Reminder of important clinical lesson

'Goose bumps'-associated anaemia

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Summary

A 36-year-old woman presented to our hospital for further evaluation of anaemia screened by regular check-up. She was diagnosed with iron-deficiency anaemia (IDA) but refractory to iron supplementation. She had negative results of occult blood in the stool and no gynaecologic disease potentially causing hyper menorrhea. Upper endoscopy revealed a nodular gastritis, which has been called 'Torihada-ien', a Japanese word meaning 'gastritis with goose bumps-like appearance', associated with *Helicobacter pylori* (Hp) infection. After Hp eradication therapy, her anaemia resolved with an improved response to iron supplementation. In an unexplained IDA patient, Hp-associated gastritis should be considered in the possible background.

BACKGROUND

Iron-deficiency is the most common cause of anaemia in the world, affecting an estimated 2 billion people.¹ In the UK, approximately 8% of adult women have iron-deficiency anaemia (IDA) and 11% have low iron stores without anaemia, according to data from the 2000–01 National Diet And Nutrition Surveys.² In an analysis of consecutive cross-sectional nationwide surveys of anaemia in adult Japanese women during the period 1989–2003,³ anaemia (haemoglobin (Hb) <12.0 g/dl) was especially significant in middle aged women, showing its prevalence increased from 16.8% to 20.6% in aged 30–39, and from 20.2% to 26.9% in aged 40–49, respectively. In young women, IDA due to low dietary iron intake or increased iron loss due to heavy menstrual blood loss or chronic disease may be a significant cause.³ Here, we present an adult woman case of IDA without evidence of increased iron loss but refractory to iron supplementation. We hope this case report will guide management for such an unexplained IDA.

CASE PRESENTATION

A 36-year non-pregnant woman visited our hospital for further evaluation of anaemia screened by regular check-up. The anaemia had been evident for several years but had never been taking further investigation or treatment. She had easy fatigability without gastrointestinal (GI) symptom. She was not taking any medication and had no history of pregnancy, GI disease or eating disorder. She maintained a normal diet and reported no weight loss. Her menstrual cycle was regular. On physical examination, the height was 160 cm and body weight was 54 kg. The blood pressure was 116/60 mm Hg, the pulse rate was 60 beats/min. She appeared slightly pale but no any other abnormality was noted. Results of haematologic profile showed hypochromic microcytic anaemia (Hb 8.8 g/dl, haematocrit 31.6%, mean corpuscular volume 70.1 fl, mean corpuscular Hb 19.5 pg, serum iron 20 µg/dl, total iron binding capacity 429 µg/dl, serum ferritin (SF) 3.7 µl/l). The laboratory examination ruled out

haemolysis, malnutrition, chronic inflammatory disease and renal failure. The occult blood tests in the stool were negative results. The gynaecologic examination revealed no abnormality potentially causing hyper menorrhea. Based on these investigations, she was diagnosed with IDA and iron supplementation of 60 mg/day was initiated. However, her Hb and SF levels remained low of 10.2 g/dl and 6.8 µl/l, respectively, even after 3-month appropriate iron supplementation.

INVESTIGATIONS

¹³C-urea breath test for *Helicobacter pylori* (Hp) infection showed a positive result for urease activity. Thus, despite negative results of occult GI bleeding, upper endoscopy was performed for assessment of a GI cause for the anaemia, revealing diffuse gastric nodularity 2 to 3 mm in diameter from the antrum to angulus without any mucosal erosion, ulcer or atrophy (figure 1). No endoscopic abnormalities, including typical markers of celiac disease, were present in the oesophagus and duodenum. On histological examination, biopsy specimens from the antrum and angulus showed marked inflammatory cell infiltration with lymphoid follicles (figure 2). Immunophenotyping study staining with the monoclonal B cell antibody CD-20 to rule out mucosa-associated lymphoid tissue (MALT) lymphoma showed a negative result. Based on these investigations, she was diagnosed having nodular gastritis (NG) associated with Hp infection.

TREATMENT

Hp eradication regimen including amoxicillin 1500 mg/day, metronidazole 500 mg/day and rabeprazole 20 mg/day for 7 days was begun with successful eradication (negative result of follow-up with ¹³C-urea breath test).

OUTCOME AND FOLLOW-UP

Two months after Hp eradication, her haematologic profile returned to normal of Hb 14.1 g/dl and SF 34.1 µl/l with an improved response to iron supplementation. One year

Figure 1 Upper endoscopy revealed diffuse gastric nodularity 2 to 3 mm in diameter from the antrum to angulus without any mucosal erosion, ulcer or atrophy.

later, her Hb was maintained almost normal with intermittent iron supplementation.

DISCUSSION

Clinical significance of NG

NG is a form of chronic gastritis that endoscopically has a miliary pattern with cobblestone appearance.⁴ In Japan, it has been called 'Torihada-ien', a Japanese word meaning 'gastritis with goose bumps-like appearance'. It is pathologically characterised by prominent lymphoid follicles and infiltration of mononuclear cells in the gastric mucosa.⁵ This phenomenon was once considered physiologically particular to young women. However, recent studies have shown that NG was highly associated with Hp infection with a high specificity (96.8%) and positive predictive value (93.3%)⁴ and after successful Hp eradication, endoscopic NG pattern disappeared or improved.⁶ In addition, it might be a risk factor for gastric cancer with some specific features.⁵ However, absence of NG cannot rule out Hp infection due to low sensitivity.⁴ This particular gastritis in patients with Hp infection may occur resulting from some factors such as variations in Hp strains, individual disease susceptibility, or a complex bacteria-host interaction.⁶

The association between IDA and Hp infection

In prospective studies of patients with IDA, conventional endoscopic investigation failed to identify a culprit lesion potentially responsible for blood loss in a large proportion of patients.⁷⁻⁸ Recent epidemiologic studies have suggested a highly association between Hp infection and IDA. In a systematic review, Hp infection was a risk factor for IDA; pooled odds ratio (OR) 2.8 (95% CI 1.9, 4.2) and also for iron-deficiency; pooled OR 1.38 (95% CI 1.16-1.65).⁹ In a case series, 91.7% of IDA patients with Hp-associated gastritis recovered from anaemia even with discontinuation of iron supplementation 12-month after Hp eradication therapy.¹⁰ In a meta-analysis of IDA patients with Hp infection, Hp eradication therapy combined with iron supplementation was associated with a more significant increase in haematologic parameters than iron supplementation alone.¹¹

The possible pathologic mechanism of IDA associated with Hp infection

Several mechanisms have been proposed to explain the possible relationship between IDA and Hp infection. Iron in food is available in two forms—hem iron (in muscle as myoglobin and Hb), which is readily absorbed, and non-

Figure 2 On histological examination, a biopsy specimen from the antrum showed marked inflammatory cell infiltration with lymphoid follicles (Haematoxylin-Eosin stain, $\times 10$).

hem iron (in vegetables, cereals and meat), which accounts for 80% of dietary iron in industrialised countries.¹² Both hydrochloric acid and ascorbic acid in gastric secretion are essential for the effective solubility and absorption of non-hem iron.¹² Hp infection might inhibit the non-hem iron absorption by lowering hydrochloric acid and ascorbic acid concentration in the gastric secretion.¹³

Hp infection might cause IDA by utilising iron for growth, competing with the human host. It has been shown that human lactoferrin (HLf) serves as a source of iron for Hp in gastric mucosa and Hp produces a HLF-binding protein that is highly specific for HLF.¹⁴ The level of HLF in gastric mucosa increased in Hp infection and decreased significantly after Hp eradication therapy, while the blood Hb level correspondingly increased.¹⁵

In a current study, strains of Hp isolated from IDA patients showed enhanced iron uptake and iron dependent rapid growth compared with those from non-IDA patients.¹⁶ It has been shown that Hp binds iron to a specific receptor by iron-repressible outer membrane proteins (IROMPs).¹⁷ In the iron-depleted state, strains of Hp-associated with IDA demonstrated an advantage in iron acquisition due to a higher expression of IROMPs.¹⁷ Based on the experimental evidence, colonisation of specific Hp strains with enhanced iron uptake or binding ability might predispose to IDA.

Our comments of the present case

In case of a refractory IDA, the potential causes should be ruled out. In the present case, careful history taking and laboratory investigations excluded incorrect diagnosis (thalassemia, etc.), presence of coexisting non-GI disease impairing response (haemolysis, chronic inflammation,

renal failure, etc.), lack of adherence to medication, concomitant use of drugs impairing response (antacids, etc.). But, given that she needed to take intermittent iron supplementation even after Hp eradication, we may fail to identify comorbid GI source, in addition to the possibility of relatively low dietary iron intake compared with regular menstrual iron loss as with typical Japanese IDA women.

Based on current literature, autoimmune atrophic gastritis and celiac disease as well as Hp infection have been proposed as significant factors in refractory or unexplained IDA.¹⁸

Autoimmune atrophic gastritis is manifested by hypergastrinaemia in combination with antiparietal antibodies.¹⁸ Despite no data of serum gastrin concentration or antiparietal antibody titers in this case, both endoscopic findings and histopathology excluded the condition.

In western countries, celiac disease should be considered in the differential diagnosis of IDA and needs histopathology to confirm a definite diagnosis. However, she had neither characteristic GI or extra-GI manifestations nor typical endoscopic markers associated with celiac disease.¹⁹ The possibility of coexisting subclinical condition may be considered but less likely due to the extremely low prevalence in Japan.²⁰

Occasionally, gastric MALT lymphoma can occur endoscopically in cobblestone appearance, which is hard to differentiate from NG. However, she had a negative immunophenotyping study.

In the present case, Hp infection was likely to be one of significant factors predisposing to refractory IDA because successful Hp eradication readily improved response to iron supplementation. However, careful follow-up,

regardless of repeatedly negative results of occult blood in the stool, is required and further GI investigations including work-up for colonic or small bowel lesions should be taken into consideration if refractory IDA progresses during the course.

CONCLUSION

In a refractory IDA patient, Hp infection should be considered in the possible background. In such an unexplained IDA patient, a search for Hp-associated gastritis should be undertaken even when GI manifestation is absent. NG is highly associated with Hp infection with a high specificity and positive predictive value. Hp eradication could improve haematologic parameters along with an improved response to iron supplementation.

Learning points

- ▶ In a refractory IDA patient, Hp infection should be considered in the possible background.
- ▶ In such an unexplained IDA patient, a search for Hp-associated gastritis should be undertaken even when GI manifestation is absent.
- ▶ NG is highly associated with Hp infection with a high specificity and positive predictive value.
- ▶ Hp eradication could improve haematologic parameters along with an improved response to iron supplementation.

Competing interests None.

Patient consent Obtained.

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