Immune Thrombocytopenia Induced by Helicobacter pylori Infection: A Case Report and Literature Review

Haleema Sadia 1, Sheeraz Abro 2, Muneeba Ali 3, Khalid Uddin 4, Adesola A. Agboola 5, Shehar Bano 6, Chinyere L. Anigbo 7, Romil Singh 8

1. Internal Medicine, Khyber Teaching Hospital, Peshawar, PAK
2. Internal Medicine, Chandka Medical Hospital, Larkana, PAK
3. Internal Medicine, Foundation University Medical College, Rawalpindi, PAK
4. Neurology, Henry Ford Health System, Detroit, USA
5. Pathology and Laboratory Medicine, Dele Medical Hospital, Lagos, NGA
6. Internal Medicine, University of Health Sciences, Lahore, PAK
7. Internal Medicine, University of Nigeria, Enugu, NGA
8. Critical Care, Allegheny Health Network, Pittsburgh, USA

Abstract
Immune thrombocytopenia (ITP) is an autoimmune disease characterized by the production of autoantibodies against the platelet surface antigens. ITP is a diagnosis of exclusion and is further categorized into primary and secondary ITP. The etiology of primary ITP is idiopathic, and secondary ITP is caused by infections and autoimmune disorders. Among infectious etiology of ITP, human immunodeficiency virus, herpes virus, and hepatitis B and C virus are common. *Helicobacter pylori* (*H. pylori*) is a rare cause of ITP, and the relationship between ITP and *H. pylori* is highlighted in the literature. We report a case of ITP in an adult female who presented with hematemesis and petechial rash in the lower limbs. Her initial laboratory results demonstrated thrombocytopenia, and the results of her gastric biopsy and stool antigen were positive for *H. pylori*. She was diagnosed with ITP induced by *H. pylori* because additional causes of ITP were not identified. Her clinical improvement and platelet recovery after initiating *H. pylori* eradication therapy were consistent with *H. pylori*-induced ITP.

Introduction
Immune thrombocytopenia (ITP) is a type of platelet disorder. ITP is an immune-related syndrome presented with isolated thrombocytopenia, leading to an increased bruising and bleeding tendency. Bleeding usually results from transient or persistent low platelet count [1,2]. Secondary ITP can be inherited or acquired and includes all forms of thrombocytopenia except for idiopathic ITP. Among acquired causes of secondary ITP, various autoimmune disorders and chronic infections are more common. The chronic infections that lead to ITP include human immune deficiency virus (HIV), hepatitis C virus (HCV), and Epstein-Barr virus (EBV) [2]. *Helicobacter pylori* (*H. pylori*) can also trigger ITP; however, the association between ITP and *H. pylori* is not widely reported in the literature [3]. The first association between ITP and *H. pylori* was reported in 1998 when an Italian study highlighted an increase in the platelet cell count in diagnosed patients treated with eradication therapy [4]. Herein, we report a case of ITP in a patient diagnosed with *H. pylori* infection.

Case Presentation
A 37-year-old female without significant past medical history was brought to the emergency department after bloody vomiting. She reported three episodes of hematemesis, and her blood was bright red in each episode. She denied any history of fever, trauma, alcohol abuse, abdominal pain, melena, heartburn, hematochezia, or nonsteroidal anti-inflammatory drugs (NSAIDs) use. She also complained of multiple episodes of petechial rash and gingival bleeding in the past, for which she did not seek any medical advice.

On admission, she was hemodynamically stable and oriented to time, place, and person. On examination, she had dried blood on her nares and an evolving petechial rash in her lower limbs. Her abdominal, respiratory, and cardiovascular examinations were unremarkable, with no lymphadenopathy noted in cervical, axial, and groin regions. Her results from initial laboratory tests are shown in Table 1.
Hemoglobin: 12.9 g/dL  
MCH: 27 pg  
MCV: 80.9 fL  
MCHC: 29.4 g/dL  
Red cell count: 4.1 million cells/µL  
White cell count: 13,200/µL  
Platelet count: 4,000/µL  
LDH: 297 IU/L  
ESR: 12 mm/hr  
Haptoglobin: 102 mg/dL

Peripheral blood smear and protein electrophoresis were unremarkable. Iron studies were within the normal range, including folic acid (7.0 ng/ml), vitamin B12 (840 pg/ml), and copper levels (87 mcg/dl). Her chest X-ray was normal, and the abdomen ultrasound showed no hepatosplenomegaly and ascites. The autoimmune screening was not performed because she had no significant medical history. Owing to her low platelet count, a provisional diagnosis of ITP was made, and she was commenced on oral dexamethasone and pantoprazole infusion for concern of acute upper gastrointestinal (GI) bleed. She developed another episode of hematemesis of bright red blood six hours later. She underwent upper GI endoscopy urgently, which revealed diffuse erosive gastritis. She was continued on pantoprazole infusion and her bleeding resolved without further hematemesis. She was also commenced on 40 mg dexamethasone orally for four days and intravenous immunoglobulin for ITP management.

Her serology was negative for HIV, hepatitis B virus, HCV, and herpes virus. She was tested for H. pylori infection through an H. pylori stool antigen test, and the result was positive. She was also commenced on eradication therapy, which included amoxicillin 1 g twice daily, metronidazole 500 mg three times daily, pantoprazole 40 mg twice daily, and clarithromycin 500 mg twice daily for 14 days. She was discharged in stable condition with a platelet count of 125,000/µL and was evaluated three days later. Her gastric biopsy results from upper GI endoscopy were positive for H. pylori infection. She reported improvement in her condition with an increased platelet count of 145,000/µL. An increasing trend in platelet count was observed subsequently. She was evaluated one month after completing eradication therapy, demonstrating almost full recovery with a platelet count of 202,000/µL and no bleeding recurrence. Her repeated stool antigen test for H. pylori was negative after one month.

**Discussion**

ITP is characterized by an isolated decrease in platelet count (<150,000/µL) in the absence of other etiologies or factors that might be associated with thrombocytopenia [1]. ITP is a diagnosis of exclusion and is further categorized into primary and secondary ITP. Secondary ITP is caused by infections and autoimmune disorders, including systemic lupus erythematosus disease, thyroid disorders, antiphospholipid antibody syndrome, HCV, and HIV [2,5]. A few case studies have reported the relationship between ITP and H. pylori. Gasbarrini et al. reported that eight out of 11 patients diagnosed with ITP responded to eradication therapy [4]. Vanegas et al. reported platelet improvements after eradication therapy in patients with H. pylori infection; however, there was a variable response to platelet resolution with no response to complete recovery [6]. It is also concerned that either thrombocytopenia severity or disease duration impacts platelet resolution [7]. We have tabulated the cases of ITP that showed full recovery after H. pylori eradication therapy (Table 2) [5,8-11].
| Author            | Age/sex | Clinical presentation | Investigation                  | Platelet count before treatment | Treatment                              | Clinical outcome                                           |
|-------------------|---------|-----------------------|---------------------------------|---------------------------------|----------------------------------------|-----------------------------------------------------------|
| Marques et al.    | 57/M    | Petechial rash, gingivorrhagia | HP stool antigen positive        | <10,000/uL                      | HP eradication therapy                | 151,000/uL after six months and negative stool antigen |
| Ramachandran et al. [9] | 28/M    | Hematemesis           | Gastric biopsy positive for HP   | <3,000/uL                       | Dexamethasone plus HP eradication therapy | 251,000/uL after six months and negative stool antigen |
| Goto et al. [10]  | 53/F    | Petechial rash, hematemesis | Gastric biopsy positive for HP   | 24,000/uL                       | HP eradication therapy                | 135,000/uL after eradication therapy                     |
| Elou et al. [11]  | 41/F    | Hematochezia          | Positive urea breath test        | 10,000/mL                       | HP eradication therapy                | Platelet count improved after eradication therapy        |
| Hill et al. [3]   | 54/F    | Asymptomatic          | HP stool antigen positive        | 47,000/mL                       | Prednisone plus HP eradication therapy | 145,000/mL after eradication therapy                     |
| Tiwari et al. [5] | 40/F    | Melena, bleeding gums, purpura | Gastric biopsy positive for HP antigen | 40,000/mL                       | Steroids plus triple therapy against HP | Normal platelet count after three months                  |

**TABLE 2: Summary of published immune thrombocytopenia cases induced by H. pylori infection.**

HP: Helicobacter pylori; M: male; F: female.

The pathophysiology of ITP induced by *H. pylori* remains uncertain. The proposed mechanisms included molecular mimicry, down-regulation of the endothelial system, and platelet aggregation, which errand the onset or persistence of ITP [12]. The association between ITP and cytotoxin-associated gene A (CagA) protein produced by *H. pylori* has also been demonstrated. Patients with ITP also have decreased platelet-associated immunoglobulin G (PAIgG) levels, and it was proposed that immune-complex formulations occur due to cross-reactivity between these proteins [13]. Proton pump inhibitor (PPI) use has also been implicated as a rare cause of thrombocytopenia. However, all these inferences were reported in case reports. A clinical retrospective study of 468 patients did not highlight any relationship between PPIs and ITP, and using PPIs in acute GI bleeding is recommended [14]. Regardless of an obvious relationship between ITP and *H. pylori*, platelet count resolution to *H. pylori* eradication treatment has demonstrated divergence between clinical studies. Various factors may impact the results and outcomes, such as genetic and environmental factors, *H. pylori* stains, and prevalence of infection [7].

The definitive treatment of ITP mainly comprises immunomodulatory agents, including steroids (prednisone), immunoglobulin therapy, and rarely, salvage splenectomy or monoclonal antibodies (rituximab) [2]. In cases of secondary ITP, the cause of ITP must be treated. *H. pylori* treatment therapy includes PPIs and a combination of amoxicillin, metronidazole, and clarithromycin. The duration of eradication therapy is seven to 14 days, and treatment efficacy is checked after eight-week post therapy through serum platelet count and stool antigen testing [8-10]. Our patient presented with hematemesis, petechia, and trombocytopenia. Her recovery after eradication therapy confirmed the diagnosis of ITP induced by *H. pylori* infection.

**Conclusions**

Our case highlights the possible relationship between ITP and *H. pylori*. Although *H. pylori* is a rare cause of ITP, it should be included among differentials, and diagnosis and evaluation of underlying etiology in ITP are obligatory for appropriate management. Further clinical studies are warranted to explain the unclear pathophysiology of *H. pylori* in ITP and the paradox of platelet response to anti-*H. pylori* therapy.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.
References

1. Rodeghiero F, Stasi R, Gernsheimer T, et al.: Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009, 115:2386-93. 10.1182/blood-2008-07-162503

2. Zufferey A, Kapur R, Semple IW: Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). J Clin Med. 2017, 6:16. 10.3390/jcm6020316

3. Hill LI, Tung EE: From prednisone to pylori: a case of Helicobacter pylori-induced chronic immune thrombocytopenia. BMJ Case Rep. 2014, 2014:10.1136/bcr-2014-205786

4. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G: Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. Lancet. 1998, 352:878. 10.1016/S0140-6736(05)60004-9

5. Tiwari SK, Manoj G, Khan AA, Habeeb A, Habibullah CM: Chronic idiopathic thrombocytopenic purpura and Helicobacter pylori eradication: a case study. Gastroenterology Res. 2009, 2:57-9. 10.4021/gr2009.02.1271

6. Vanegas YA, Vishnu P: Management of Helicobacter pylori in patients with immune thrombocytopenia. Hamostaseologie. 2019, 39:279-83. 10.1055/s-0039-1685974

7. Zain MA, Zafar F, Ashfaq A, Jamil AR, Ahmad A: Helicobacter pylori: an underrated cause of immune thrombocytopenic purpura. A comprehensive review. Cureus. 2019, 11:e5551. 10.7759/cureus.5551

8. Marques AR, Sousa L, Mendes M, Apolinário I: Immune thrombocytopenia associated with Helicobacter pylori - unclear associative mechanism. Hematol Transfus Cell Ther. 2019, 41:272-4. 10.1016/j.htct.2018.12.002

9. Ramachandran L, Babchi L, Dijdeh TM, Sidhu Y, Gentile N, Affinati M: Immune thrombocytopenic purpura secondary to Helicobacter pylori. Proc (Baylor Univ Med Cent). 2022, 35:60-1. 10.1080/08998280.2021.1973293

10. Goto H, Ikuta T, Ota A, Tsuji H, Hino R: Successful treatment of refractory idiopathic thrombocytopenic purpura by eradication of Helicobacter pylori. (Article in Japanese). Rinsho Ketsueki. 2001, 42:1192-4.

11. Eto U, Iizuka K, Miyazawa A, Yagisawa H, Yamano HO, Ishii T, Sagara S: Ulcerative colitis accompanied by idiopathic thrombocytopenic purpura and Helicobacter pylori infection. Intern Med. 2013, 52:547-9. 10.2169/internalmedicine.52.8856

12. Stasi R, Provan D: Helicobacter pylori and chronic ITP. Hematology Am Soc Hematol Educ Program. 2008, 2008:206-11. 10.1182/asheducation-2008.1.206

13. Jiménez-Soto LF, Haas R: The CagA toxin of Helicobacter pylori: abundant production but relatively low amount translocated. Sci Rep. 2016, 6:23227. 10.1038/srep23227

14. Dottin E, Katz R, Bratcher J, Wasserman C, Liebman M, Panagopoulos G, Spaccavento C: The prevalence of pantoprazole associated thrombocytopenia in a community hospital. Expert Opin Pharmacother. 2007, 8:2025-8. 10.1517/14656566.8.15.2025