Isolated IgG4-related gastric disease presenting as diffuse gastric wall thickening with ulcer

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ABSTRACT

An 81-year-old male presented with loss of appetite, early satiety and iron deficiency anaemia. A computed tomography (CT) scan of the abdomen and pelvis during initial work-up revealed diffuse gastric mural thickening associated with a large ulcer and adjacent gastro-hepatic lymphadenopathy. The CT appearances, together with the clinical features, were highly suspicious for an infiltrative type of gastric malignancy. Endoscopic biopsy however showed erosive inflammation, IgG4 plasmacytosis and fibrosis, raising the possibility of IgG4-related disease. A serologic assay for IgG showed normal IgG4 and elevated IgG2 serum levels. After appropriate steroid treatment, endoscopy and CT scan showed resolution of the ulcer and gastric wall thickening. This case shows yet another possible appearance of gastric involvement in IgG4-related disease on the current evolving spectrum of this disease presentation. Greater awareness and education of this disease would help in patient care, ensuring earlier diagnosis, prevention of severe organ damage and morbidity, as well as unnecessary surgery.

CASE REPORT

CASE REPORT

An 81-year-old male patient presented to the emergency department with a 1-month history of loss of appetite, associated with early satiety. There was no complaint of sarcophobia. He had a past medical history of hypertension, L4-L5 spondylolisthesis with spinal stenosis and previous decompression surgery, as well as impaired fasting glucose.

On arrival, he was pale but comfortable and had normal vital signs. The cardiorespiratory examination was unremarkable. His abdomen was soft, non-tender and with no detectable organomegaly or ascites. A digital rectal examination revealed no melaena or per rectal bleeding.

Laboratory studies revealed a haemoglobin level of 7.8 G/DL [reference range: 14.0 – 18.0 G/DL], with microcytic, hypochromic red blood cells in keeping with iron deficiency anaemia. Laboratory studies for tumour markers were not performed.

A computed tomography (CT) scan of the abdomen and pelvis revealed diffuse gastric mural thickening along the lesser curve, associated with a large ulcer and prominent gastro-hepatic lymph nodes (Figure 1a, Figure 1b). The appearance was highly suspicious for an infiltrative type gastric malignancy, with probable nodal metastases. No ascites, retroperitoneal lymphadenopathy, or other organ involvement was detected.

Four days later, oesophagogastroduodenoscopy (OGD) showed pangastritis and a Siewert type 3, large, malignant-looking ulcer in the proximal lesser curve that extended to the proximal cardio-oesophageal junction (Figure 2). The initial ulcer biopsy showed chronic inflammation and no malignancy. The result's apparent discordance with the suspicious clinical, imaging and endoscopic findings prompted a repeat biopsy of the ulcer 1 week later.

The latter showed antral-type mucosa manifesting erosive, moderate chronic inflammation with plasmacytosis and focal storiform fibrosis (Figure 3a, Figure 3b). No obliterative phlebitis or granuloma was seen.

Immunohistochemical staining showed focal IgG4 plasmacytosis with up to 16 IgG4 plasma cells / 34 IgG plasma cells in a high-power field (Figure 4a, Figure 4b). No light chain restriction could be demonstrated by in-situ hybridization with kappa and lambda light chains. AE1/3 failed to show keratin-positive infiltrating malignant epithelial cells.

Serological assay for IgG showed normal IgG4 levels at 1.22 G/L [reference range: 0.04 – 1.57 G/L] and elevated IgG2 levels at 10.74 G/L [reference range: 0.64 – 7.00 G/L].

The combination of the presentation as a tumour-like lesion, biopsy findings of storiform fibrosis and IgG4 plasmacytosis, as well as the elevation of serum IgG2 levels suggested a high probability of IgG4-related disease (IgG4-RD) [1].

The patient was referred to gastroenterology department. A repeat endoscopy with endoscopic ultrasonography was performed about 1.5 months after the initial endoscopy. At this point of time, there was already slight interval healing of the ulcer (Figure 5). Endoscopic ultrasound showed persistent thickening of the submucosa, without extension to the mucosa, or invasion of the muscularis propria (Figure 6). Given the histopathological, endoscopy and serological findings, a diagnosis of gastric IgG4-RD was made, and the patient was started on a course of corticosteroids (prednisolone, 40 mg once a day for 1 month).

Repeat endoscopy after treatment showed complete healing of the ulcer (Figure 7). CT of the abdomen and pelvis showed significant improvement of the mural thickening and reduction in size of the gastro-hepatic lymph nodes (Figure 8a, Figure 8b). A repeat CT of the abdomen and pelvis 10 months later also showed complete resolution of the mural thickening (Figure 9a, Figure 9b).

DISCUSSION

Etiology & Demographics:

IgG4-related disease (IgG4-RD) is a chronic fibro-inflammatory condition with single or multi-organ involvement. It was first proposed by Kamisawa et al in 2003 [2]. According to various studies, IgG4-RD generally affects the middle to older age group, with approximately 90% of patients aged 50–80 years old. The median ages; in these various studies, range from 58 to 67 years. It generally shows male dominance, with a male : female ratio of about 4:1 [3]. Majority of the cases of IgG4-RD have been reported in Asia, with the number in Japan estimated at 8000 cases. However, case reports from Europe and the USA are now increasing. Although the prevalence of IgG4-RD in North America is lower than in Asian countries, the exact figures are unknown. Hence, it is unclear if there are racial differences in disease epidemiology [4]. So far, there has been no reported association with smoking, dietary habits or alcohol abuse.

The exact pathogenesis of IgG4-RD is not well understood. The involvement of complex genetic susceptibility factors and resultant abnormality in immune responses as well as autoimmunity have been thought to be responsible for the development of the disease and the fibroinflammatory response.

It presents clinically as a tumour-like lesion in one or more organs / organ systems, including autoimmune pancreatitis which is seen in 60% of patients with IgG4-RD [4]. The involved organ displays variable degrees and combinations of plasma cell–rich chronic inflammation with tissue destruction, storiform-type fibrosis and obliterative phlebitis. IgG4-related autoimmune pancreatitis and sclerosing cholangitis are well known sites of involvement in the digestive system. Gastric involvement is very rare. To our knowledge, there have only been 15 case reports, only a few of which with radiological (e.g. CT) and endoscopic (optical and ultrasound) correlations.

Clinical & Imaging findings:

Of the reported 15 cases, 11 had isolated gastric involvement, and 4 were associated with other systemic manifestations of IgG4-RD. Most of the reported cases of isolated gastric involvement in IgG4-RD presented with focal masses or polypoid lesions [5–17], with a few rarer instances of focal mural thickening or ulcer. Kawano et al described a case of gastric mural thickening at the posterior antral wall [16], while Bateman et al and Fujita et al described 2 cases of gastric ulcer [5,6]. The rest of the case reports described gastric polyps or focal mass-like lesions.

To our knowledge, the only case of gastric mural thickening in IgG4-RD was described by Kawano et al [16]. In that case, mural thickening was limited to the posterior antral wall, and there was no ulceration nor any enlarged lymph nodes. In contrast, our case demonstrated relatively more diffuse mural thickening in the lesser curve, associated with a large ulcer and gastrohepatic lymphadenopathy.

On dynamic CT, delayed enhancement has been reported in IgG4-RD pancreatitis, due to parenchymal fibrosis [18]. However, in our case, the CT was performed only in arterial and portal venous phase, without the delayed phase. The imaging of gastric involvement in IgG4-RD on dynamic CT has not been described in the current literature. On Fluorodeoxyglucose Positron Emission Tomography scan (FDG PET), diffuse or heterogeneous uptake of FDG is typical of IgG4-RD autoimmune pancreatitis. Tracer uptake in extra-

pancreatic lesions has been reported in about 49-80% of such cases [19].

The related published consensus statement provides histological criteria for the probability of IgG4-RD in commonly involved organs and requires >40% IgG4/IgG plasma cell ratio [3] which our case satisfied. The threshold for increased count of IgG4 plasma cells per 1 high-power field (hpf) in rarely involved sites, including the stomach, is not yet established. The comparative figure set for bile duct and pancreas biopsy is >10, which this case met at 16 IgG4 plasma cells /1hpf.

Gastric involvement in this case took on the unusual combination of diffuse mural thickening and ulceration seen on CT and endoscopy which were highly suspicious for an infiltrative type of gastric cancer. Associated gastrohepatic lymphadenopathy was also noted on CT. Histological examination instead, showed an ulcerated fibroinflammatory mural thickening (figure 3a) by mixed inflammation and focal storiform fibrosis (Figure 3b). There were up to 16 IgG4 plasma cells per high-power field (Figure 4a) for 34 IgG plasma cells in the same area. Familiarity of the pathologist with the expanding paradigm of IgG4-RD led to its consideration and targeted workup at histological examination. This initiated the cascade of clinico-pathological assessment and correlation that culminated in rendering a fitting diagnosis and appropriate management.

Differential Diagnoses:

In an elderly patient with constitutional symptoms, as well as CT findings of diffuse gastric mural thickening with ulceration, the most important differential diagnosis to consider first would be gastric malignancy, such as primary gastric adenocarcinoma or gastric lymphoma. Sometimes, there may be other supporting features which may help in making the diagnosis. The main differential diagnoses for diffuse gastric mural thickening with ulceration on CT can be limited to the following:

a. Primary Gastric Carcinoma - About 30% of gastric cancers are located in the antrum, 30% in the body, and 30% in the fundus or cardia region. Diffuse infiltrating lesions in the stomach have been reported in the remaining 10%, such as segmental or diffuse wall thickening with ulceration. Thickened submucosa of soft tissue density can be seen, in contrast to acute gastritis which is usually of lower attenuation due to submucosal oedema [20]. On double contrast upper gastrointestinal (GI) series, malignant ulcers are irregular-shaped, with nodularity at the edge of the ulcer. Sometimes the ulcerations may be lobulated, and project into a mass [21]. Gastric carcinoma can involve the entire stomach. A subtype of gastric adenocarcinoma, signet ring cell carcinoma, can manifest as linitis plastica, which appears as diffuse thickening of the gastric wall and obliteration of the gastric folds. Limited distensibility, and small, non-peristaltic stomach can be observed on double contrast upper GI series [20]. Other possible appearances include large, polypoid, fungating lesions [22].
b. Gastric Lymphoma – Primary gastric lymphoma are predominantly non-Hodgkin lymphomas of B-cell origin. Lymphoma of mucosa-associated lymphoid tissue (MALT) is a distinct type of extranodal lymphoma that has a better prognosis than gastric carcinoma [22]. Imaging of gastric lymphoma on double contrast upper GI series may demonstrate shallow, irregular ulcers. In the higher grade or advanced lymphoma, there may be massively thickened folds with distortion or blunting of the folds. Despite the diffuse involvement, the stomach still remains distensible [23]. On CT, there can be diffuse or segmental gastric wall thickening, associated with regional or widespread lymphadenopathy. Gastric ulceration can also be seen [24]. Gastric lymphoma rarely causes linitis plastica or gastric outlet obstruction, in contrast to gastric carcinoma.
c. Acute gastritis – In acute gastritis, double contrast upper GI series can demonstrate complete or varioliform erosions, which are essentially erosions with a radiolucent halo or mound of oedematous, thickened mucosa. Benign ulcers have a smooth surface, with smooth, straight folds radiating to the edge of the ulcer. Associated thickened or nodular gastric folds can also be appreciated [21] . Findings on CT can include mural thickening, which can also be diffuse or focal in nature. In severe cases, the gastric wall will demonstrate low attenuation due to submucosal oedema and inflammation. At the same time, the mucosa may enhance due to hyperaemia. This enhancement may give the wall a layered appearance, or a "halo", which has been reported to be most pronounced on the arterial phase [25]. This can help to distinguish gastritis from other conditions that can cause gastric wall thickening, although correlation with histology or treatment response would still be necessary.
d. IgG4-RD stomach – As mentioned above, isolated IgG4-RD stomach is rare, with only a few case reports. Most of them present with focal masses or as a polypoid lesion, with a few rarer instances of focal mural thickening or ulcer. Diffuse mural involvement can also be seen, as with our case. Associated lymphadenopathy can also be present.
e. Crohn Disease – Usually affects the antrum and body. In the acute phase, the imaging findings are indistinguishable from that of acute gastritis as described above. On double contrast upper GI series, the "target" or bull's-eye appearance of aphthoid ulcers can sometimes be visualised. In advanced disease, nodular or "cobblestone" mucosa is characteristic. On CT, findings can be non-specific, with mucosal thickening and oedema in keeping with gastric wall inflammation [20].

Treatment & Prognosis:

Firstline treatment of IgG4-RD is with corticosteroids. Daily prednisolone at an initial dose of approximately 0.6 mg/kg is appropriate. Our patient was started on 40 mg of prednisolone per day. It is recommended that the initial dose of prednisolone be continued for 2–4 weeks, after which time, the dose should be tapered by 10% every 2 weeks [4]. Although the initial prognosis of patients with IgG4-RD is generally good, relapse of disease after tapering or discontinuing the steroids altogether is high. The efficacy of concomitant use of immunosuppressants, such as calcineurin inhibitors and azathioprine in treatment of IgG4-RD has not been conclusively demonstrated. There have however been reports of success with biologic agents, specifically rituximab, in the treatment of steroid refractory IgG4-RD. Further studies regarding treatment options with these agents would be needed for the future [4].

In our case, histopathology and follow-up imaging proved to be especially important in making the correct diagnosis. The endoscopic ultrasound images of the proximal lesser curve and cardio-oesophageal junction also showed only submucosal involvement, with sparing of the mucosa and no invasion of the muscularis propria (Figure 6). This correlated with the CT findings which showed diffuse gastric wall thickening with a smooth mucosal layer (Figures 1a and 1b).

The follow-up CT images after steroid therapy demonstrated dramatic and eventually complete resolution of gastric wall thickening and ulceration. This shows that radiological imaging is useful for the assessment of steroid therapy treatment response in patients with IgG4-RD. This was also correlated with healing of the ulcer which was documented on endoscopy.

Serum IgG4 levels remain important for evaluation and longitudinal assessment, but elevated serum levels are neither necessary nor sufficient for IgG4-diagnosis, as illustrated in our case, in which the patient had normal IgG4 serum levels. In fact, up to 30% of patients with IgG4-RD can have normal serum IgG4 levels [26]. Our patient did however have elevated serum IgG2 levels. A recent study has suggested that serum IgG2 levels may play a role in IgG4-RD [27]. We trended the serum IgG2 levels of our patient during the course of treatment, which showed significant decrease in levels after appropriate treatment (Figure 10).

TEACHING POINT

Isolated gastric IgG4-related disease can masquerade as an infiltrative gastric malignancy, showing both diffuse gastric mural thickening and an ulcer on CT, with associated lymphadenopathy. Serum IgG4 levels remain important for evaluation and longitudinal assessment, but elevated serum levels are neither necessary nor sufficient for IgG4-diagnosis.

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FIGURES

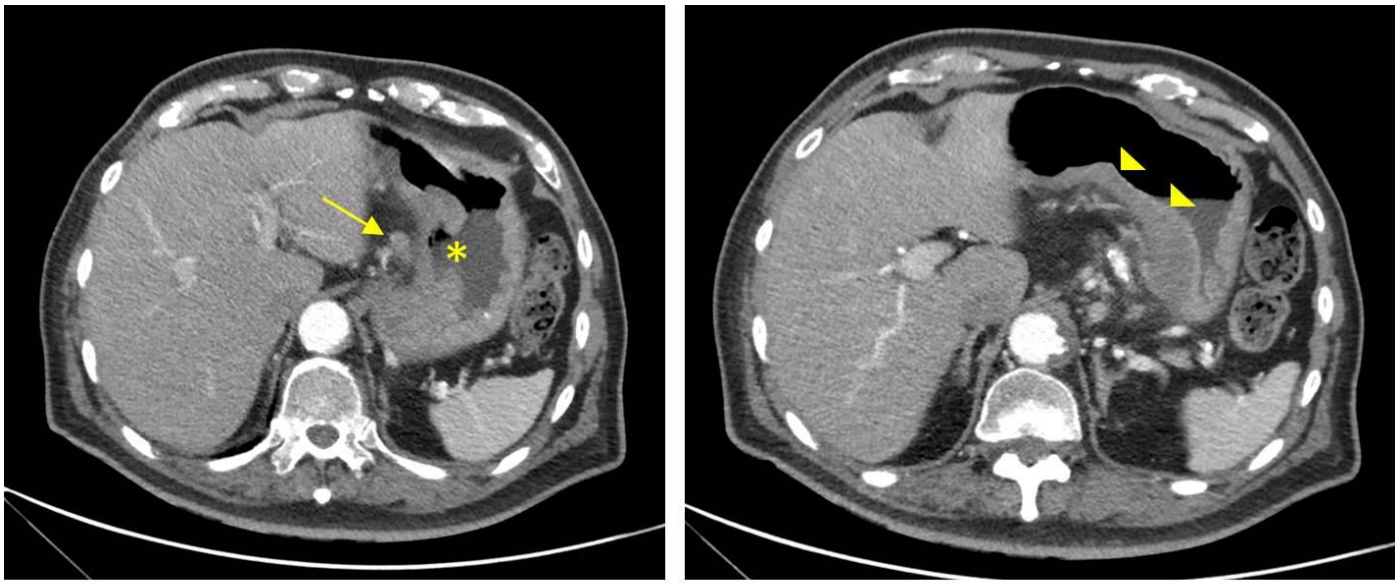

Figure 1a. Figure 1b.

Figure 1: 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Axial contrast enhanced CT abdomen and pelvis done at initial presentation, showing ulcer (asterisk in figure 1a) and diffuse mural thickening (arrowheads in figure 1b) at the lesser curve of the stomach. Mild diffuse mural enhancement is seen. Prominent gastrohepatic lymph nodes (short arrow in figure 1a) were present. The CT appearance is highly suspicious for a gastric malignancy.

TECHNIQUE: CT (Philips iCT 256) arterial phase, 150 mAs, 120 kV, 3.00 mm slice thickness, 80 ml Omnipaque 350

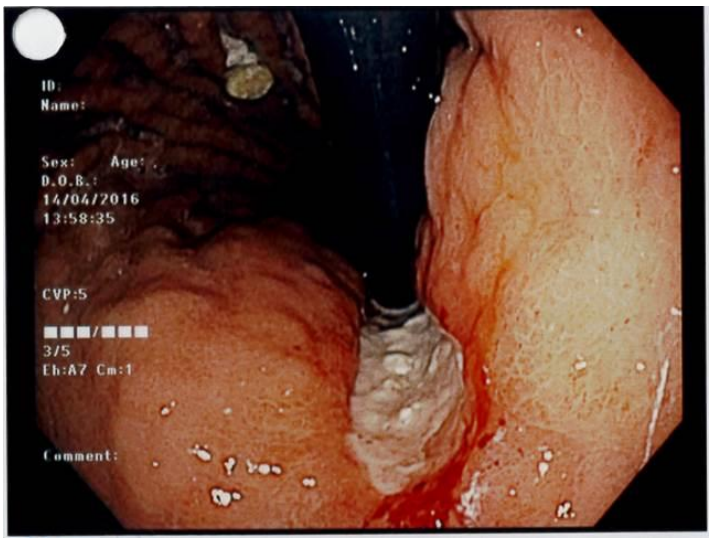

Figure 2 (left): 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Initial endoscopic image, confirming the presence of an ulcer along the lesser gastric curve, with thickened irregular margins suspicious for a malignancy.

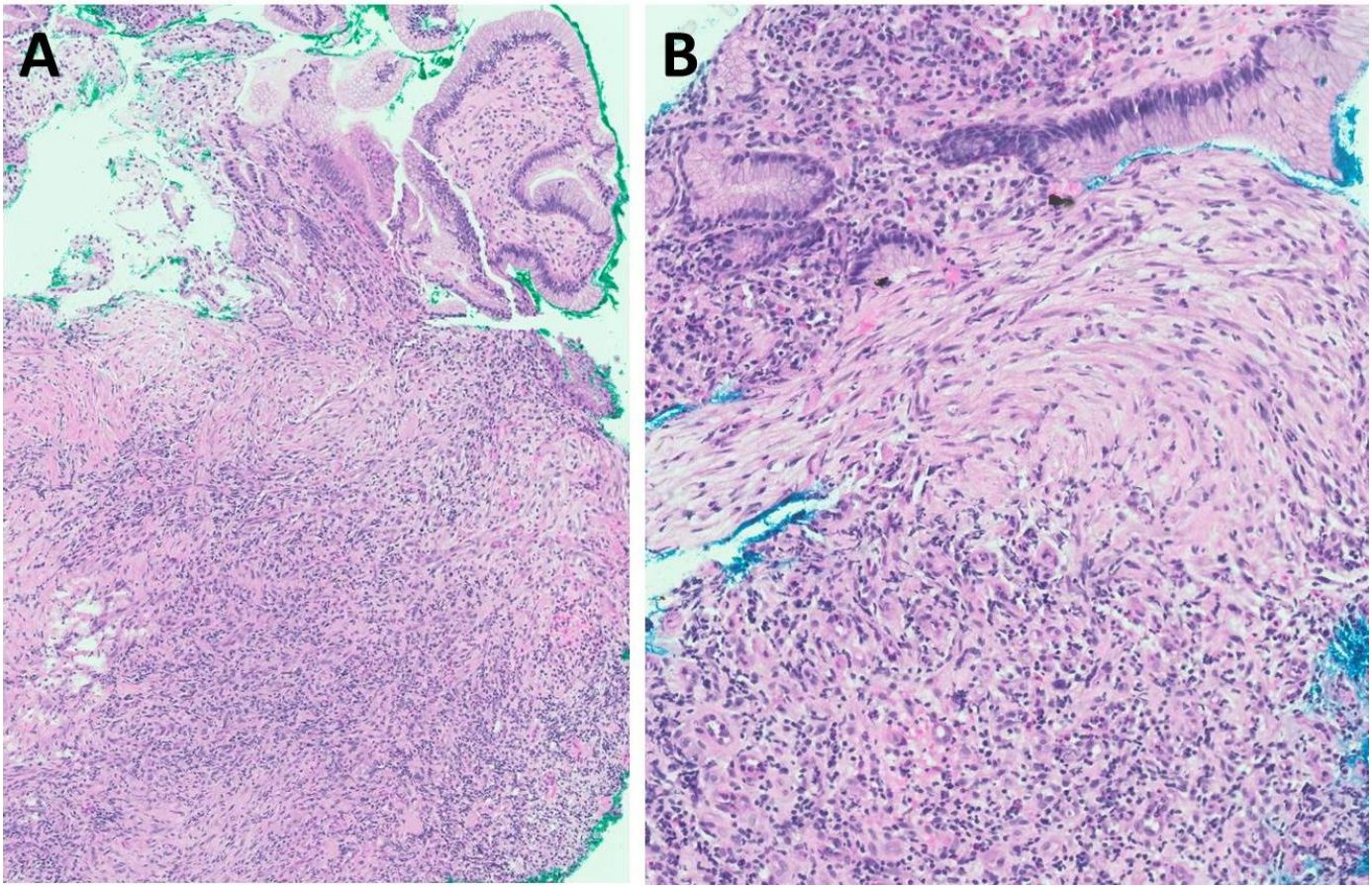

Figure 3: 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Hematoxylin and Eosin stained section; (a) Ulcer overlying fibroinflammatory mural thickening; (b) Storiform fibrosis 400x magnification.

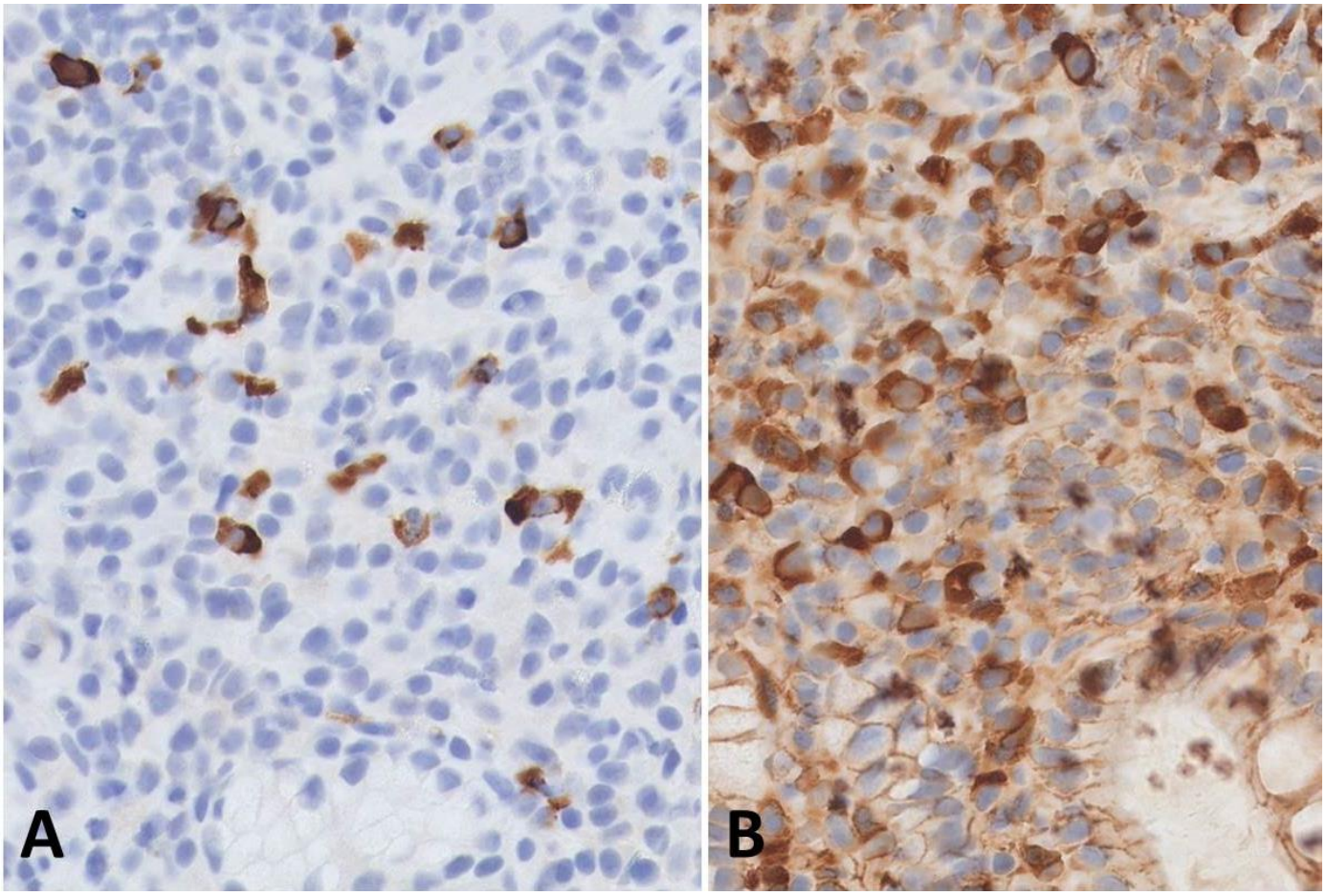

Figure 4: 81-year-old male with IgG4-related disease of stomach.

FINDINGS: (a) Immunohistochemical staining for IgG showing nearly 34 plasma cells in this high power field ; 400x magnification.
(b) Immunohistochemical staining for IgG4 in same area with up to 16 plasma cells; 400x magnification.

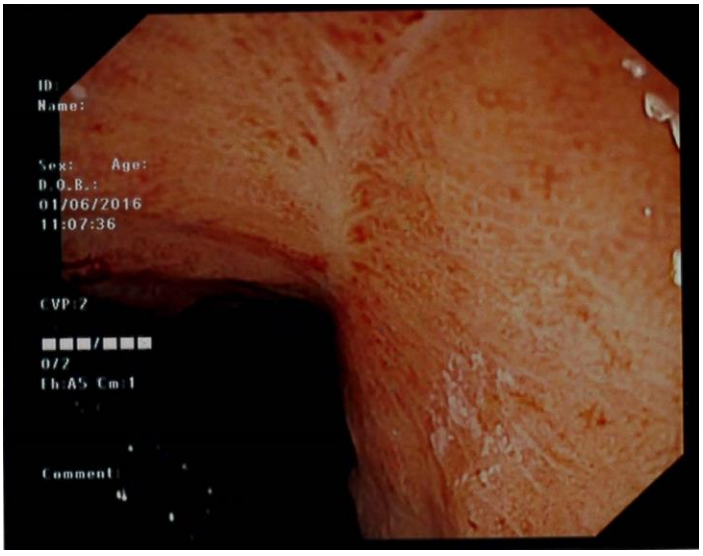

Figure 5 (left): 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Follow-up endoscopy 1.5 months after the initial endoscopy, demonstrating partial healing of the gastric ulcer. (Patient has so far only been given oral Omeprazole since the initial endoscopy for treatment of the ulcer.)

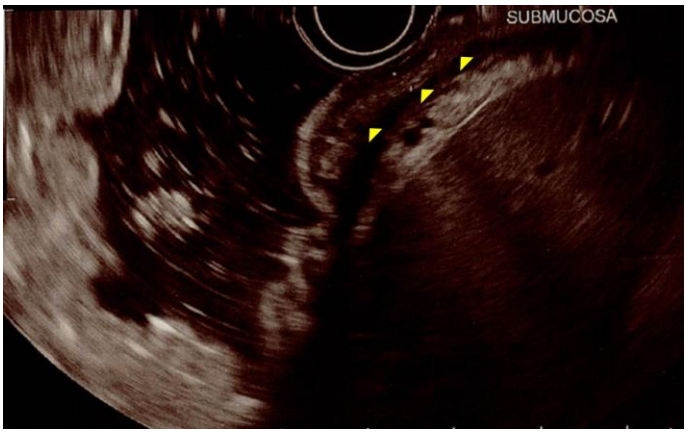

Figure 6: 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Endoscopic ultrasound performed 1.5 months after the initial endoscopy showed a thickened submucosa (up to 5.8 mm thick, indicated by arrowheads) along the lesser curve of the stomach, corresponding to the CT findings. There was no distinct invasion across the muscularis propria. (Patient has so far only been given oral Omeprazole since the initial endoscopy for treatment of the ulcer.)

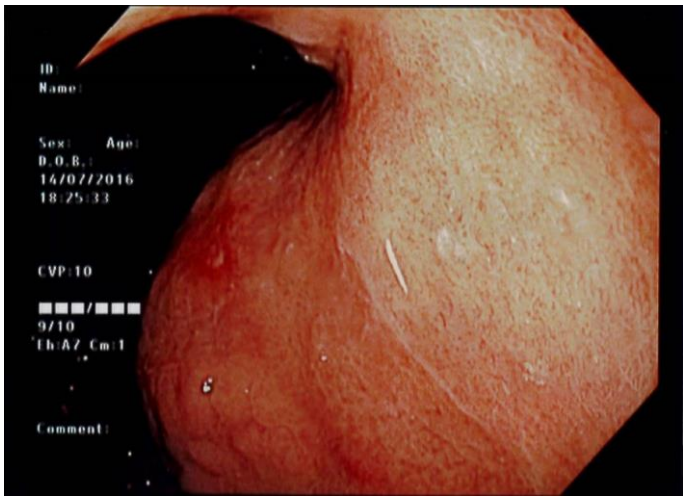

Figure 7: 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Final follow-up endoscopy performed 3 months after the initial endoscopy, and after approximately 1 month of steroid treatment. It demonstrates complete mucosal healing at the site of the previously noted gastric ulcer after treatment with steroids.

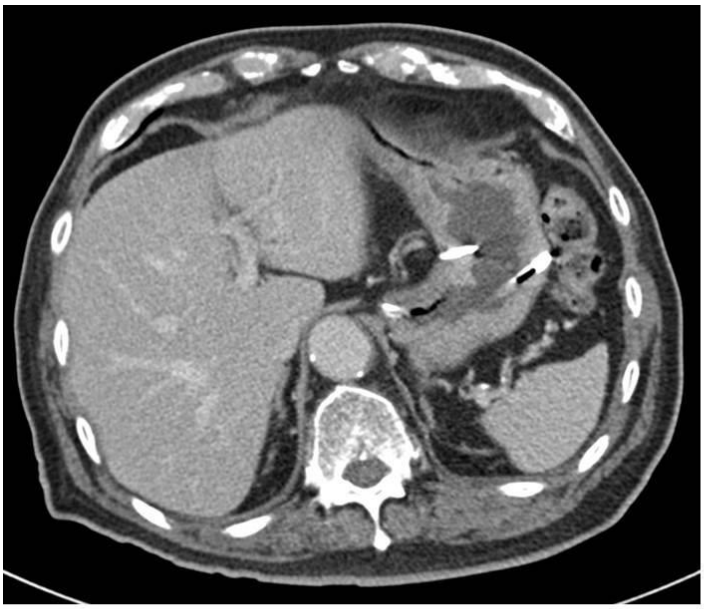

Figure 8a.

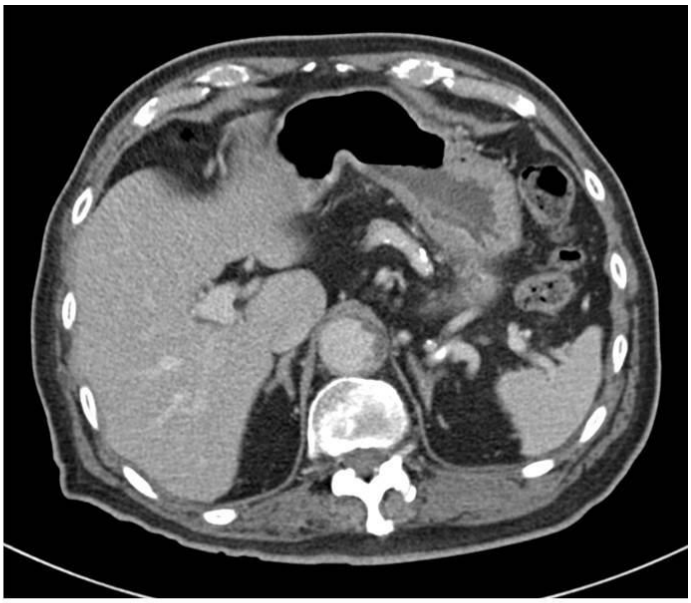

Figure 8b.

Figure 8: 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Follow-up contrast enhanced CT abdomen and pelvis performed 3 months after the initial presentation, showing improvement of the previously noted gastric ulcer, mural thickening and gastrohepatic lymphadenopathy. An endoscopic clip is seen at the site of the ulcer, and a partially imaged nasogastric tube is also present in the stomach (figure 8a).

TECHNIQUE: CT (SIEMENS SOMATOM Definition) portal venous phase, 197 mA, 120 kV, 3.00 mm slice thickness, 80 ml Omnipaque 350

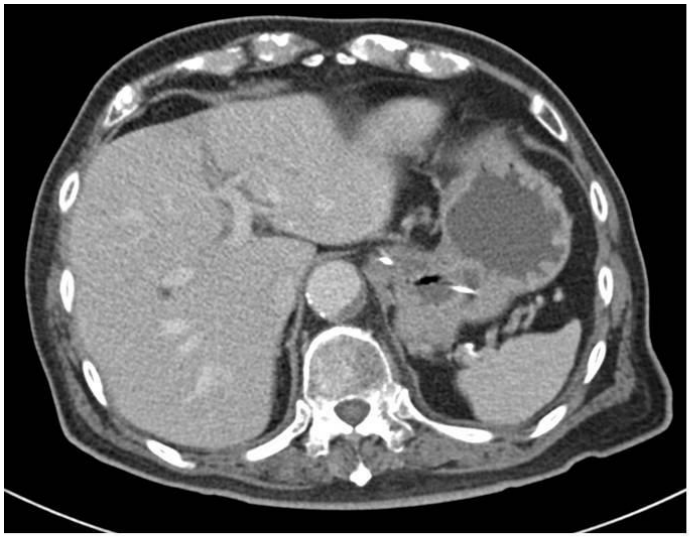

Figure 9a.

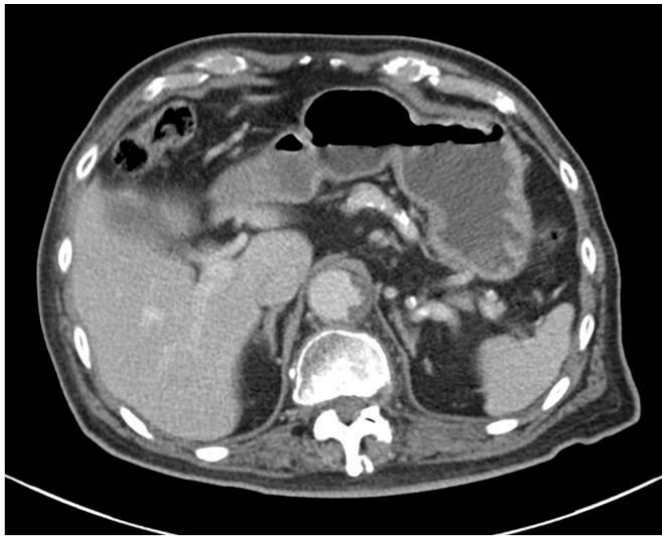

Figure 9b.

Figure 9: 81-year-old male with IgG4-related disease of stomach.

FINDINGS: Final follow-up CT study performed 10 months from the initial presentation, showing complete resolution of the previously noted gastric ulcer and gastrohepatic lymphadenopathy after treatment with steroids. There is also complete resolution of the mural thickening at the lesser curve (comparing figure 8b and figure 9b). A partially imaged nasogastric tube is present in the stomach (figure 9a). Further mild interval reduction in the mural thickening at the gastro-oesophageal junction is also noted (figure 9a).

TECHNIQUE: CT (SIEMENS SOMATOM Definition) portal venous phase, 170 mA, 120 kV, 3.00 mm slice thickness, 75 ml Omnipaque 350

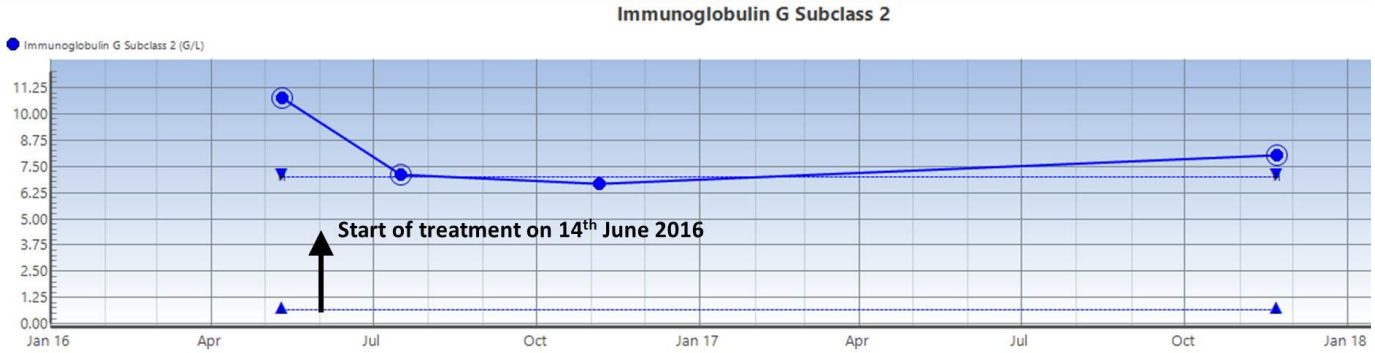

Figure 10: 81-year-old male with IgG4-related disease of stomach.
FINDINGS: Serum IgG2 levels showing improvement after treatment in June 2016

Etiology	Complex genetic susceptibility factors and resultant abnormality in immune responses as well as autoimmunity have been thought to be responsible for the development of the disease.
Incidence	Unknown. To our knowledge, there have been 15 case reports for gastric involvement of IgG4-RD.
Gender ratio	In IgG4-RD, 4:1 (male : female). However, for IgG4-RD of the stomach, it is unclear.
Age predilection	Median ages in various studies range from 58 to 67 years
Risk factors	Unclear. Most cases of IgG4-RD are reported from Asia, however there are increasing reports from North America and Europe. No reported association with smoking, dietary habits or alcohol.
Treatment	- First line: Corticosteroid. - Concomitant use of immunosuppressants has been reported but efficacy has not been demonstrated. - Reports of successful therapy with rituximab for steroid resistant IgG4-RD.
Prognosis	Generally excellent response, although relapse rates are high after tapering or discontinuing steroid therapy.
Findings on imaging	CT Mostly focal masses or polypoid lesion. Few rarer instances of focal mural thickening or ulcer. Diffuse mural thickening with an ulcer. Delayed enhancement on dynamic CT. FDG-PET Tracer uptake of extra-pancreatic involved organ in IgG4-RD reported in 49-80 % of cases with IgG4-RD pancreatitis.

Table 1: Summary table for IgG4-related disease of stomach.

Entity	**Computed tomography**	**Double contrast upper gastrointestinal (GI) fluoroscopy study**
IgG4-RD stomach	Focal masses or polypoid lesions. Focal mural thickening or ulcer. Diffuse mural thickening with ulcer. Delayed enhancement on dynamic CT.	Has not been described in literature. May have thickened gastric folds, focal masses or ulceration.
Primary Gastric Carcinoma	Focal area of mural thickening +/- ulceration. Polypoid lesion. Generalized mural thickening. Thickened submucosal layer of soft tissue density. Diffuse involvement of entire stomach (linitis plastica).	Irregular-shaped ulcers, with nodularity at the edge of the ulcer. Lobulated ulceration, projecting into mass. Linitis plastica – small, non-distensible, non-peristaltic stomach.
Gastric Lymphoma	Diffuse or segmental gastric wall thickening, associated with lymphadenopathy. Gastric ulceration can also be seen.	Shallow, irregular ulcers. Can have massively thickened folds with distortion or blunting of the folds. No linitis plastica or gastric outlet obstruction.
Acute gastritis	Diffuse or focal mural thickening. Low attenuation in gastric wall due to submucosal oedema and inflammation. Mucosal enhancement due to hyperaemia resulting in a layered or "halo" appearance.	Complete or varioliform erosions. Thickened or nodular gastric folds. Smooth ulcer surface, with smooth, straight folds radiating to the edge of the ulcer.
Crohn Disease	Usually in gastric body and antrum. Mucosal thickening and oedema.	"Target" or bull's-eye appearance of aphthoid ulcers. Nodular or "cobblestone" mucosa.

Table 2: Differential diagnosis table for IgG4-related disease of stomach.

ABBREVIATIONS

CT = Computed tomography
FDG-PET = Fluorodeoxyglucose Positron Emission Tomography
GI = gastrointestinal
Hpf = High-power field
IgG4-RD = IgG4-related disease

KEYWORDS

Immunoglobulin G; radiology; endoscopy; stomach; IgG4; IgG2; IgG4-RD

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