Case Report

Gastric Calcifying Fibrous Tumor: A Case of Suspected Immunoglobulin G4-related Gastric Disease

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ABSTRACT

Gastrointestinal lesions resulting from immunoglobulin G4-related disease are classified into two types: One is a gastrointestinal lesion showing marked thickening of the wall, and the other is an IgG4-related pseudotumor. We report the case of a woman with gastric calcifying fibrous tumor undergoing endoscopic resection that contained 62 IgG4+ plasma cells per high-power field and an IgG4-to-IgG ratio of 41% in lesional plasma cells, which shared clinical and histopathological features associated with gastric IgG4-related pseudotumor. So, we postulate that calcifying fibrous tumor as part of the spectrum of IgG4-related disease might be the unifying concept with IgG4-related pseudotumor. Meanwhile, the patient had coexistent autoimmune diseases, including autoimmune atrophic gastritis, Hashimoto's thyroiditis, and possible primary biliary cirrhosis. The clinical follow-up evaluation was uneventful.

Key Words: Calcifying fibrous tumor, IgG4-related disease, IgG4-related pseudotumor, stomach

Received: 21.07.2015, Accepted: 15.09.2015
How to cite this article: Zhang H, Jin Z, Ding S. Gastric calcifying fibrous tumor: A case of suspected immunoglobulin G4-related gastric disease. Saudi J Gastroenterol 2015;21:423-6.

Calcifying fibrous tumors (CFTs) are benign lesions with unknown etiology and pathogenesis, characterized by the presence of abundant paucicellular and hyalinized collagen, psammomatous and/or dystrophic calcifications, and patchy lymphoplasmacytic infiltrates as described by the World Health Organization, which rarely involve the gastrointestinal tract. Recently, a novel theory of CFT as an Immunoglobulin G4 (IgG4)-related disease has been proposed.[1] We present a case of gastric CFT undergoing endoscopic submucosal dissection, which shared similar clinicopathological features with IgG4-related pseudotumor. Gastric IgG4-related pseudotumor is rare, and so far about six cases have been reported in PubMed. Meanwhile, the current patient had coexistent autoimmune diseases, including autoimmune atrophic gastritis, Hashimoto's thyroiditis, and possible primary biliary cirrhosis.

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.170950

CASE REPORT

A 55-year-old woman presented with epigastric pain and flatulence. Physical examination was unremarkable. The laboratory tests revealed mild normocytic anemia (hemoglobin 106 g/L) and a mildly decreased free thyroxine (0.81 ng/dL, normal 0.89–1.80). Very high thyroglobulin antibodies (265.8 U/mL, normal <60) and thyroid peroxidase antibodies (>1300 U/mL, normal <60) were noticed. Other serum autoantibodies, including antinuclear antibody (1/80, normal <1/40), antiparietal cell antibody (APCA) (1/320, normal <1/40), antimitochondrial antibody M2 subtype (75R U/mL, normal <20R U/mL), were also positive. Other laboratory findings were all normal.

Gastroscopy revealed a submucosal tumor with intact overlying mucosa in the posterior wall of the upper corpus, and a Yamada type III polyp was found at its proximal side [Figure 1a]. Endoscopic ultrasonography visualized the tumor mainly within the third layers of the gastric wall, measuring 20 mm in its maximal diameter. These findings

were interpreted as suggestive of a gastrointestinal stromal tumor, endoscopic submucosal dissection and endoscopic mucosal resection were performed to remove the submucosal tumor and the polyp, respectively.

Microscopic examination of whole-mount serial sections of tumor showed a well-circumscribed but nonencapsulated tumor in the submucosa associated with the multiple lymphoid follicles showing prominent germinal centers. Psammomatous calcifications were scattered throughout [Figure 1b]. Some psammomatous calcifications could be observed in the minute vascular lumina [Figure 1b insert]. The tumor consisted of paucicellular, densely hyalinized, collagenous matrix, which exhibited a predominant pattern of storiform arrangement. Uniform, spindle-shaped cells were dispersed among thick collagen bundles, and did not show any cellular atypia or mitotic activity. Lymphoplasmacytic infiltrates were present among the sclerotic stroma [Figure 1c]. Obliterative phlebitis was not observed. Immunohistochemically, the spindle-shaped cells showed Vimentin expression and no immunoreactivity for DOG-1, CD117, CD34, S-100, SMA, desmin, and Ki-67. Based on the above characteristic morphologic and immunohistochemical findings, a diagnosis of CFT was rendered. IgG4+ plasma cells were observed [Figure 1d]. Examining three high-power fields (HPFs, ×400) within the same hotspot produced a mean of 152/HPF IgG+ plasma cells and 62/HPF IgG4+ plasma cells. The IgG4-to-IgG ratio was 41%. The serum IgG4 level was within normal range (0.169 g/L).

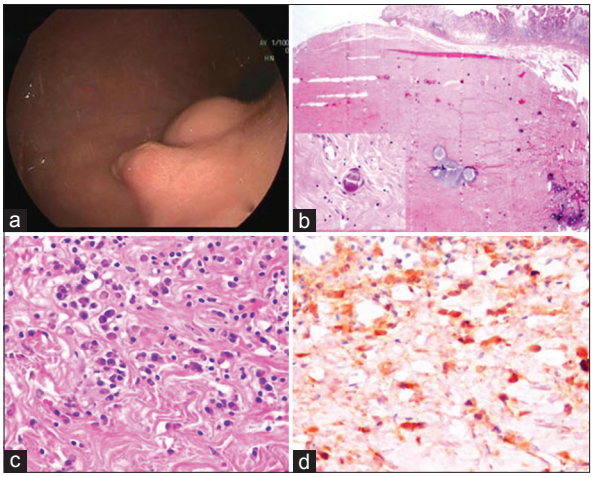

Figure 1: Gastroscopic and pathological findings of the Calcifying fibrous tumor. (a) Endoscopic photographs revealed a submucosal tumor and a Yamada type III polyp. (b) Microscopic examination of whole-mount serial sections showed the resected submucosal tumor; the hypocellular, spindle-cell tumor demonstrates the characteristic densely collagenous matrix with storiform arrangement, multiple lymphoid follicles, and scattered psammomatous calcifications (H and E; ×10). Some psammomatous calcifications could be observed in the minute vascular lumina (insert, H and E; ×400). (c) Prominent lymphoplasmacytic infiltrates were present among the sclerotic stroma. (d) Immunostaining with IgG4 shows positive reaction in a number of plasma cells (H and E; ×400)

The histology of overlying mucosa showed chronic atrophic gastritis, with pseudopyloric metaplasia and mild intestinal metaplasia [Figure 2a]. Parietal cell pseudohypertrophy [Figure 2b] and nodular enterochromaffin-like cell hyperplasia (immunostain for synaptophysin) [Figure 2c] were observed. The histology of the polyp revealed classic hyperplasic polyp [Figure 2d]. Combined with the serological findings (APCA, 1/320), a diagnosis of autoimmune atrophic gastritis was made. IgG4+ plasma cells were not observed in the mucosa. Additionally, taking into account the serological results above, the diagnoses of Hashimoto's thyroiditis and possible primary biliary cirrhosis were also made. The patient refused to undergo biopsies from thyroid gland and liver. The patient was discharged with a good recovery and has been followed for 5 months without any signs of disease recurrence.

DISCUSSION

IgG4-related gastrointestinal diseases were classified into two types: One is a gastrointestinal lesion showing marked thickening of the wall, and the other is an IgG4-related pseudotumor.[2] A summary of reported cases of gastric IgG4-related pseudotumor (no. 1–6)[3-6] is described in Table 1. Histologically, there are obvious similarities between gastric IgG4-related pseudotumor and our case. Interestingly, obliterative phlebitis was not identified in all these cases,

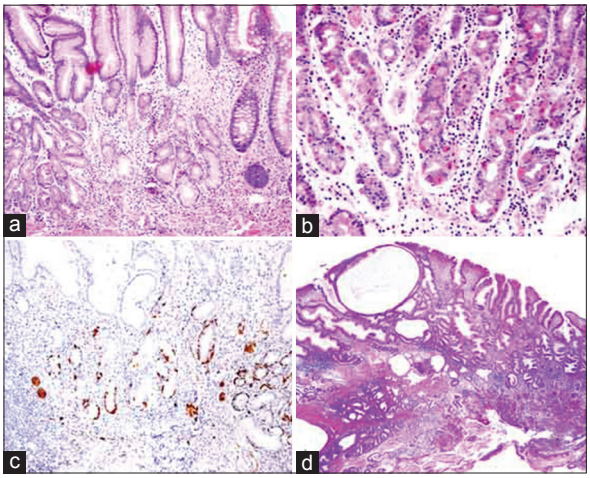

Figure 2: Histologic features of the overlying mucosa. (a) The overlying mucosa shows chronic atrophic gastritis with pseudopyloric metaplasia and mild intestinal metaplasia (H and E; ×100). (b) Parietal cell pseudohypertrophy was observed in the remnant oxyntic glands (H and E; ×200). (c) Immunostain for synaptophysin showed nodular and linear enterochromaffin-like cell hyperplasia in the mucosa (×100). (d) The histology of the polyp in the corpus revealed classic hyperplasia polyp (H and E; ×20)

Table 1: Summary of reported cases of gastric IgG4-related pseudotumor in the literature and our current case

Case no. (ref. no)	Age/ gender	Symptoms	Location	Size (mm)	Involved layer (s)	Serum IgG4	IgG4+ plasmocytes (HPF)/IgG4-to-IgG ratio	Therapeutic procedure	Follow-up	Associated history/ diseases
1[3]	45/F	Iron deficiency anemia	Fundus	15	SM	Normal	363/0.78	WR	NER at 6 months	Raynaud's disease and hypertension
2[3]	60/M	Symptoms due to peptic ulcer	Antrum, pyloro-antral junction and serosa	20, 21, 22, and 19	MP to SS	NR	298/0.84	Distal gastrectomy	NR	Autoimmune polyendocrinopathy with hypothyroidism and adrenal insufficiency
3[4]	75/F	Vomiting, weight loss and anaemia	Gastric midbody	56	SM	Normal	39/NR	WR	NER at 2 weeks	None
4[5]	59/F	NR	Gastric midbody	33	MP	Normal	More than 50/NR	WR	NR	NR
5[5]	54/F	NR	Serosa	21	SS	Normal	More than 50/NR	WR	NR	NR
6[6]	56/M	Incidental finding	Low body	8	SM	NR	102/0.9	ESD	NER at 4 months	Type 2 DM
7 (present case)	55/F	Epigastric pain and flatulence	Posterior wall of the upper corpus	20	SM	Normal	62/0.41	ESD	NER at 5 months	AIG; HT; possible PBC; multiple liver cysts; anemia and hysterectomy

WR: Wedge resection, ESD: Endoscopic submucosal dissection, NR: Not reported, NER: No evidence of recurrence, AIG: Autoimmune atrophic gastritis, HT: Hashimoto's thyroiditis, PBC: Primary biliary cirrhosis, SM: Submucosa, MP: Muscularis propria, SS: Subserosa

and psammomatous calcifications could only be observed in case no. 5[5] and our case. In the present case, some psammomatous calcifications, as described in the literature, could be observed in the minute vascular lumina, suggesting that psammomatous calcifications may be the calcified vascular channels and the result of obliterative phlebitis.[1,7] In all cases, an elevated serum IgG4 was not found [Table 1].

Coexistent autoimmune disease in gastric IgG4-related pseudotumor had been described in case no. 2, while our case also had other autoimmune diseases. Increased numbers of IgG4+ plasma cells were found in the gastric mucosa of some autoimmune atrophic gastritis patients.[8] However, in the present case, IgG4+ plasma cells were not observed in the mucosa. Hashimoto's thyroiditis is the most frequently associated autoimmune condition in autoimmune atrophic gastritis patients. IgG4-related Hashimoto's thyroiditis, characterized by thyroid inflammation rich in IgG4+ plasma cells and marked fibrosis, has been identified.[9] Because the current patient refused to undergo a thyroid biopsy, it was uncertain whether there was a IgG4+ plasma cell infiltrate in the thyroid gland.

Whilst the histopathological differential diagnosis for sclerotic lesions within the gastroenterological tract is extremely wide and varied, the most important to be considered are "burnt-out" examples of GIST, smooth muscle neoplasm, nerve sheath tumor, inflammatory myofibroblastic tumor, solitary fibrous tumor. Immunohistochemistry is the obvious aid to reaching the correct diagnosis.

Gastric CFT described herein, with a significant IgG4-postive plasma cell infiltrate (62/HPF) and a high IgG4-to-IgG ratio (41%), supports the view that CFT may represent different stages of IgG4-related disease[1,7] and fits with the unifying concept of IgG4-related pseudotumor.[10] IgG4-related pseudotumor may respond to conservative treatment with steroids. Therefore, treatment with steroids should be attempted before surgical or endoscopic resection.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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