Histopathology 2008, **53**, 311–317. DOI: 10.1111/j.1365-2559.2008.03081.x

Iron-induced mucosal pathology of the upper gastrointestinal tract: a common finding in patients on oral iron therapy

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Date of submission 18 December 2007
Accepted for publication 25 February 2008

Kaye P, Abdulla K, Wood J, James P, Foley S, Ragunath K & Atherton J
(2008) *Histopathology* **53**, 311–317

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Aims: Upper gastrointestinal injury from iron tablets at therapeutic dose is not widely recognized. The aim was to document cases of iron-related upper gastrointestinal (GI) pathology and to determine frequency of occurrence.
Methods and results: We prospectively studied patients with iron deficiency anaemia undergoing upper GI endoscopy from November 2005 to July 2006. Cases of upper GI iron deposition from these and other cases extracted retrospectively between 1999 and 2006 were examined histopathologically and patient notes were reviewed. In the prospective study, 15/160 patients investigated for iron deficiency anaemia [16.1% (15/93) of those taking oral iron tablets] had iron deposition noted on routine haematoxylin and eosin staining. In this plus the retrospective series, 59 patients were identified with 64 episodes of iron deposition. Eighty-six percent (6/7) with oesophageal iron deposition had associated erosion. Sixty-three percent (29/46) with gastric iron deposition had erosion and 80% (37/46) had reactive gastritis. Duodenal deposition was usually (91%, 10/11) within macrophages in villous tips with no erosion. Ninety-eight percent (58/59) of iron deposition cases had documented oral iron intake.
Conclusions: Iron deposition in the upper GI tract is common in patients taking iron tablets. It is frequently associated with mucosal disruption in the oesophagus and stomach.

Keywords: anaemia, erosions, haemosiderin, iron, ulcer

Abbreviations: GI, gastrointestinal; H&E, haematoxylin and eosin; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor

Introduction

Oral iron is widely used in the treatment of iron deficiency anaemia, most commonly in the form of ferrous sulphate tablets. Although iron poisoning in overdose with associated mucosal necrosis and stricture formation is well described,[1,2] this is rare, and lesser degrees of injury with standard dosages are not as well recognized. Despite this, many patients on oral iron complain of upper gastrointestinal (GI) symptoms including dyspepsia and nausea,[3–5] which they associate with the tablets and which may result in non-compliance with treatment. In recent years pathologists have become aware of iron in upper GI biopsy specimens, as shown by a substantial case series from Abraham *et al.* in 1999[6] and a further two smaller series in 2006.[7,8] In these series, explanations for iron deposition varied from coexistent haemochromatosis to liver disease and oral iron tablets.

Over the past few years we have noticed iron deposition in mucosal biopsy specimens with increasing

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frequency. Our first aim was to determine the frequency of iron-associated pathology in patients being investigated for iron deficiency anaemia, the majority of whom are taking oral iron tablets. We also aimed to document cases of iron-associated upper GI pathology diagnosed in our hospital between 1999 and 2006, to relate these to clinical findings and record of preceding iron therapy and to describe the morphology of iron-induced pathology. This represents the largest reported series of iron-induced upper GI pathology.

Patient population and methods

For the prospective study, unselected patients with iron deficiency anaemia undergoing upper GI endoscopy as part of their investigations were collected between November 2005 and July 2006. These patients had gastric and duodenal biopsies as part of their work-up, and our practice is routinely to biopsy abnormal appearing areas. For the retrospective series, the pathology files of the Queen's Medical Centre in Nottingham were searched for cases of possible iron deposition between 1999 and 2006.

Slides from each case were reviewed by two pathologists to determine the site and pattern of iron deposition and note associated pathology. We classified the iron deposition into four patterns (Table 1). The typical patterns of iron deposition are shown in Figure 1.

All cases were initially identified on haematoxylin and eosin (H&E) staining and then confirmed by staining for iron with Perls' Prussion Blue method. The patient notes were reviewed to determine details of treatment, haematological parameters, associated diseases and endoscopic findings.

Statistical analysis was performed using SPSS 14 (SPSS Inc., Chicago, IL, USA). Tests used were Pearson's χ^2 and *T*-test for age distribution.

Table 1. Patterns of iron deposition

Pattern	Name	Description
A	Luminal	Iron deposited in a crystalline form, often in a linear fashion over intact or eroded epithelium
B	Lamina propria	Granular iron present, usually in large amounts, within lamina propria and/or granulation tissue with overlying intact or ulcerated epithelium
C	Epithelial	Iron within glandular or surface epithelial cells
D	Reticuloendothelial	Iron in histiocytes within lamina propria

Results

PROSPECTIVE SERIES

Between November 2005 and July 2006, 160 unselected patients [median age 71 years, interquartile range (IQR) 56–80, 38% male] undergoing upper GI endoscopy to investigate iron-deficient anaemia were included in the study. Fifteen patients had iron visible on H&E-stained sections from upper GI biopsy specimens. These patients were in the group of 93 documented as taking oral iron therapy at the time of endoscopy; thus, 16% of patients known to be taking oral iron had iron deposition visible on H&E staining. No patient not known to be on iron showed iron deposition. Of 15 patients with iron deposition, six had endoscopically visible erosions, significantly greater than the 14/141 patients without deposition ($P < 0.01$). There were no significant differences between patients with or without iron deposition with regard to age, gender, aspirin or non-steroidal anti-inflammatory drug (NSAID) use or degree of inflammation or atrophy. Proton pump inhibitor (PPI) use, however, was significantly greater in patients with iron deposition (8/13 with iron deposition were taking PPIs versus 40/123 without, $P = 0.037$).

PATIENTS IDENTIFIED THROUGH PATHOLOGY RECORDS

An additional 44 patients were identified retrospectively from pathology records. Records were searched by oesophageal, gastric and duodenal biopsies coded as pigmentation or haemosiderosis from 1999 to 2006. A word-searchable database available between 1999 and 2002 was also searched for cases including haemosiderin, iron, haemosiderosis and pigment described in report. A total of 59 patients (median age 72 years, IQR 60–82, 69% female) were thus identified with a total of 64 sites of iron deposition. In keeping with the elderly population, there was a high degree of comorbidity in these patients (Table 2). There was an increase in frequency of pathological diagnosis of iron deposition throughout the study period, possibly related to heightened awareness of this entity by the pathologists in our department.

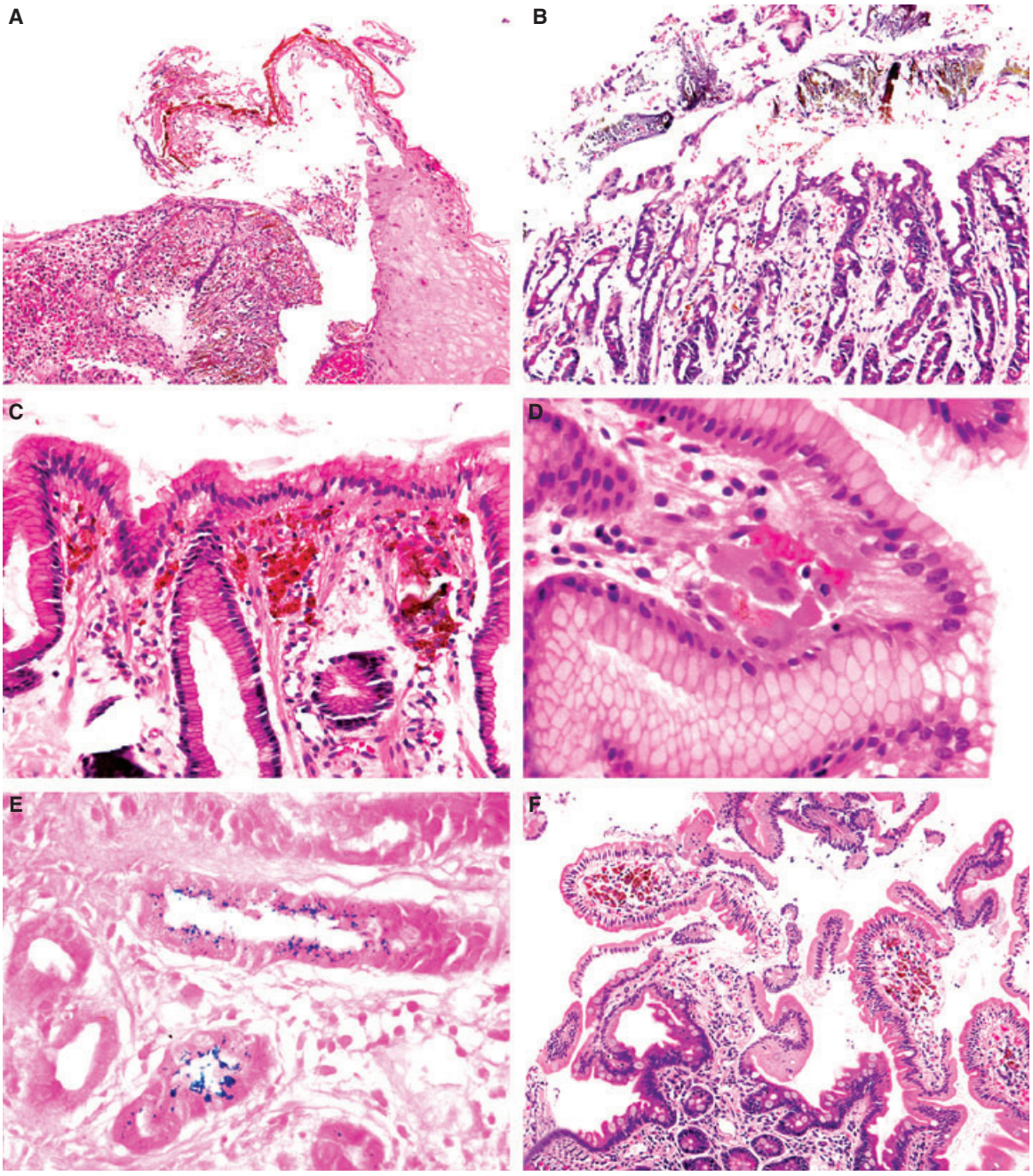

Figure 1. Patterns of iron deposition. **A,** Oesophageal ulcer showing crystalline iron coating the surface (pattern A) and haemosiderin in granulation tissue (pattern B) (H&E). **B,** Gastric biopsy specimen showing surface iron (pattern A) with underlying reactive gastritis (H&E). **C,** Gastric biopsy specimen with haemosiderin in lamina propria (pattern B) (H&E). **D,** Gastric biopsy specimen showing more subtle focal iron deposition engulfed by foreign body giant cell (H&E). **E,** Perls' Prussian Blue stain showing iron (blue) in glandular epithelium (pattern C). **F,** Duodenal biopsy specimen showing haemosiderin in histiocytes at villous tips (pattern D) (H&E).

CLINICAL INDICATION, IRON MEDICATION AND ASPIRIN/NSAID INTAKE

In the 44 retrospective patients, anaemia was the main indication for endoscopy in 28, GI bleeding in five and dysphagia in three, with the rest being a variety of indications. In the prospective series in all 15 patients the primary indication was investigation for anaemia, as this was the defining criterion for recruiting to this study.

Table 2. Comorbidity

Ischaemic heart disease/peripheral vascular disease	20
Connective tissue disease	11
Chronic obstructive airways disease	3
Chronic renal failure	3
Liver disease	3
Inflammatory bowel disease	2
Cancer	6
Coeliac disease	1
Diabetes	6
None	10

Review of medication showed that 98% (58/59) patients were documented as receiving oral iron prior to endoscopy. In one case prescription details were unable to be retrieved, but this patient had a haemoglobin of 7.7 and had received a blood transfusion and was probably being treated with iron. Of 52 patients where the iron preparation was known, 51 were on ferrous sulphate in varying doses As expected, most patients were anaemic [54/59 (91.5%)]. However, of the 38 patients with measured ferritin, eight had very high ferritin levels often associated with normal or high mean corpuscular volume and a further 11 were well within the normal range (>50 μg/l). Of the 59 patients with iron deposition, 49% (29) were taking either NSAIDs or aspirin. However, taking these drugs was not associated with ulceration or erosion in this population. Of the 31 patients with histologically proven ulceration/erosion in the upper GI tract, 58% (18) were taking aspirin/NSAIDs, not significantly different from the 41% (11/27) without erosions.

ENDOSCOPIC FINDINGS

Endoscopic information was available in all cases; 11 were described as normal and in 29 there were descriptions of erosions or ulcers. Of these, 26 corresponded to histological erosions/ulcers, whereas in three cases erosions were not histologically proven. In five cases, small polypoid areas were described which corresponded to the site of iron deposition in the stomach. In eight cases, generalized ''gastritis'' was reported and in a further seven particular descriptions of abnormal areas were reported. These included ''red area'', ''focal oedema'', ''inflamed fold'' and ''abnormal area''. Three of these mentioned brown or yellow discoloration described as ''a linear brown streak'' (Figure 2), ''yellow stained mucosa'' or ''brown villi''.

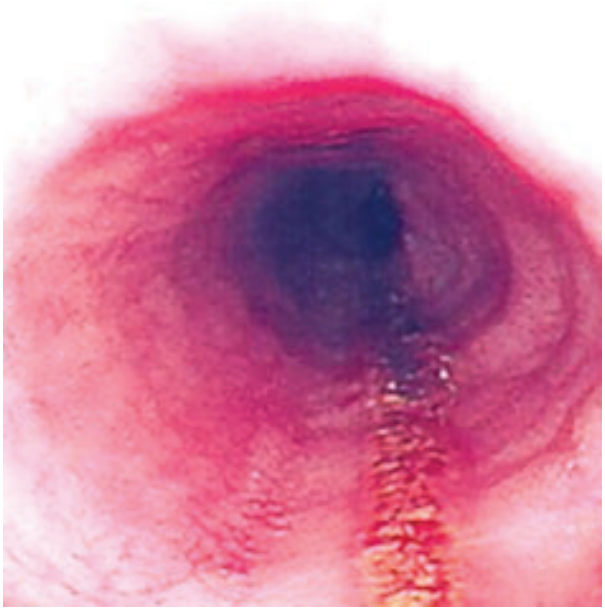

Figure 2. An endoscopic appearance associated with iron deposition in the oesophagus. Note the linear brown streak.

HISTOLOGICAL FINDINGS

All cases were identified on the routine H&E stain. The distribution of iron deposition in different parts of the upper GI tract and in the four different patterns is shown in Figure 3. Of the 15 patients from the prospective series, seven showed antral deposition, seven body and one duodenal, and none showed oesophageal deposition. All the gastric and oesophageal cases showed crystalline iron on the luminal surface (pattern A) and/or granular deposition in the lamina propria or granulation tissue (pattern B). Iron in this distribution was easily identified on H&E once pathologists were aware of its significance. Although many cases also showed epithelial iron deposition (pattern C), this was never the feature which attracted attention on the H&E and was more easily appreciated on the Perls' stain. The pattern of iron deposition within duodenal biopsy specimens was quite different. Here, the iron was usually present as collections of brown-stained histiocytes in the villous tips (pattern D) with or without concurrent epithelial staining. In one case the iron was exclusively within the villous epithelium, and in this case the endoscopic appearance was described as ''brown villi''. There was no significant difference in duration of iron treatment or cumulative dose between

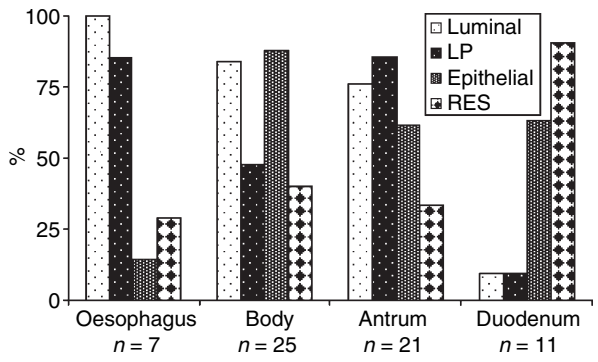

Figure 3. Iron deposition by site and pattern.

patterns or sites of iron deposition. However, there was a highly significant difference in the indication for endoscopy in the cases with oesophageal deposition compared with the rest of the group. Whereas 43/52 antral, body and duodenal cases had anaemia as the primary indication, this was never the indication in the seven oesophageal cases ($P < 0.001$). In these patients, the indication was usually related to symptoms directly attributable to the oesophageal ulceration, including dysphagia in three, coffee ground vomiting, nausea and reflux symptoms.

At most sites of iron deposition (55%, 35/64), histological erosion or ulceration was seen, but this was site dependent. All but one of the oesophageal cases were associated with ulceration/erosion (6/7, 86%), as were 63% (29/46) of gastric cases; none of the duodenal cases showed mucosal breaks (0/11). Associated local pathology for gastric cases varied. The vast majority of gastric cases (80%, 37/46) had an associated reactive gastritis; 9% (4/46) had a *Helicobacter pylori*-associated gastritis, 3/46 (6.5%) had a non-specific mild chronic or quiescent gastritis and 2/46 were otherwise normal. In 19% of cases (9/46) there was associated gastric atrophy.

Discussion

The toxic effect of iron on the gastrointestinal mucosa has been recognized for many years,[1,2,9] largely through studying cases of iron overdose. The mechanism is probably mediated by oxygen free radical production[10] resulting in a cytopathic effect and tissue necrosis when iron concentrations locally overwhelm the normal energy-dependent absorption mechanism.[11] It is therefore perhaps surprising that the toxic effect of iron in therapeutic doses has been discounted for so long, apart from isolated reports of iron tablet-induced pathology.[12–14] Iron pill-associated upper GI pathology is, however, being increasingly recognized by pathologists, with four published series in the past 10 years.[6–8,15] However, many gastroenterologists are less aware of iron as a possible cause of upper GI pathology. This is all the more important given the propensity of oral iron treatment to cause unpleasant upper GI symptoms in a large number of patients.[3–5] Despite some work on developing alternative, less toxic iron preparations,[4] ferrous sulphate remains the first-line agent, and alternative preparations and routes appear to be rarely considered, even when symptoms appear.

Although the problem of iron-induced upper GI pathology is increasingly recognized, there are few prospective data. In one study, ferrous sulphate tablets were given to 14 healthy volunteers for 2 weeks.[16] Antral erosions were found in two patients, but no positive histological findings were found. These volunteers were young, without concurrent disease or concomitant drug exposure. One prospective patient study found 18 cases out of 500 endoscopies (3.6%), of which six were on oral iron and a further three had extensive glandular deposition (pattern C in this study)[8]. However, unlike other series, the authors identified cases by staining all gastric biopsy specimens with Perls' Prussian Blue, which highlights iron deposition. They specifically point out that in most cases the iron was not easily visible by H&E alone, making it likely that some of these cases represented a different phenomenon to that seen in our and other studies and probably explaining the weaker association they found with preceding iron tablet treatment.

Abrahams *et al.* included a prospective element to their study[6] and found 12 cases of iron deposition from a total of 1300 upper endoscopies (0.9%) over a period of 6 months. In contrast, we limited our prospective evaluation to patients being investigated for iron deficiency anaemia, and our study is the first in a relevant patient population to quantify the prevalence of iron deposition and related pathology that would be detected on routine histology. Amongst our patients under investigation for iron-deficient anaemia, 9.3% had detectable iron deposition on routine H&E examination of upper GI biopsy specimens. All the patients with iron deposition were taking oral iron and 16% on oral iron had iron deposition noted. Thus, it is evident that in this group of patients iron deposition is very common.

Our retrospective series is the largest series of iron-induced upper GI pathology so far reported. The first reported series was by Ecksteen and Symons in 1996, where nine patients with iron deposition in the oesophagus and stomach were described.[15] Our series is perhaps most comparable to that of Abraham *et al.*, who evaluated 36 cases retrospectively[6] and, like us,

described frequent association with ulceration or erosion. Our proportion of erosion-associated cases was less than they describe (52% versus 83%), but an interesting new finding from our series was the marked difference in iron-induced pathology at different sites in the upper GI tract. Thus, our oesophageal cases were almost always associated with ulceration, as were 63% of our gastric cases but none of our duodenal cases. The pattern of duodenal haemosiderin deposition in macrophages at the tips of villi was interesting (pattern D). Only 1/8 of these patients had low ferritin and 5/8 had high ferritin. Several had other diseases such as rheumatoid arthritis and renal failure, which could have accounted for the anaemia. It is likely that many of these patients actually had iron overload rather than iron deficiency and were inappropriately on iron tablets. This pattern is akin to pseudomelanosis duodeni, a term for endoscopically visible, mottled pigmentation of the duodenum. Previous case reports and very small series have associated it with hypertension, drugs and systemic disease, but the largest and most convincing report of nine cases linked it to patients with chronic renal failure on oral iron.[17] This supports our contention that it might be an indicator of unnecessary oral iron treatment for an anaemia of chronic disease.

We classified pathological changes into four patterns and described associated pathology, particularly in the stomach. Several of the previous series have attempted similar classifications. Haig and Driman have suggested that cases with erosions associated with surface crystalline iron are due to direct iron tablet damage, whereas iron deposition in the lamina propria and glands is an incidental finding and/or marker of iron overload.[7] We consider it more likely that, apart from the rare patient with gastric siderosis due to haemochromatosis, the main difference between these two patterns is one of timing. In the acute phase of iron administration, iron will coat the mucosal surface, sometimes causing erosion or ulceration (pattern A). As the mucosa heals and epithelium regenerates, haemosiderin will remain behind in the lamina propria and some will be taken up by surrounding glands (pattern B). This does not reflect systemic iron overload. The situation in the duodenum may be different, as acute erosion due to iron appears less common in this location. Here, collections of haemosiderin-laden histiocytes at the tips of villi (pattern D) may well reflect systemic overload, but this pattern is quite distinct from the more chaotic and focal lamina propria deposition seen in gastric biopsy specimens.

Associated pathology in the stomach has been described in several series. Abraham *et al.* reported that 51% of patients had associated pathology, which included mechanical problems such as delayed gastric emptying, drug ingestion and histological features such as Helicobacter gastritis, chemical gastritis and cytomegalovirus infection, which could have contributed to mucosal injury.[6] In our series, reactive gastritis was very common in the gastric biopsy specimens, and several patients had atrophic gastritis and Helicobacter infection. We feel it is unlikely that these conditions would have predisposed to iron deposition and it is likely that the iron deposition would have been the cause of the reactive gastritis as a response to the chemical irritation. On the other hand, many of our patients were elderly with comorbidity and on multiple drugs and these factors might have impaired oesophageal and GI motility, rendering them more liable to local effects of iron and other irritants. The question of whether iron-associated pathology is truly a primary event or just represents engulfment within pre-existing lesions still remains. Although the latter may certainly occur in some cases, particularly within large benign or malignant ulcers, in many cases the histological appearances, with crystalline iron coating a very superficial erosion with reactive changes in the epithelium, argue strongly for iron deposition being the primary event. Although many of the patients in our series were taking NSAIDs and aspirin, there was no significant difference in iron-associated erosions/ulceration between these patients and those not on these drugs, making them an unlikely explanation for most erosions in this setting. Furthermore, in our prospective series anaemic patients with iron deposition were significantly more likely to demonstrate endoscopic erosions than those without iron deposition, a difference that could not be explained by differences in other drug use or any other clinical, demographic or pathological feature examined.

Interestingly, there was a significant positive association between PPI use and iron deposition. This could be due to increased prescribing of PPI in this group due to symptoms caused by iron-induced erosions. Another possibility is that iron deposition in the stomach is enhanced by alkaline conditions.

The endoscopic appearance of iron-related pathology may vary from superficial erosions to frank ulceration, and in some cases small regenerative polyps are seen which on histology do not show polypoid architecture, but rather reactive gastritis with iron encrustation. Endoscopists who are aware of the entity could suspect it by a yellow-brown discoloration of the mucosa, but in our series in only two cases was iron deposition prospectively mentioned by the endoscopist as a possibility.

The clinical importance of recognizing iron-induced upper GI pathology is several fold. First, it potentially

provides a rational pathological explanation for the symptoms commonly encountered by patients receiving oral iron. This potential association with symptoms deserves further research. If it is confirmed, consideration should be given to alternative iron preparations. For example, liquid iron is recognized to be better tolerated with fewer local effects than tablet form and also requires lower dosage.[18,19] Second, endoscopists investigating iron-deficient anaemia should be careful of attributing it to upper GI erosions that they may see at endoscopy in patients on iron therapy. These may be the effect of iron treatment rather than the cause of the anaemia, whether or not the patient is on NSAIDs or aspirin. Lastly, in patients with the pattern D of iron distribution in the duodenum, the diagnosis of iron deficiency (if made) should be critically re-evaluated.

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