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A Patient With Persistent Immune Thrombocytopenic Purpura Associated With Helicobacter Pylori Infection And Esophageal Candidiasis Following Long-Term Corticosteroid Therapy

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ABSTRACT

Background: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia and has been associated with Helicobacter pylori (H. pylori) infection. Long-term corticosteroid therapy, the mainstay of ITP treatment, may cause infectious complications. Case: We report a 23-year-old woman with persistent, steroid-refractory ITP who presented with fatigue and multiple ecchymoses without overt bleeding or signs of infection. Initial evaluation showed severe thrombocytopenia, pancytopenia, and high immature platelet fraction, with no evidence of autoimmune disease, viral hepatitis, or HIV. During hospitalization, she required repeated transfusions and high-dose methylprednisolone, yet platelet counts remained low. Further work-up revealed positive anti-H. pylori IgM and biopsy-proven H. pylori gastritis. Esophagogastroduodenoscopy also demonstrated extensive esophageal candidiasis, likely related to prolonged corticosteroid and immunosuppressive exposure. Triple therapy for H. pylori and systemic plus topical antifungals were initiated. The clinical course was complicated by hospital-acquired pneumonia with Pseudomonas aeruginosa and Klebsiella pneumoniae bacteremia, leading to sepsis, respiratory failure, transfer to intensive care, and death. Conclusion: This case illustrates the complex interaction between H. pylori–associated ITP and long-term steroid toxicity, underscoring the need for H. pylori screening, eradication therapy, and vigilant monitoring for opportunistic infections in patients with chronic or refractory ITP. Careful risk–benefit assessment of immunosuppression remains essential.

KEYWORDS: Immune thrombocytopenia; Helicobacter pylori; Corticosteroids; Opportunistic infections; Esophageal candidiasis; Case report..

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INTRODUCTION

Immune thrombocytopenic purpura (ITP) results from the destruction of platelets in the reticuloendothelial system due to platelet autoantibodies and other immune mechanisms, leading to increased platelet turnover and inadequate platelet production (Provan and Semple, 2022; Song and Al-Samkari, 2021) . This disease is characterized by low platelet counts (<150,000/μL), purpura, and bleeding episodes, which are not associated with systemic disease. The incidence of ITP in the United States (US) population is approximately 6.1 per 100,000 people per year, or 13.7 per 100,000 people per year in those aged 65 years or older. The clinical presentation of ITP can vary from asymptomatic to severe bleeding complications. (Song and Al-Samkari, 2021; Vaillant and Gupta, 2022; 2019) . The pathophysiology of this disorder has revealed a potential association with *Helicobacter pylori* (H. pylori) as one of the etiologies. H. *pylori* is associated with gastritis, peptic ulcer disease, gastric adenocarcinoma, and *mucosa-associated lymphoid tissue* (MALT) lymphoma. Additionally, several studies have reported an association between H. *pylori* and extragastrointestinal diseases.

A pathophysiological relationship between ITP and *H. pylori* was first discovered by Gasbarrini *et al*. in 1998. Although the pathogenesis of *H. pylori-associated* ITP remains unconfirmed, several studies have suggested that the cytotoxin-associated gene A (cagA), which is a virulence factor of H. *pylori*, triggers the production of anti-cagA antibodies that *cross-react* with platelet surface antigens, resulting in thrombocytopenia. A study by *Pezeshki et al*. showed that eradication of H. *pylori* infection increased platelet count. Glucocorticoid treatment is the standard initial therapy for patients with ITP. However, long-term steroid administration is associated with various side effects such as *cushingoid*, glucose intolerance, mood swings, and the risk of infection (Cooper and Ghanima, 2019).

The following case describes a patient with persistent ITP who was eventually found to have an asymptomatic *H. pylori* infection, and incidentally, fungal infection was detected in the esophagus to the duodenum.

CASE REPORT

A woman (Ms. M, 23 years old) and her family came to Dr. Soetomo General Hospital in Surabaya with a referral from Mataram General Hospital, NTB, with a diagnosis of steroid-resistant ITP. The patient complained of weakness that had been felt for 2 weeks before admission, accompanied by bruises on the body, which were initially reddish in color and then turned bluish. However, there was no active bleeding, such as nosebleeds, bleeding gums, vomiting, or red/black bloody stools. The patient also

had no complaints of fever, cough, shortness of breath, chest pain, hair loss, or mouth ulcers. Currently, her appetite and thirst are good, and she has no nausea, vomiting, or abdominal pain. There has been a weight loss of approximately 3-5 kg over the past 2 months, and the patient also mentioned that her cheeks have appeared swollen over the past 3 months. There are no complaints regarding bowel movements or urination.

In the past medical history, in May 2021, the patient was admitted to the Emergency Room of Sumbawa Regional General Hospital with a laboratory result of hemoglobin 3 mg/dl and a history of heavier and longer menstruation than usual, lasting up to 2 weeks. The patient received treatment for 5 days with 5 bags of PRC transfusion and 8 bags of *Thrombocyte Concentrate* (TC) transfusion. The patient was discharged with a hemoglobin level of 9 mg/dl and a platelet count of 80,000. In June 2021, the patient was readmitted to the hospital in Mataram and received PRC and TC transfusions. In early December 2021, the patient was readmitted to the hospital due to fatigue related to her work. In December, the patient was diagnosed with ITP by a medical hematology-oncology consultant and received therapy. The patient received methylprednisolone 1x48 mg for one and a half months, followed by 1x8 mg, then reduced to 1x4 mg, and was given additional mycophenolate mofetil 2x500 mg, Imuran 2x50 mg, and Rebozet 1x25 mg. The patient does not take any medications, herbal remedies, or supplements, and has no history of previous illnesses. The patient works at a company in the civil engineering field.

Physical examination revealed general weakness, compos mentis consciousness, blood pressure of 110/65 mmHg, pulse of 115 beats per minute, respiratory rate of 22 breaths per minute, temperature of 36.6 degrees *Celsius*, and oxygen saturation of 98%. Head and neck examination revealed anemic conjunctiva, *moonface* but no icteric sclera, *dyspnea*, cyanosis, or enlarged lymph nodes. Cardiac examination revealed single, regular S1-S2 heart sounds, with no additional sounds such as gallop or murmur. Vesicular breath sounds were heard in both hemithoraces, with no rales or wheezing. Abdominal examination revealed slight distension, striae on the abdomen and thighs on both sides, normal bowel sounds, suppleness, no tenderness in all quadrants of the abdomen, and no palpable masses or organomegaly. Acral extremities were warm, dry, and red with *a capillary refill time (RFT)* of less than 2 seconds, no edema, muscular atrophy in the upper and lower extremities, multiple hematomas of varying sizes with a diameter of 5-6 cm, purple in color and painless.

Supporting examinations were performed at Dr. Soetomo General Hospital with the following results: Hb 8.3 g/dl, Hct 26.6%, Mcv 88.7 fl, Mch 27.7 pg, Leukocytes 4.5 x 10^3/mm^3, Neutrophils 62%, Lymphocytes 10.2%, Platelets 44,000, Ret 0.21%, IPF 82 (increased), SGOT 16 U/L, SGPT 27 U/L, Direct Bilirubin 0.13 mg/dl, Total Bilirubin 0.54 mg/dl, Albumin 3.22 g/dl, GDA 112, Bun 26 mg/dl, SK 0.51 mg/dl, Sodium 140 mmol/l, Potassium 3.2 mmol/l, Chloride 103 mmol/l, PPT 9.7 seconds, APTT 19.7 seconds, INR 1.0, CRP 3.1 mg.dl, Procalcitonin 0.01, HBsAg Non-reactive, Anti-HIV Non-reactive, COVID-19 Antigen Swab Negative, ANA Test 8.87. BGA Free Air, pH 7.49, pCO2 38 mmHg, pO2 161 mmHg, HCO3 29 mmol/l, BE 5.7 mmol/l, SaO2 99%. Pre-transfusion HDT examination showed normochromic normocytic erythrocytes with poikilocytosis (ovalocytes), polychromasia (+), normoblasts (-). Leukocytes appeared decreased in number, dominated by segmented neutrophils, immature granulocytes (+) (myelocytes, metamyelocytes), atypical lymphocytes (+), blasts (-). Platelets appeared decreased in number, giant platelets (+). Impression: normochromic normocytic poikilocytosis anemia, thrombocytopenia, pancytopenia. Laboratory tests in June 2021 showed ANA (IF) negative, Anti-dsDNA 10 IU/mL (<100). Chest *X-ray* at RSDS on 28/04 showed no abnormalities in the heart and lungs. Ultrasound at RSUD Mataram showed ascites and no abnormalities in other organs.

Based on the medical history, physical examination, and supporting tests, the patient was diagnosed with persistent ITP, normochromic normocytic anemia, thrombocytopenia, hypokalemia, and hypoalbuminemia. The patient received a 2100 kcal/day TKTP diet, extra vegetables, fruits, and egg whites, 1500 ml of Asering infusion every 24 hours, Rebozet 1x25 mg orally, methylprednisolone 1x16 mg orally, folic acid 2x1 mg orally, paracetamol 3x500 mg orally if fever, KSR 2x600 mg orally.

COURSE OF THE DISEASE

On the fourth day of treatment, the patient complained of still feeling weak, with new and old bruises visible on the patient's hands, thighs, and abdomen. Physical examination revealed that the patient was in fair general condition, alert and oriented, with a blood pressure of 115/72 mmHg, pulse rate of 110 beats per minute, respiratory rate of 22 breaths per minute, temperature of 36.8 degrees *Celsius*, and oxygen saturation of 97% without oxygen support. Laboratory examination revealed Hb 7.6 g/dl, Hct 24.2%, Mcv 88.7 fl, Mch 27 pg, leukocytes 2.2 x 10^3/mm^3, platelets 14,000, GDA 175, Bun 18 mg/dl, SK 0.71 mg/dl, sodium 141 mmol/l, potassium 3.8 mmol/l, chloride 102 mmol/l. The patient was given a PRC transfusion of 2 units and a TC transfusion of 10 units. After , the patient was given methylprednisolone injections of 3x125 mg for 3 days, then reduced to methylprednisolone injections of 3x63.5 mg. On the tenth day of treatment, the patient complained of intermittent headaches that were getting worse. Laboratory tests showed Hb 9.3 g/dl, Hct 27%, Mcv 84 fl, Mch 28 pg, Leukocytes 2.3 x 10^3/mm^3, platelets 9000, SGOT 16 U/L, SGPT 44 U/L, Direct Bilirubin 0.13 mg/dL, total bilirubin 0.70 mg/dL, albumin 3.38 g/dL, GDA 197, BUN 19 mg/dL, SK 0.68 mg/dL, sodium 146 mmol/L, potassium 3.8 mmol/L, chloride 103 mmol/L, anti-HCV non-reactive. On the fourteenth day of treatment, vital signs were within normal limits. Laboratory tests showed IgM Anti-H. pylori Positive (≥100), IgG Anti-H. pylori Negative. CT scan results indicated *acute thromboembolic cerebral infarction* in the cortex-subcortex of the left parieto-occipital lobe corresponding to the left posterior cerebral artery. The patient received triple therapy for H. *pylori* infection with omeprazole 20 mg every 12 hours orally, amoxicillin 1000 mg every 12 hours orally, and clarithromycin 500 mg every 12 hours orally (for 14 days). Endoscopy revealed esophageal candidiasis extending to the duodenum, erosive gastritis, and angiodysplasia in the fundus, followed by biopsy. The patient received additional antifungal therapy with fluconazole 200 mg orally once daily and Nystatin drops 1 ml four times daily.

On the twenty-fourth day of treatment, the patient complained of fever for the past 2 days, accompanied by cough without phlegm

production and occasional shortness of breath. New bruises appeared on the upper thighs. Physical examination revealed general weakness, alert and oriented, blood pressure 109/69 mmHg, pulse 115 beats per minute, respiratory rate 22 breaths per minute, temperature 38.8 degrees *Celsius*, oxygen saturation 97-98% with 2-3 liters of oxygen per minute. Laboratory examination revealed Hb 9.3 g/dl, leukocytes 4.2 x 10^3/mm^3, platelets 53,000, SGOT 13 U/L, SGPT 68 U/L, direct bilirubin 0.50 mg/dl, total bilirubin 0.13 mg/dl, albumin 2.98 g/dl, Bun 19 mg/dl, SK 0.63 mg/dl, sodium 138 mmol/l, potassium 3.1 mmol/l, chloride 99 mmol/l, GDA 280, Hba1C 7.4, procalsitonin 26.56, BGA nasal cannula 2 liters per minute, pH 7.55, pCO2 35 mmHg, pO2 70 mmHg, HCO3 27 mmol/l, BE 4.1 mmol/l, SaO2 97%. Blood culture results showed *Pseudomonas aeruginosa.* Sputum culture showed *Klepsiela pneumoniae, pseudomonas aeruginosa, Streptococcus viridans.* Chest X-ray showed pneumonia. Biopsy results from gastric and duodenal tissue were positive for H. pylori bacteria. The patient was diagnosed with sepsis, *hospital-acquired pneumonia*, and *steroid-induced hyperglycemia.* The patient then received antibiotic therapy with meropenem 1000 mg every 8 hours according to culture results, novorapid insulin injections 8 units subcutaneously 15 minutes before meals, and continued steroid administration.

On the twenty-seventh day of treatment, the patient's condition worsened, with fever accompanied by severe shortness of breath. General condition was weak, alert and oriented, blood pressure 94/58 mmHg, pulse 130 beats per minute, respiratory rate 26 breaths per minute, temperature 38.6 degrees *Celsius*, oxygen saturation 97% with NRM oxygen support at 10-12 liters per minute. Arterial blood gas results with NRM oxygen at 12 liters per minute: pH 7.44, pCO2 40 mmHg, pO2 93 mmHg, HCO3 27 mmol/l, BE 3 mmol/l, SaO2 97%, PF ratio 258. The patient was transferred to *the intensive care unit* (ICU). During the ICU care period, the patient was pronounced dead.

DISCUSSION

ITP is referred to as *'immune* thrombocytopenia', replacing the term *'idiopathic thrombocytopenic* purpura' because it is now known that ITP is caused by immune system dysregulation. Primary ITP is defined as thrombocytopenia <100 x$10^{(9)}$/L with no identifiable cause or other abnormalities that may be associated with thrombocytopenia (Song and Al-Samkari, 2021; Matzdorff *et al*, 2018) . Primary ITP is further categorized into three phases based on the timing and duration of symptoms. *Newly diagnosed* ITP is defined as the period from the time of diagnosis until 3 months. Persistent ITP is the continuation of ITP between 3 and 12 months from the initial diagnosis. Chronic ITP is the continuation of ITP after 12 months from the initial diagnosis until resolution (Hodeib et al., 2021; Matzdorff et al., 2018; Sari, 2018) . Overall, the incidence of ITP ranges from 2 to 4 cases per 100,000 person-years, with two age peaks: one between 20 and 30 years with a slight female predominance (Cooper and Ghanima, 2019) . The rate of fatal bleeding is estimated at 1.62–3.89 cases per 100 patients/year, and the predicted 5-year mortality rate varies from 2.2% for those over 60 years old (Song and Al-Samkari, 2021)(Cooper and Ghanima, 2019; Vaillant and Gupta, 2022).
In patients with ITP, thrombocytopenia is found with normal hemoglobin levels and white blood cell counts, unless bleeding has occurred (Zainal *et* al, 2019) . The diagnosis of ITP is confirmed after other causes of thrombocytopenia have been ruled out. Several infectious causes need to be ruled out, such as HIV, Hepatitis C, *Helicobacter pylori*, and CMV (Sari, 2018) . Autoantibodies bound to epitopes on GP Ib and IIb/IIIa can be detected in 60-80% of patients. In patients with persistent or chronic ITP and atypical findings, detection of platelet antibodies may sometimes help confirm the diagnosis of ITP or rule out other differential diagnoses (Matzdorff *et al*, 2018; Sari, 2018) . Bone marrow biopsy cannot confirm ITP but helps rule out other diagnoses. Therefore, if all symptoms and other findings are consistent with ITP, bone marrow examination is not necessary (Grade 1B). Bone marrow examination is also not performed if the patient does not respond after receiving IVIG (Grade 1B), before corticosteroid administration or splenectomy (Grade 2C), or does not respond within 3 months (suggesting persistent ITP) (Sari, 2018).

The patient is weak and has bruises on the body. Laboratory tests show Hb 8.3 g/dl, Hct 26.6%, Mcv 88.7 fl, Mch 27.7 pg, Leukocytes 4.5 x 10^3/mm^3, platelets 44,000, Ret 0.21%, IPF 82 (increased), Procalsitonin 0.01, HbsAg Non-reactive, Anti-HIV non-reactive, ANA test 8.87. ANA (IF) negative, Anti-dsDNA 10 IU/mL (<100). HDT examination showed normochromic normocytic poikilocytosis anemia, leukopenia with immature granulocytes and atypical lymphocytes, thrombocytopenia, pancytopenia. Ultrasound examination showed ascites and no abnormalities in other organs.

The patient is a young woman with clinical symptoms of weakness accompanied by multiple petechiae and ecchymoses on her limbs, but no clinical symptoms of infection such as fever, cough, shortness of breath, or urinary or genital tract infection. No autoimmune conditions (*ANA test 8.87. ANA (IF) negative, Anti-dsDNA 10 IU/mL (<100)),* viral hepatitis infection, HIV, or other infectious conditions (normal procalcitonin levels) were found. The patient also had no history of heparin or other drug use. The abdominal ultrasound results also showed no *splenomegaly.* The HDT results showed no signs of malignancy such as leukemia (no *blasts* were found*)*. The IPF test results showed a very significant increase, which was suspected to be a form of intravascular platelet destruction. The patient presented with anemia without hemolytic signs such as jaundice or normal indirect bilirubin levels, but due to multiple petechiae/purpura and menometrorrhagia. Therefore, the patient was diagnosed with persistent primary ITP as the condition had persisted for more than three months.

The patient received intravenous steroid therapy during treatment but showed no increase in platelet count. Serological testing for H. pylori showed positive IgM anti-H. pylori (≥100) and negative IgG anti-H. pylori. Further diagnostic tests, including endoscopy and biopsy, revealed esophageal to duodenal candidiasis, erosive gastritis, angiodysplasia in the fundus, and positive H. pylori results in gastric and duodenal tissue biopsies.

H. pylori infection

Globally, 4.4 billion people are infected with *H. pylori*. In developing countries, the prevalence of *H. pylori* infection ranges from

85% to 90%. The prevalence of H. *pylori* infection in Indonesia is relatively low compared to other countries in Southeast Asia and Asia, at 22.1% (Iman et al., 2021; Miftahussurur et al., 2021) . *Helicobacter pylori* is a spiral-shaped, gram-negative pathogenic bacterium found in the human stomach (Brito et al., 2019; Hodeib et al., 2021; Zain et al., 2019) . H. *pylori* is the cause of several gastric disorders, and extra-gastric manifestations have been reported to be associated with H. *pylori* infection, such as neurological, dermatological, hematological, ocular, cardiovascular, metabolic, and allergic diseases. Most H. *pylori* infections are usually asymptomatic. (Sabbagh et al., 2019) . H. *pylori* testing can be done through non-invasive tests: serology, *urea breath test,* and detection of H. *pylori* antigen in feces (Siddique et al., 2018) . The 2007 ACG (*American College of Gastroenterology)* guidelines recommend 14 days of treatment with PPI, clarithromycin, and amoxicillin (clarithromycin-based *triple* therapy) or—in patients with penicillin allergy—metronidazole as an alternative to amoxicillin. For clarithromycin-based *triple therapy*, higher eradication rates were reported with 14 vs. 7 days of treatment (34 studies, RR 0.65, 95% CI 0.57–0.75; NNT 12, 95% CI 9–16) (Chey *et al.*, 2017).

Correlation between *H. pylori* Infection and ITP

Various literature describes the relationship between ITP and *Helicobacter pylori* infection in the gastric mucosa. This association appears to be more relevant in Asia than in Europe and North America (Matzdorff et al., 2018) . Research by Hodeib *et al.* revealed *H. pylori* infection in 63% of chronic ITP patients. Previous research conducted in Italy showed an estimated prevalence of H. *pylori* of 50% in chronic ITP patients. Another study in Japan showed that 75% of chronic ITP cases were identified as having H. *pylori* infection. However, surveys conducted on Caucasian French and North American chronic ITP patients revealed low prevalence rates. It was found that after H. pylori eradication therapy, chronic ITP with a shorter duration responded better than those with a longer disease duration (Hodeib et al., 2021) . Current guidelines recommend H. *pylori* testing in adult ITP patients and its eradication if the test is positive. This is reasonable because ITP patients often receive corticosteroids and have a higher risk of developing peptic ulcer disease. (Matzdorff et al., 2018).

After entering the *host* body, *H. pylori* successfully colonizes the gastric mucosal layer by evading *the host's* innate immunity through various adaptive mechanisms, including neutralizing the acidic gastric environment by producing ammonia using the urease enzyme, altering mucus viscosity to facilitate movement, motility with flagella to avoid gastric washing by peristalsis, anergic lipopolysaccharides (LPS) in the cell wall/flagella, and possessing various adhesion proteins to help attach to gastric epithelial cells. According to various reports, the postulated mechanisms for the role of H. *pylori* in chronic ITP include molecular mimicry, increased numbers of plasmacytoid dendritic cells, impaired phagocytosis, and a variable *host* immune response to H. *pylori* virulence factors (Zain et al., 2019).

H. pylori has a variety of genes that encode several *outer membrane proteins* (OMPs) and virulence factors. These OMPs, such as blood group A antigen-binding adhesin (BabA), outer inflammatory protein A (OipA), and sialic acid-binding adhesin (SabA), facilitate the binding of *H. pylori* to gastric epithelial cells. Among the various virulence factors, the two most important are the *vacuolating cytotoxin A (*VacA) gene and *the cytotoxin-associated gene* A (CagA). The CagA gene is located in a 40kb terminal gene cluster in *the cytotoxin antigen pathogenicity island* (Cag PAI), and encodes the type IV secretion system (T4SS) along with the CagA protein. Patients infected with H. *pylori strains* that are Cag PAI^{+} are more likely to develop peptic ulcers or gastric cancer due to the oncoprotein CagA. The T4SS acts as a "vehicle" to translocate the CagA protein into the *host* gastric epithelial cells. Once phosphorylated within the epithelial cell, the CagA protein elicits a systemic immune response *in the host* by inducing IL-8, a potent proinflammatory cytokine. In gastric epithelial cells, phospho-CagA activates eukaryotic phosphatase (SHP-2) and ERK, a member of the MAPK family, which causes changes in epithelial cell signaling and stimulation *of the growth* factor.

CagA protein is highly antigenic and induces anti-cagA antibodies. It has been suggested that there is molecular mimicry between cagA and *platelet-associated* IgG (PAIgG). Anti-cagA antibodies (Abs) *cross-react* with platelet surface antigen GPIIb/IIIa and result in accelerated immune complex formation and platelet clearance in *the host* reticuloendothelial system (RES). Another theory suggests increased platelet activation and clearance in the *host* RES due to the interaction of *H. pylori-bound* von Willebrand factor (VWF) with platelet surface antigens (GPIb). On the other hand, monocytes from *H.* pylori-positive patients show low levels of inhibitory Fc-γ IIB receptors, resulting in increased platelet phagocytosis ( ), thus supporting the theory of increased phagocytic dysfunction. This is further supported by the upregulation of inhibitory Fc-γ IIB receptor signaling after successful HP eradication. The second most important virulence factor is VacA, which inhibits Th cell proliferation by disrupting the interleukin 2 (IL-2) T cell receptor pathway. It is estimated that the binding of VacA to multimerin-1 on platelets may cause increased platelet activation and clearance (Ihtesham et al., 2021; Zain et al., 2019).

Mechanism of *H. pylori* Eradication on Platelet Increase in ITP

Based on a systematic review, more than half of patients successfully increased their platelet count after *H. pylori* eradication therapy (Kim et al., 2018) . However, due to differences in *Helicobacter* infection prevalence across populations, conflicting results have made *H. pylori* eradication in ITP patients controversial (Lee et al., 2020) . ITP treatment primarily involves immunosuppressive agents, such as corticosteroids (prednisone), immunoglobulin therapy (IVIG), Rituximab, and splenectomy. These treatment modalities are not only expensive but also have numerous side effects. Additionally, approximately 10-20% of patients are unable to maintain normal platelet counts or experience relapses despite undergoing the aforementioned treatments. With recent clinical reports showing an emerging correlation between H. *pylori* and ITP, it is highly recommended to detect and treat this bacterial infection. H. *pylori* eradication therapy involves a combination of antibiotics (clarithromycin, metronidazole, amoxicillin) with *a proton pump inhibitor (*PPI). The usual duration of treatment is seven to 14 days. H. *pylori* fecal antigen tests and blood platelet counts are performed eight weeks after therapy to check the efficacy of treatment. H. *pylori* eradication has shown promising results with an increase in platelet count and normalization of auto-platelet antibodies without relapse. Another

interesting finding is the correlation between treatment and geographic location, with higher response rates in Japan and Italy (28–100%) compared to the US and other European countries (<13%). This highlights the importance of patient biogeography and regional *H. pylori strain* variation in the treatment *of H. pylori-induced* ITP (Zain et al., 2019).

Research by Lee *et al.* shows that successful eradication of *H. pylori* plays a role in restoring platelet counts in ITP patients with *H. pylori* infection. In this study, successful eradication in ITP patients infected with *H. pylori* tended to increase platelet counts. Eradication therapy resulted in an overall response rate of 46.2% two months after eradication. Research by Hodeib *et al.* also supports the role of H. *pylori* eradication therapy in increasing platelet counts in pediatric ITP patients. A significant increase in platelet count was observed, with the mean platelet count rising from $70.6 \pm 4.8 \times 10^{(9)}$/L to $110.8 \pm 15.1 \times 10^{(9)}$/L after H. *pylori* eradication therapy (P value < 0.001). This can be explained by the fact that the CagA antigen of H. *pylori* may account for *cross-mimicry* between H. *pylori* and platelet glycoproteins, and the levels of cross-reactive antibodies decreased after H. *pylori* eradication in patients showed platelet recovery (Hodeib et al., 2021) . Literature reviews by Zain *et al.* and Ihtesham *et al.* found similar results (Ihtesham et al., 2021; Zain et al., 2019).

A systematic review and meta-analysis by Pezeshki *et al.* showed that among the articles reviewed, only seven studies discussed the relationship between *H. pylori* eradication and response to treatment in patients with ITP in the Middle East. All studies used standard *triple therapy* consisting of amoxicillin, clarithromycin, and omeprazole for 14 days to eradicate *H. pylori* infection. Three studies defined complete response as a platelet count of $100 \times 10^{(9)}$/L, while four studies defined a platelet count of $150 \times 10^{(9)}$/L as complete response in their patients. Furthermore, the highest percentage of patients eradicated with an increase in platelet count was 85.3%, while the lowest was 7.3%. The results also revealed that after H. *pylori* eradication, ITP patients showed a significant increase in platelet count ($P < 0.05$) in all studies. Moreover, patients who received eradication treatment for H. *pylori* infection showed a significantly higher *odds ratio* (OR) (8.83; 95% CI 2.03-38.35; P=0.004) compared to patients who did not receive eradication therapy. However, the review showed significant heterogeneity between studies ($I^{(2)}$= 88.3%, P = 0.00) and some evidence of publication bias based on the asymmetric *funnel plot*. This may be due to the small sample size of patients used and the different thresholds for determining complete and partial response in some studies (Pezeshki et al., 2021).
In a study by Lee *et al.*, persistent *H. pylori* infection due to failed eradication attempts showed poor response to platelet recovery. The eradication success rate with first-line therapy was 71.4% (35 out of 49 patients). Twelve of the 14 patients who failed eradication with first-line treatment were given second-line treatment, with 11 of them achieving eradication success. The eradication success rate with first- and second-line treatment was 93.9% (46 out of 49 patients). However, the study did not explain the causes of eradication therapy failure (Lee et al., 2020) . A retrospective study evaluated factors associated with H. *pylori* eradication failure. Multivariate analysis showed that older age, previous therapy history, and administration of omeprazole or pantoprazole increased the risk of eradication failure (Yan et al., 2020)

The patient received oral steroid therapy from December to June 2022 and developed moonface as a side effect of long-term steroid use. In this case, fungal growth was incidentally found in the esophagus and duodenum based on endoscopy results, although no hyphae or spores were found in the biopsy results.

Long-Term Steroid Side Effects
Glucocorticoid treatment is the standard initial therapy for patients with ITP. However, long-term steroid use is associated with various side effects such as weight gain, insomnia, acne, mood swings, *cushingoid features*, glucose intolerance, osteoporosis, increased risk of infection (especially with prednisone or prednisolone use), gastrointestinal symptoms, neuropsychiatric symptoms (especially with dexamethasone) (Cooper and Ghanima, 2019) . Esophageal candidiasis is considered an opportunistic infection, usually developing in *immunocompromised* individuals due to underlying medical conditions or pharmacotherapy. Currently, there has been an increase in cases of esophageal candidiasis in non-HIV patients, possibly due to comorbidities such as diabetes mellitus and the use of antibiotics and corticosteroids (Mohamed et al., 2019) . In several reports, the incidence of esophageal candidiasis has been associated with the use of inhaled and topical steroids, as well as systemic immunosuppressive drugs such as long-term oral corticosteroids and cytotoxic agents (Nassar et al., 2018) . According to the 2016 *Infectious Disease Society of America* (IDSA) guidelines, esophageal candidiasis is treated with systemic antifungal therapy. Oral fluconazole, 200–400 mg (3–6 mg/kg) daily, for 14–21 days, is recommended. If the patient cannot tolerate oral therapy, intravenous fluconazole, 400 mg (6 mg/kg) daily, or echinocandin may be recommended (Pappas et al., 2015).

CONCLUSION

A young female patient, 23 years old, with *immune thrombocytopenia* (ITP) and *Helicobacter pylori* infection as complicating factors, which affected the response to treatment for increasing platelet counts in patients. Several studies have revealed a correlation between *H. pylori* eradication and the response to ITP therapy. However, a fungal infection in the esophagus was also found, suspected to be a side effect of long-term steroid therapy.

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