Iron deficiency and *Helicobacter pylori*–induced gastric cancer: too little, too bad

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Clinical vignette: A 38-year-old man consults you in the GI clinic because of frequent episodes of epigastric pain, nausea, and tiredness. His blood count shows signs of mild iron deficiency anemia. Upper GI endoscopy was normal, but antral and corpus biopsy specimens show evidence of gastric atrophy and *Helicobacter pylori* infection. Colonoscopy and capsule endoscopy showed no evidence of lesions in the large or small bowel. He receives a standard one-week course eradication therapy consisting of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin. His symptoms improve, but his infection persists and he remains mildly anemic. He asks you whether the infection must be eradicated, as he read on the Internet that it can cause stomach cancer. He is also concerned about the anemia.

Current therapy

*Helicobacter pylori* is the most common chronic bacterial infection worldwide and is causally linked to the pathogenesis of peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma (1). Most management guidelines across the world suggest that this infection should be sought and eradicated in patients with peptic ulcers (active or otherwise) or low-grade gastric MALT lymphoma, following endoscopic resection of early gastric cancer, as well as in patients with uninvestigated dyspepsia (the so-called test-and-treat strategy) (2, 3). Over the past decade, the eradication rates using one-week standard triple therapy (as in the case described above) have dipped below 70%, which is not an acceptable cure rate (4). The optimal first-line eradication regime depends on the level of resistance to clarithromycin. Thus, in areas with clarithromycin resistance below 15%–20%, it is generally recommended that a 7- to 14-day course of triple therapy comprising a PPI, clarithromycin, and amoxicillin (or metronidazole) is sufficient (2). Extending the duration of a PPI/clarithromycin-containing triple treatment from 7 to 10–14 days improves the eradication success by approximately 5%. In areas of high clarithromycin resistance (>20%), bismuth-containing quadruple treatments (PPI, bismuth salts, tetracycline, and metronidazole) are recommended for first-line empiric treatment (2). After failure of a PPI/clarithromycin-containing therapy, either a bismuth-containing quadruple therapy or levofloxacin-containing triple therapy is recommended. Other approaches that have gained success include sequential therapy (PPI + amoxicillin for 5 days, followed by PPI + clarithromycin + metronidazole for 5 days) or concomitant therapy (all 4 drugs given for 10–14 days). In the patient above, most experts would attempt further eradication with quadruple bismuth-based therapy for 14 days, preferably after checking antibiotic resistance. The patient is at increased risk of gastric cancer due to the presence of gastric atrophy. His iron deficiency anemia is another factor that should be taken into consideration, and he may require endoscopic surveillance beyond eradication (5).

Knowledge gaps

Gastric adenocarcinoma remains the second most common cause of cancer-related death and is characterized by a well-defined, multistage pathway that starts with *H. pylori*–induced chronic gastritis and progresses to gastric atrophy, intestinal metaplasia, dysplasia, and cancer. The more virulent *H. pylori* strains, e.g., *cagA* strains, induce more gastric inflammation/atrophy and a greater risk of cancer (1). Gastric atrophy and its associated hypo/achlorhydra are also complicated by poor absorption of iron, and there is evidence to suggest that the resulting iron deficiency anemia could be reversed by eradication of the infection (6). Epidemiological data suggest that iron deficiency increases the risk of gastric cancer, but the mechanism is not clear (7).

Research advances

In this issue of the *JCI*, a study by Noto et al. (8) offers a fascinating mechanism to explain why iron deficiency could increase the risk of *H. pylori*–induced gastric cancer. Using the Mongolian gerbil as the host model and infecting it with an oncogenic *H. pylori* cag+ strain, they show that iron depletion accelerates the development of premalignant (dysplasia) and malignant (adenocarcinoma) lesions in a cagA-dependent manner. Crucially, the authors show that *H. pylori* strains harvested from iron-depleted gerbils, or grown under iron-limiting conditions, become more virulent, as evidenced by increased assembly of the cag type IV secretion system (T4SS), translocation of CagA protein, and increased expression of the chemokine IL-8. To prove this beyond doubt, the pre-inoculation parental *H. pylori* strain was grown in vitro under iron-replete or iron-restricted conditions and then cocultured with gastric epithelial cells. There was a significant increase in the number of visualized T4SS pili per bacterial cell in strains grown under iron-restricted conditions, and this phenotype was abrogated following the addition of exogenous iron. To take the laboratory findings into the clinical arena, the authors examined a human population at increased risk of gastric cancer. They isolated *H. pylori* strains from patients with the lowest ferritin levels and showed that these induced more robust proinflammatory responses compared with strains isolated from patients with the highest ferritin levels, irrespective of histologic status.

Implications and future directions

The study by Noto et al. (8) provides for the first time an important insight into the mechanism by which iron deficiency could increase the risk of gastric cancer in...
subjects colonized by \textit{H. pylori} infection. Although clearly relevant to gastric cancer, the findings will shed considerable light on other poorly understood malignancies. For example, the role of colonic microbiota in colorectal cancer is just beginning to be realized, and it is known that iron deficiency is also associated with such malignancy. The findings in this study will focus attention on the interaction among the host, the microbiota, iron (and other micronutrients), and neoplastic pathways in many organs within the body. Because iron deficiency is easily detectable and readily reversible, the findings from this study have huge translational potential. The addition of an easily measurable biomarker for identification of populations of infected persons at high risk for gastric cancer is very welcome indeed.

When guidelines for treatment of \textit{H. pylori} are revised, this work will provide direct evidence for the desirability of eradication therapy in the context of iron deficiency anemia and gastric cancer prevention.

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