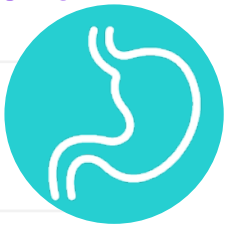
Severe, Refractory Anaemia Associated with *Helicobacter Pylori* Infection Managed With *L. Reuteri* DSMZ17648 (Probiotic) and Haeme Iron Supplements: A Case Report



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Abstract

Helicobacter pylori infection can be observed with increased frequency in patients with iron deficiency anaemia (IDA), especially in resistant cases. This case report describes a case of resistant IDA that responded to probiotic (*Lactobacillus reuteri* DSMZ17648) and oral haeme iron polypeptide supplementation, highlighting that oral probiotic supplement trial may be considered before antibiotic therapy for *H. pylori* treatment in a patient with IDA.

Key Points

1. This case report addresses the iron deficiency anaemia (IDA), a global health problem occurring primarily due to nutritional deficiency, and resistant IDA due to the presence of *Helicobacter pylori* infection.

2. The authors' case report highlights that screening for *H. pylori* is recommended in refractory IDA, and this treatment approach should also include probiotics and iron supplements.

3. The remission of IDA in patients using a unique strain of probiotic (*Lactobacillus reuteri* DSMZ17648) before using antibiotics shows a novel approach to using probiotics before antibiotics, especially in patients with antibiotic resistance or hypersensitivity.

INTRODUCTION

Iron deficiency anaemia (IDA) is a global health problem affecting both developing and developed countries, particularly in Asia.[1] Nutritional deficiency, menstrual blood loss, and chronic gastrointestinal blood loss are the common causes of IDA.[2] Association between *Helicobacter pylori* infection and IDA has been known for the past three decades.[3] *H. pylori* infection affects over 4.4 billion individuals, and its prevalence varies from 18.9–70.1%.[4] Besides gastric disease, *H. pylori* is associated with extra-gastric diseases. Though the exact mechanism remains unclear, a few postulated causes could be gastric and intestinal inflammation; erosions and ulcers leading to chronic occult blood loss; iron malabsorption from alteration of gastric acidity; atrophic gastritis; reduction in ascorbic acid in gastric secretions; and alteration in iron metabolism due to increased hepcidin level and decreased haeme oxygenase-1 levels.[3,5] IDA is observed in *H. pylori* infection irrespective of the presence or absence of peptic-ulcer disease.[6] The American College of Gastroenterology (ACG) guidelines suggest testing for *H. pylori* infection in patients with unexplained IDA despite an appropriate evaluation.[7] Most patients with *H. pylori* respond to the initial combination treatment of a proton pump inhibitor, clarithromycin, amoxicillin, and metronidazole.[7] However, a significant failure rate for eradication therapy has been reported due to poor compliance and antimicrobial resistance. This has led to the increased role of probiotics species along with standard iron therapy. Prominent probiotic strains, such as *Saccharomyces boulardii* and *Lactobacillus johnsonii* La1, reduce the *H. pylori* bacterial load.[8] With this background, in this paper the author reports on the case of an adult female with severe IDA associated with *H. Pylori* infection, who had significant improvements with the use of probiotic strain *Lactobacillus reuteri* DSMZ17648.

CASE DESCRIPTION

A 38-year-old female visited the Aarti Clinic, Navi Mumbai, India, with complaints of extreme fatigue, dyspnoea on exertion, and palpitations. They also had constipation and bloating after meals. Their relevant medical and menstruation history were normal. On examination, the patient had severe pallor, tachycardia, and hypotension. Systemic examination revealed no significant abnormalities. Their haemoglobin (Hb) was 6.8 g/dL, with a microcytic hypochromic picture. In other indices, haematocrit was 26.9%, mean corpuscular volume was 66.6 fL, and mean corpuscular haemoglobin was 16.8 pg. Platelets and total leukocyte counts were normal. There were no thyroid hormone abnormalities. The patient's Hb electrophoresis was also normal. They had been experiencing these complaints for the last 3 months.

For severe anaemia, the patient was treated with oral and intravenous iron at different centres, but the haematology picture did not change significantly. Based on their non-specific abdominal symptoms, their stool was examined for routine and opportunistic pathogens, which were normal. Stool test for *H. pylori* antigen was positive. The author's centre counselled the patient, and advised upper gastrointestinal (GI) endoscopy, but the patient refused to undergo any invasive procedure.

Based on clinical presentation and antibody report (the patient had a history of allergic reactions to multiple antibiotics, and was very afraid of consuming antibiotics), they were started with *L. reuteri* DSMZ17648 probiotic twice a day for 1 month, accompanied by supplementation of oral iron as haeme iron polypeptide administered twice a day, along with an iron-rich diet. At 1 month follow-up, the patients' Hb had increased to 11.1 g/dL, their haematocrit was normal, and they had stable haematological indices. They had complete relief from their fatigue and abdominal symptoms. The probiotic was continued once a day for another

month while the iron supplement was continued for another 3 months once a day. At 3 month follow-up, Hb had increased to 13.5 g/dL with improvement in microscopic features. The patient was completely symptom-free at the end of 3 months, and there was no recurrence of anaemia at 3 month follow-up.

DISCUSSION

Moderate to severe IDA that does not respond to corrective measures with iron supplementation warrants further investigation. *H. pylori* infection has been identified to be a cause of IDA. However, it may not be suspected in routine anaemia evaluations. Such a situation is a diagnostic and treatment challenge for the treating physician.

In refractory IDA, a full gastroenterology workup with upper and lower GI endoscopies is necessary to establish the IDA cause, and thereby plan and optimise specific treatment success. Multiple studies have established the higher prevalence of *H. pylori* infection in patients with refractory IDA.[6,9,10] In this case, severe anaemia was observed that did not respond to oral or iron supplementation. Given the substantial presence of *H. pylori* infection in the Indian subcontinent, the patient was evaluated for this infection, which turned out to be present. Studies have established that 14 days of triple therapy for *H. pylori*, along with iron supplements, is effective in improving Hb concentration, haematological indices, and anaemic symptoms.[10,11] However, antibiotic treatment may often lead to GI side effects and cause alterations in the gut microbiome. The use of probiotics along with triple-therapy of *H. pylori* has been shown to reduce the GI upset and improve the microbial environment.[12]

The use of probiotic strains, especially *S. boulardii, L. reuteri,* and *Lactobacillus rhamnosus GG,* is effective in *H. pylori* eradication, and reduces the antibiotic-associated GI adverse effects.[8] The *L. reuteri* DSMZ17648 strain that was used is a highly specific and antagonist to *H. pylori*. This strain co-aggregates *H. pylori*, and probably masks the bacterial surface structures, thereby interfering with its motility and impairing ability to bind with gastric mucosa. Also, this probiotic strain may compete with *H. pylori* for binding with specific strains. Thus, *H. pylori* is cleared from the stomach. This probiotic strain does not interfere with other commensal intestinal flora.[13] An Indian study[14] reported a significantly improved rate of *H. pylori* eradication rate of 86.6%, reduced intensity of GI symptoms, and also treatment-related side effects with the addition of *L. reuteri* DSMZ17648 to standard triple drug therapy.[14]

In addition, the author's centre used haeme iron polypeptide for iron supplementation because conventional oral iron (non-haeme) supplementation is associated with poor compliance, GI side effects, and suboptimal GI absorption of iron.[15] Haeme iron polypeptide is a new generation of oral iron therapy that lacks any dietary or drug interactions, and can be taken irrespective of mealtimes, and co-administered with other medications.[16] Compared to conventional oral irons, haeme iron polypeptide has seven times greater bioavailability and negligible side effects, and is postulated to be absorbed by dual mechanisms.[17,18] Gastrointestinal absorption of haeme iron is far less affected by dietary constituents such as polyphenolic tannins, phytates, and soy and dairy products (calcium).[15,16,19] This could have also supplement in the improvement of IDA.

In this case, the underlying cause of IDA was *H. pylori* infection. *H. pylori* can cause anaemia by several different mechanisms, especially by blood loss and iron malabsorption. The remission of IDA in a patient with probiotic treatment even before the use of antibiotics shows a novel approach to using probiotics before antibiotics, especially in patients with antibiotic resistance or hypersensitivity.

In this report, a major limitation was the patient's unwillingness to undergo upper GI endoscopy. This would have revealed bleeding lesions in the GI tract, or other GI disorders causing IDA, which could not be ruled out. However, even in the absence of ulcerative GI disease, IDA can occur.[6] The author's clinic did not find occult bleeding in the stool examination. The use of probiotics in this case was a very considerate decision that added to the treatment success without an aggressive standard antibiotic regimen. The probiotic preparations administered contained *L. reuteri* DSMZ17648, which is known to be effective.

CONCLUSION

This case highlights that screening of *H. pylori* should be undertaken in patients with refractory IDA. It is emphasised that the root cause should be identified in all cases of anaemia, especially the resistant ones, and it is important to understand that merely replacing iron may not help in restoring IDA conditions. *H. pylori* might not always be presented with classical symptoms of reflux, acidity, and abdominal pain. However, constipation and bloating are lesser common presentations that need attention.

Apart from the standard regimen, the use of probiotics should be recommended as a supportive treatment option. A trial of probiotics even before prescribing antibiotics can help improve symptoms, and also assist in reducing the resistance. The author emphasises that the use of an oral iron supplement with lesser gastric intolerance can ensure a good level of compliance. Therefore, it is important to rule out *H. pylori* infection, especially in moderate to severe anaemia, in the Indian context. A trial of probiotics before *H. pylori* antibiotic therapy can be helpful for patient management.

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