association between *H. pylori* infection and ITP seems clear, we believe that more clinical studies are needed to elucidate the unclear underlying mechanism and the discrepancy of the platelet response to eradication therapy.

Conflicts of interest

The authors declare no conflicts of interest.

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