JPPT | Case Report

Iron Pill–Induced Gastritis in a Pediatric Patient Taking Ferrous Sulfate Tablets

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Iron supplementation is frequently used in the treatment of iron deficiency anemia in the pediatric population. We describe a case of an 11-year old male who developed adverse side effects following treatment with oral ferrous sulfate tablets for 2 months. The diagnosis was made following findings of iron deposition on histology obtained during endoscopy. The iron supplementation was changed from tablet to liquid form, and repeat endoscopy 4 months following initial diagnosis showed resolution of the histologic findings of iron pill–induced gastritis.

ABBREVIATIONS IPIG, iron pill–induced gastritis; PPI, proton pump inhibitor

KEYWORDS acid suppression; anemia; ferrous sulfate; gastritis; iron deficiency

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Introduction

Iron supplementation may cause a wide range of side effects, including constipation, abdominal pain, and gastrointestinal hemorrhage. Although complications following overdose or acute ingestion of large quantities of iron have been widely reported, iron pill–induced gastritis (IPIG) following routine therapeutic iron supplementation is an underreported complication. We report a case of an 11-year old male who was started on iron supplementation and who subsequently developed IPIG.

The causes of gastritis are numerous and include medications, infection, corrosive agents, and severe illness. *Helicobacter pylori* is one of the most common infectious etiologies and has been found in more than one third of pediatric patients on upper endoscopy.[1] Although non-steroidal anti-inflammatory drugs and corticosteroids are frequently implicated, iron supplementation is a rarely recognized cause of gastritis.[2]

IPIG is one form of gastric siderosis, which is characterized by the deposition of excessive iron in the gastric mucosa. Iron deposits hemosiderin, which can erode gastric mucosa, causing localized ulceration.[3] It is thought that iron tablets or pills lead to a concentrated corrosive effect, which is absent when patients are switched to liquid iron supplementation. Iron oxidation itself also leads to injury to the gastric epithelium.[4] Several patterns of gastric siderosis have been described based on the location and pattern of iron deposition on histopathology.[2] The histologic pattern typically seen in IPIG includes predominantly extracellular deposition of iron, although less frequently iron deposition is seen in the epithelium and macrophages.[2]

Case Report

An 11-year-old African American male with a history of asthma, eczema, and allergic rhinitis was referred to a pediatric gastroenterology clinic for evaluation of persistent hematochezia, abdominal pain, dysphagia, and iron deficiency anemia. He had a several-year history of abdominal pain and regurgitation for which he had taken histamine-2 blockers and proton pump inhibitors (PPIs) because his symptoms were thought to be due to gastroesophageal reflux disease. The regurgitation had occurred frequently since early infancy, but at the time of his presentation it was only occurring several times per month. He also incidentally reported difficulty swallowing pills, but he was not sure of the duration of this symptom. He had initially been taking famotidine but could not recall when this was changed to omeprazole. At the time of his initial presentation, he had been taking omeprazole 20 mg twice daily for 3 years. He had previously been taking omeprazole once daily, but he continued to have persistent abdominal pain, which led to the increase in dose. He had an upper endoscopy performed 2.5 years prior to initial presentation, and it was visually and histologically unremarkable. He had been having intermittent hematochezia for several years and also had a history of excessive wiping and straining with bowel movements.

For his asthma, he had been maintained on aerosolized fluticasone propionate and salmeterol. He did not have a history of frequent non-steroidal anti-inflammatory drug or oral corticosteroid use. He did not have any known medical allergies. His weight was 60.9 kg. His physical examination was unremarkable aside from dermatologic findings consistent with eczema.

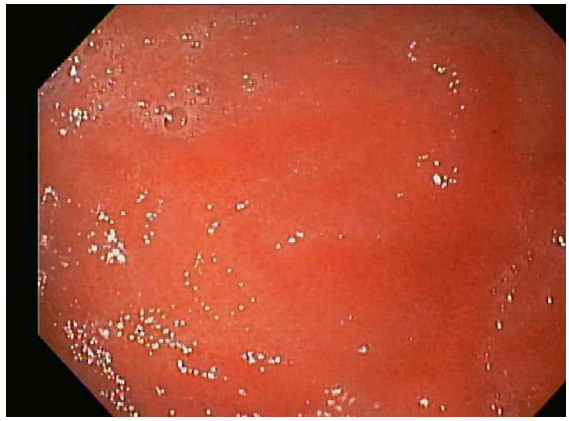
One month prior to his initial gastroenterology clinic visit, laboratory evaluation performed by his primary care provider revealed microcytic anemia with a hemoglobin of 11.9 g/dL and mean corpuscular volume of 75.5 fL. Iron studies showed serum iron of 51 mcg/dL (normal, 59–158), TIBC 465 mcg/dL (normal, 171–504), and ferritin of 33.9 ng/mL (normal, 30–400). Thyroid studies and celiac titers were unremarkable. Abdominal x-ray showed moderate stool burden. Although his anemia was mild, he was started on ferrous sulfate (oral tablets) 325 mg twice daily by his primary care provider.

Given his chronic regurgitation and dysphagia, there was concern for reflux esophagitis and eosinophilic esophagitis. Although constipation was felt to be a likely cause of his hematochezia, given the duration of his bloody stools and mild anemia, there was concern for inflammatory bowel disease. Given these concerns, he underwent upper endoscopy and colonoscopy with biopsies 1 month after his initial gastroenterology clinic visit. His omeprazole had been changed to famotidine at the time of the gastroenterology visit because there was concern that taking a PPI may potentially mask histologic evidence of eosinophilic esophagitis.

The upper endoscopy showed furrowing and edema in the esophagus. Erythema was noted in the gastric body and antrum (Figure 1). The colonoscopy was visually unremarkable. At the time, he had been taking ferrous sulfate tablets for approximately 2 months. Biopsies were obtained from the areas of erythema in the stomach along with multiple regions of the esophagus and duodenum. Hematoxylin-eosin staining was initially performed and Perl iron stain was subsequently added to assess for the presence of iron deposition (Figures 2 and 3).

In addition to a diagnosis of eosinophilic esophagitis, the biopsies showed evidence of chronic gastritis. There was no evidence of *H pylori*. Given the findings on iron stain, the diagnosis of IPIG was established.

Figure 1. Endoscopy shows mild erythema in the gastric body.



Given these findings, his ferrous sulfate was switched from tablet to liquid formulation. His famotidine was also changed back to omeprazole. He was also started on a 4-food elimination diet for his eosinophilic esophagitis.

On repeat endoscopy 4 months later, his stomach appeared visually normal. Biopsies showed minimal

Figure 2. Hematoxylin-eosin–stained section at magnification. Iron is noted as refractile brown deposition in the pink and purple background (original magnification ×400).

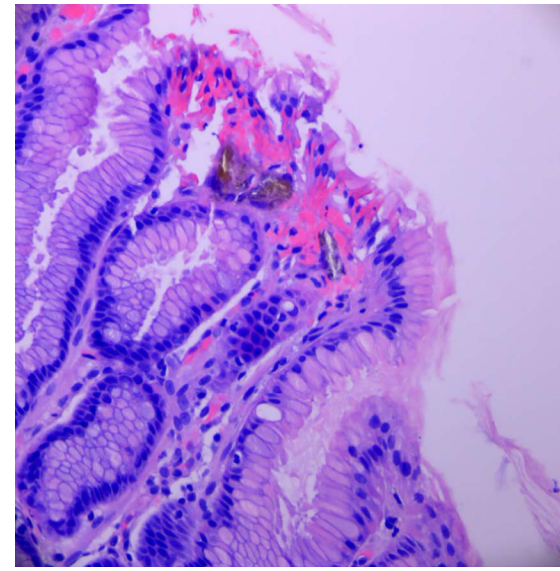
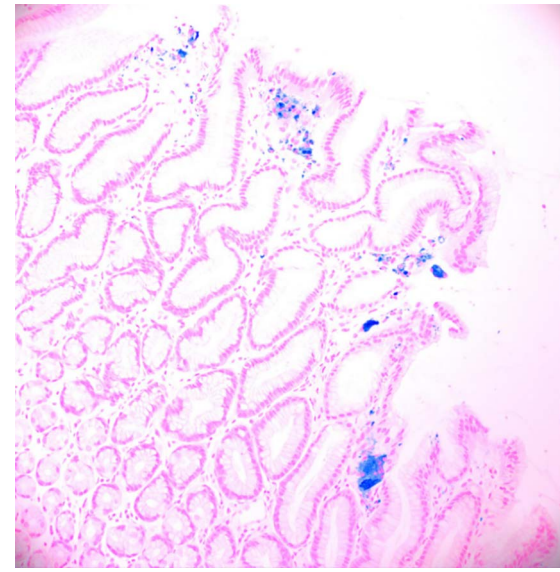


Figure 3. Iron-stained section. Iron is noted as blue granules in the pink background (original magnification ×200).



chronic gastritis but no evidence of iron deposition. His iron supplementation was later discontinued given the resolution of his anemia. Eight months after his diagnosis of IPIG, laboratory studies showed hemoglobin 12.8 g/dL and a mean corpuscular volume of 82.9 fL. His anemia remained resolved on subsequent laboratory evaluations.

Discussion

The clinical presentation of IPIG can mimic other causes of gastritis and patients may report epigastric pain, vomiting, and dark stools. Endoscopic findings are often nonspecific, and ulcers and erosions are frequently seen. Histology often reveals brown or black pigmented deposition in the mucosa.

Iron deposition has been reported in less than 1% of endoscopic evaluations in adults.[5] However, greater iron deposition is found in gastric biopsies with more extensive mucosal injury. Many patients have underlying conditions that already cause mucosal injury that is further exacerbated with the use of iron tablets. Underlying conditions or therapies that predispose patients to iron overload, such as blood transfusions, also exacerbate gastric siderosis.[6,7] Despite multiple reports in adults, there are currently only a few reports of IPIG in the pediatric population.[8,9] This is noteworthy because iron deficiency is common in children, and special attention needs to be paid to the adverse effects of iron replacement therapy. This is often a reversible complication; however, long-term use may lead to more significant gastric ulceration and gastrointestinal bleeding.

The main treatment for IPIG is switching from a tablet to liquid formulation. Because the concentration of iron is more spread out over the gastric mucosa with a liquid preparation, there is less of a directed corrosive effect on the epithelium. Additionally, starting the patient on a PPI or prescribing a short course of sucralfate may be beneficial in healing existing gastrointestinal injury.

In the patient described in this case, iron supplementation was initiated despite a very mild anemia. There is evidence supporting the use of iron supplementation in patients with iron deficiency even without anemia.[10] Especially in this patient where there was concern for inflammatory bowel disease, iron supplementation has been shown to improve quality of life.[11] Ferrous sulfate is the most commonly prescribed oral iron preparation, with 1 study showing that 84% of hematology/oncology specialists would prescribe it in a scenario of a toddler with iron deficiency anemia.[12] Other iron formulations, such as iron polysaccharide and carbonyl iron, were much less frequently used. Although ferrous sulfate tablets are most commonly associated with IPIG, the frequency of this adverse effect with other iron formulations has not been well studied. There is also a lack of data on the duration and dosing of oral iron supplementation that would increase a patient's risk of developing this complication. The lack of consensus guidelines on the duration and frequency of therapy and the idea that iron supplementation is generally safe often lead to overuse of the medication. Given the side effects associated with iron supplementation, it is prudent to continue the iron for the shortest time necessary. This is of course affected by significant variation in clinical practice in the treatment of iron deficiency anemia. A survey of 398 members of the American Society of Pediatric Hematology/Oncology showed recommended duration of iron therapy after resolution of anemia to range from no additional therapy (33% of respondents) to 3 or more months of therapy (20% of respondents).[12] Additionally, in many pediatric patients, hemoglobin and iron levels are not routinely reassessed or the iron is continued as part of a patient's routine medications without further consideration of its necessity. The frequency of iron administration is another subject of debate that may affect the risk of developing IPIG. A meta-analysis of 34,564 children showed that iron administration of 3 to 7 times per week did not improve factors such as anemia and iron deficiency compared with iron administration 1 to 2 times per week.[13]

In patients with signs of gastropathy, iatrogenic causes should be considered, including evaluation of the patient's medications and supplements. Health care providers should be cognizant of the adverse effects of long-term iron supplementation in children and consider weaning or discontinuing iron in patients when their anemia has resolved and their iron supplies have been sufficiently repleated. If children do require long-term iron supplementation, the use of oral ferrous sulfate tablets should be monitored and there should be consideration to switch to a liquid formulation.

Article Information

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