Case report

Helicobacter pylori-related iron deficiency anemia in children

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SUMMARY

In this report we described two cases of children with chronic active *Helicobacter pylori* gastritis without evidence of esophagogastrointestinal bleeding associated with iron-deficiency anemia. In these cases, long-standing iron supplementation had been necessary, but replacement therapy, without considering the role of *Helicobacter pylori*, was ineffective. The anemia returned after the discontinuation of the iron therapy. Only the eradication therapy of *helicobacter pylori* led to a complete resolution of the hematologic disorder.

Key words: Helicobacter pylori, Iron-deficiency anemia, gastritis

INTRODUCTION

Helicobacter pylori (*HP*) has been established as a major cause of chronic active gastritis and peptic ulcer disease in adults and even in children. Gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma present mainly in adults[1].

It is well know that peptic ulcers and gastric carcinomas are likely to bleed, either as overt or occult bleeding, and may eventually cause iron-deficiency anemia (IDA)[2]. However, *HP* gastritis has not always been shown to be associated with gastrointestinal bleeding[3]. Recent studies have suggested an association between *HP* gastric infection and IDA in children refractory to iron therapy, which reversed only after bacteria eradication; this suggests possible interference of *HP* in iron metabolism[3-7].

We describe two cases of chronic active *HP* gastritis without evidence of hemorrhage or clinical symptoms other than sideropenic anemia. They had regular balanced diet and a medical history of long-standing oral iron therapy. The complete resolution of IDA was achieved by the eradication of *HP*.

CASE 1

A 13 year-old boy was admitted to our department with severe anemia, despite having oral and parenteral iron supplements. He had no gastrointestinal symptoms. On examination he appeared pale but in good health; his weight was 54.5 kg (50th percentile) and height 173 cm (97th percentile). He was not on any medication. Blood tests confirmed severe hypochromic microcytic anemia [hemoglobin: 5.4 g/dl, mean corpuscular volume (MCV): 54.8 fl, mean corpuscular hemoglobin (MCH): 14.7 pg, red distribution width (RDW): 18.8%] due to iron deficiency [serum iron: 7 μg/dl, total iron binding capacity (TIBC): 495 μg/dl, 1.5% transferrin saturation, undetectable ferritin]. Findings in an extensive initial work-up (including erythrocyte sedimentation rate; levels of C-reactive protein; total serum proteins and immunoglobulins; D-xylose absorption test; IgA antigliadin and antiendomycial antibody tests; bilirubin; lactate dehydrogenase; folate; B12 vitamin were normal; the laboratory investigation ruled out hemolysis, hemoglobinopathies, hematologic malignancies, autoimmune diseases, renal and lung diseases. Multiple stool examinations for ova, parasites and occult blood; duodenal fluid examinations for

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Abbreviations:

IDA: iron deficiency anemia, HP: Helicobacter pylori

Giardia lamblia; barium meal and follow-through; technetium-99m pertechnetate imaging scans for ectopic gastric mucosa and occult gastrointestinal blood loss) were all normal. IgG and IgA antibodies to *HP* in serum were positive. Upper gastrointestinal endoscopy showed nodular antral gastritis. Sources of the blood loss such as erosive esophagitis and gastritis, gastric and duodenal ulcers were not found on endoscopy. Antral biopsy specimens were taken for rapid urease test (CLO-test) and histological examination was performed. Gastric mucosa was infiltrated by chronic and acute inflammatory cells and sections stained with Giemsa revealed the presence of a large number of spiral organisms like *HP*. Total colonoscopy revealed no lesions to explain the blood loss. Iron in the form of 800 mg iron polymaltosate was administered intramuscularly for 14 days and 20 mg omeprazole per day, 2 g amoxicillin twice daily and 500 mg clarithromycin twice daily was administered for 2 weeks[8-10].

Eradication of *HP* was confirmed six months after the end of treatment, by endoscopy that revealed remission of the nodular gastritis and by histology of biopsy specimens obtained through endoscopy and rapid urease test. Hemoglobin was 8.9 g/dl, MCV: 64 fl and 15 months later, the hematological profile normalized. To exclude the recurrence of *HP* infection the follow-up 13C-urea breath test results were negative.

CASE 2

A girl aged 12 years and 6 months presented with IDA refractory to oral iron therapy for six months. Her menarche had started at 11 years of age and her menstrual cycles were regular. She was not on any medication and had no gastrointestinal symptoms. Her weight and height were at the 50th and 75th percentile respectively. Results of hematologic studies revealed hypochromic microcytic anemia due to iron deficiency (hemoglobin 7.9 g/dl, hematocrit 26%, mean corpuscular volume (MCV) 61 fl, mean corpuscular hemoglobin (MCH) 21 pg, serum iron 15μg/dl, serum ferritin 10.5μg/l, serum transferrin 4g/l, 3.5% transferrin saturation). Tests performed in our hospital ruled out hemolysis, hemoglobinopathies, chronic intestinal and extraintestinal processes, celiac disease or other forms of malabsorption, infections, and worm or protozoal infestations. Several stool examinations for occult blood all gave negative results. A technetium-99m (99mTc) scan for Meckel's diverticulum was negative. The levels of serum IgG and IgA antibody to *HP* were positive. Findings in upper gastrointestinal fiber endoscopy and biopsy confirmed active chronic antral gastritis and the presence of a large number of *HP* organisms. The results of urease test were positive. Following three months treatment with amoxicillin (50mg/kg/d for 2 weeks), clarithromycin (15mg/kg/d for 2 weeks), and omeprazole (0.8mg/kg/d for 2 weeks), without iron supplementation, IDA sterted to resolve (hemoglobin: 9.6 g/dl, hematocrit: 30%, MCV: 75fl, serum iron: 48μg/dl, and serum ferritin: 15μg/l). The response to treatment (hemoglobin: 12.7 g/dl, hematocrit: 39.6%, MCV: 84fl, serum iron: 97μg/dl, serum ferritin: 46μg/l), as well as the eradication of *HP* infection (follow-up with 13C urea breath test results were negative), persisted after nearly 2 years.

DISCUSSION

In this report we described two cases of children with IDA in association with *HP* infection gastritis and no evidence of gastrointestinal bleeding. Long-standing oral iron supplementation proved ineffective as the anemia recurred after discontinuation of the iron therapy. Upper endoscopy revealed a marked antral nodularity without evidence of bleeding lesions. Only the eradication of *HP* infection led to a complete resolution of hematologic disorder for the following-up period (to date). *HP* infection contributed to IDA, and that infection should be suspected when IDA is refractory to iron administration[11].

Several possible mechanisms for the association between anemia and *HP* infection have been suggested. One possibility is that intermittent bleeding may be present, although in our patient no bleeding lesions in the stomach and duodenum or occult bleeding was ever detected in stool specimens during the follow-up periods[6,12-14].

Another possible explanation is that *HP* may have an iron-acquisition mechanism in vivo, forming a parasitic relationship to compete with the host for iron. It is well known that microorganisms need the host's iron to grow[15]. The possibly highly efficient acquisition system of *HP* in vivo, essential for its survival, may compete with the iron-withholding systems of the host. Husson et al. reported that human lactoferrin and heme supported full growth of *HP* in a medium that had no other iron sources[16]. The iron uptake is thought to be mediated through specific ligands. Worst et al. showed that *HP* synthesizes three iron-repressive outer membrane proteins that may be involved in heme binding and/or uptake[17]. Dhaenens et al. identified a 70-kd lactoferrin-binding protein from outer membrane proteins of *HP*. This lactoferin-binding protein was present only when *HP* was grown in an iron-starved medium, which suggested a connection to the

iron acquisition process of *HP*[18]. Because lactoferrin has been found in significant amounts in stomachs resected from patients with superficial or atrophic gastritis, it is highly likely that the iron uptake by *HP* through a specific human lactoferrin-binding protein may play a major role in the virulence of *HP*[19]. Thus, it can be hypothesized that iron acquisition in vivo by *HP* could be mediated by the lactoferrin-binding protein and, as previously suggested, iron administration would not replete host iron stores but would rather enhance *HP* growth[12]. Barabino et al. hypothesized that *HP* infection enhances gastric lactoferrin, which, in turn, subtracts iron bound to transferring. This allows the bacterium higher iron uptake from lactoferrin, resulting in a vicious circle in which iron supply is unable to increase hemoglobin but enhances *HP* growth[20].

Furthermore, the absorption of iron takes place in the duodenum and the proximal jejunum[21]. Iron is absorbed either as organic heme iron or as inorganic ferrous iron (non-heme iron)[22]. *HP* infection may progress into diffuse corpus gastritis and atrophic gastritis[23]. These conditions are mostly accompanied by gastric hypoacidity and achlorhydria[24,25]. As high gastric acidity facilitates the solubilization of non-heme iron, iron uptake may be impaired in people with *HP*-induced hypoacidity[26].

Infection with *HP* is thus a possible confounder that should be accounted for in studies on human iron metabolism. The mechanisms by which *HP* infection might lead to IDA are still unclear. Further studies will be needed.

Choe et al. suggest that investigations for *HP* infection should be instiged in the presence of IDA in adolescents. If they are found to have both, the IDA should be treated by the eradication of *HP* along with iron supplementation[27].

In conclusion, failure of response to iron supplementation or a recurrence of anemia at puberty may be associated with *HP* infection, thus suggesting possible interference of *HP* in iron metabolism. The eradication of *HP* could resolve the refractory IDA.

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