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CASE REPORT

IgG4-Related Disease Mimicking Crohn's Disease: A Case Report and Review of Literature

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic, immune-mediated inflammatory condition of unknown aetiology first described by Yoshida et al. [1].

Its clinical features mimic a tumour-like mass that can involve the skin, orbit, salivary glands, thyroid, pancreas, hepatobiliary tract, lymph nodes, retroperitoneum, kidney, and GI tract [2–5]. Its main histopathological features include a lymphoplasmacytic infiltrate rich in IgG4-positive (+) plasma cells, a storiform fibrosis pattern, and artery-sparing phlebitis [6, 7]. Elevated serum IgG4 levels are found in about 2/3 of patients [8].

We present a case of IgG4-RD involving the ileocecal region that was misdiagnosed as Crohn's disease (CD) after surgical resection for suspected appendicitis and provide a systematic review of the literature on IgG4-RD involving the GI tract.

Case Report

Clinical Features

A 38-year-old woman with a recent histological diagnosis of CD was referred to the Inflammatory Bowel Disease (IBD) outpatient centre of our institution.

Three months earlier she had presented to the Emergency Department of another hospital with the first episode of right lower abdominal pain and fever. The clinical and laboratory picture was suggestive of acute appendicitis, and a laparoscopy was performed; however, the appendix appeared to be normal, whereas the detection of oedematous wall thickening of the terminal ileum and of a 10-cm caecal mass led to a right hemicolectomy. The localization of lesions in the distal ileum and right colon and the transmural acute and chronic inflammatory infiltrates and fibrosis initially led the pathologist to suggest a diagnosis of CD.

Referral of the patient from a small local hospital to our institution involved histopathological re-evaluation of the surgical specimen at our Pathology Unit, which led to a

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change of diagnosis to IgG4-RD of the terminal ileum and right colon.

When she came to our attention, the patient reported mild abdominal pain and a single episode of mild non-bloody diarrhoea, but no rash, fever, or arthralgia.

The serum levels of the inflammation markers, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were, respectively, 34 mm/h (normal range, nr. 1–10 mm/h) and 0.17 mg/dL (normal value, nv < 0.5 mg/dL). IgG4 serum levels were normal (46 mg/dL; nr, 6–121 mg/dL). There was no evidence of autoimmune disease or vasculitis (anti-nuclear antibodies, anti-mitochondrial antibodies, anti-smooth muscle antibodies, anti-liver kidney microsomal antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, anti-Saccharomyces cerevisiae antibodies, anti-cyclic citrullinated peptide), coeliac disease (anti-tissue transglutaminase (anti-tTG) antibodies, anti-endomysial antibodies (EmA)), infection (*Mycobacterium tuberculosis*, Epstein–Barr virus, Cytomegalovirus) or of signs or symptoms suggesting the involvement of the pancreas or the biliary tract.

Histopathological Features of Surgical Specimens

Surgical specimens, including 5 cm of terminal ileum, ileocecal valve, and caecal mass with the appendix, were immediately immersed in 4% formaldehyde solution in phosphate buffer saline, pH 7.4, at room temperature and paraffin-embedded. Serial sections 3 μm in thickness were stained with haematoxylin–eosin to assess the degree and type of inflammatory infiltration based on its density and extension. Stained sections were viewed under a Zeiss Axio Imager A2 Light Microscope (Carl Zeiss Microscopy, LLC, One Zeiss Drive, Thornwood, NY 10594, USA). The histological sections were examined and scored independently by three pathologists (G.C., G.C., G.C.) in a double-blind fashion. Sections 3 μm in thickness were cut from the paraffin block, mounted on charged slides and placed into a Dako OMNIS system (Dako Denmark A/S, Produktionsvej 42, DK-2600 Glostrup, Denmark). Immunohistochemical stains for IgG4 were performed using IgG4 primary antibody at dilution 1:200 (clone HP6025–A10651, Invitrogen, Molecular Probes Inc, 29851 Willow Creek Road, Eugene, OR 97402, USA).

Microscopically, re-evaluation of the surgical specimen (ileocecal valve and the right colon) disclosed a lymphoplasmacytic infiltrate, especially in the upper epithelial layer, some eosinophils, neutrophils and nodular lymphocytic aggregates, and no granulomas. The inflammatory infiltrate was dense and rich in plasma cells, especially in the submucosa, the thick muscle layers, and the serosa (Fig. 1).

In the serosa and pericolic adipose tissue some areas exhibited marked sclerosis and thickening. Fibrin and granulocytes were found at the serosal level. Sclerosis and plasma cells were also detected in lymph nodes, which showed reactive hyperplasia and cortical expansion. Intense sclerosing fibrosis was observed in the submucosa. Evidence of periphlebitis not involving the arteries and perineuritis with nervous fibre destruction was noted (Fig. 2).

Immunohistochemical staining revealed an increased number of IgG4+ plasma cells (180 per high-power field (HPF) (Fig. 3). The IgG4+/IgG ratio was 50%.

Follow-Up

Six months after surgery the follow-up included clinical, laboratory, radiological, endoscopic, and histopathological evaluation.

The patient was asymptomatic, and no treatment was started.

The laboratory tests including blood count, ESR, CRP, transaminase, bilirubin, amylase and lipase, electrolytes, and faecal calprotectin were in the normal range. Serum IgG4 was also normal (44 mg/dL).

A total-body CT scan failed to disclose any intestinal or extraintestinal involvement.

Ileocolonoscopy (with multiple biopsies of terminal ileum, right colon, transverse colon, descending colon, sigmoid colon and rectum) and upper endoscopy (with biopsies of oesophagus, stomach, duodenum, and proximal jejunum) revealed no macroscopic lesions.

Histological examination of the endoscopic biopsies demonstrated some IgG4+ plasma cells in the capillaries of ileal mucosa of the pre-anastomotic tract, as well as in the lamina propria of the colon and rectum.

Histological examination of the upper GI tract biopsies showed a normal jejunal mucosa without intraepithelial lymphocytosis, rare IgG4+ plasma cells, and several IgG4+ cells in the lumen of mucosal capillaries. Findings were similar in the duodenum, where a slightly larger number of IgG4+ plasma cells were detected in the mucosal capillaries. The gastric antrum and fundus showed a mild inflammatory lymphocytic infiltrate and no evidence of IgG4+ plasma cells or *Helicobacter pylori*. Pathological infiltrate was not detected in the oesophagus.

Altogether, the clinical, laboratory, radiological, endoscopic, and histopathological features ruled out CD, while the report of our pathologists strongly suggested a diagnosis of IgG4-RD of the ileocaecal tract.

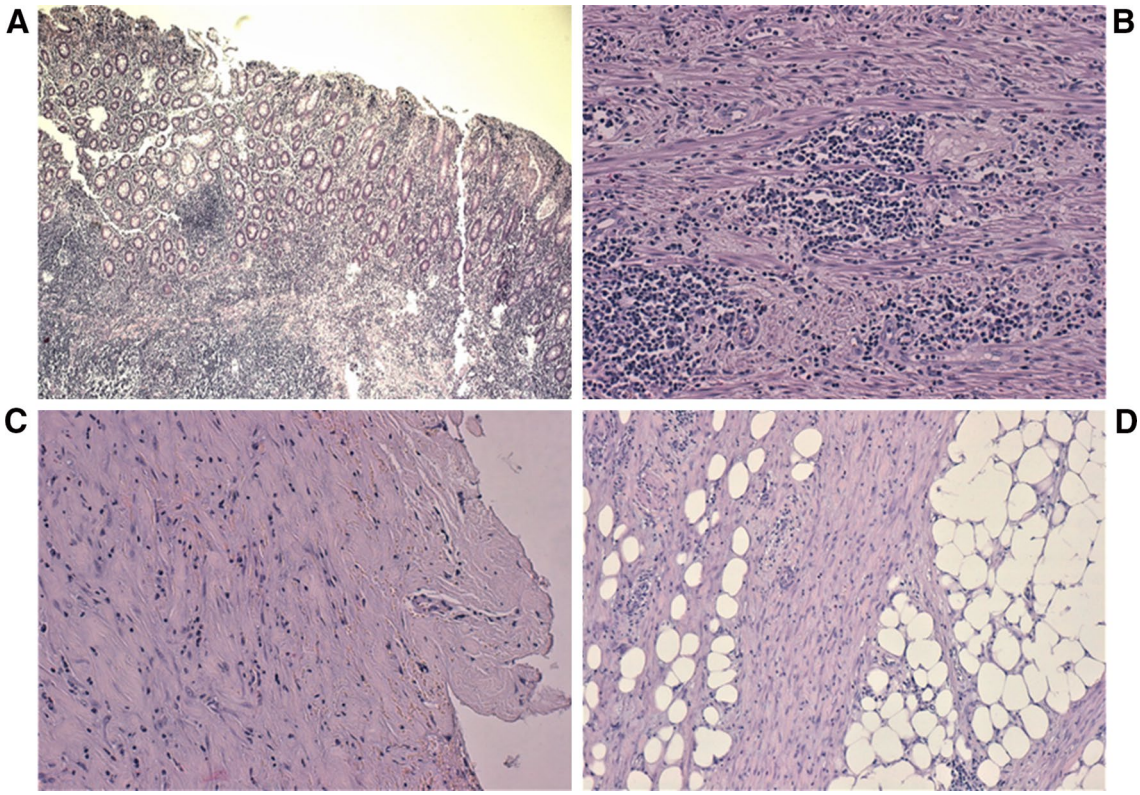

Fig. 1 Haematoxylin–eosin staining. Mucosa shows erosions of surface epithelium and a significant inflammatory lymphoplasmacellular infiltrate with nodular lymphoid aggregates (**a**, original magnification ×5). Substantial inflammatory infiltrate is also observed in the submucosa, muscle layers (**b**, original magnification ×20) and serosa, which also exhibits intense sclerosing fibrosis (**c**, original magnification ×20). Large areas affected by sclerosing fibrosis are noted in pericolic adipose tissue (**d**, original magnification ×10)

Discussion

IgG4-RD is a systemic condition characterized by the accumulation of IgG4+ plasma cells and fibrosis. Most patients have raised serum IgG4 levels; the disease generally responds to steroids [7, 9].

Since its first description in the pancreas in 1995, several case reports have described autoimmune pancreatitis, high IgG4 serum levels, and involvement of other tissues such as lymph nodes, kidney, urinary tract, lung, pleura, breast, salivary and lacrimal glands, pituitary gland, meninges, hypothalamus, mediastinum, thyroid, orbit, skin, prostate, liver, gallbladder, bile ducts, retroperitoneum, and mesentery, sometimes even without concomitant pancreatic disease [6, 10–18].

The GI tract can also be involved. The histological features of IgG4-RD are non-specific, and the definitive diagnosis requires the demonstration of an inflammatory infiltrate rich in IgG4+ plasma cells. In 2010 Cheuk and Chan proposed new diagnostic criteria that include > 50 IgG4+ plasma cells per HPF and an IgG4+/IgG ratio > 40% [6].

To the best of our knowledge, all cases reported in the literature with upper and lower GI tract involvement are summarized in Tables 1 [3, 15, 19–36] and 2 [29, 37–53], respectively.

There are only four case reports of IgG4-RD involving the oesophagus. These patients have a history of severe dysphagia, odynophagia, weight loss with tumefactive or ulcerative oesophageal lesions at upper endoscopy and a previous diagnosis of chronic oesophagitis [19–22].

Several patients with IgG4-RD with gastric lesions such as ulcers, polyps, nodular fibrosing tumour or pseudotumour, and wall thickening have been described [3, 23–35].

In 2014, Matsunaga et al. [36] reported a case of IgG4-RD complicated by duodenal bulbitis.

Undetermined sclerosing mesenteritis is the most frequently described manifestation of IgG4 indirectly involving the small bowel; it causes abdominal pain and intestinal obstruction that requires surgical resection [37].

Kim Soo et al. and Comtesse et al. have described the involvement of appendix [38, 39].

There are only two case reports of IgG4-RD involving the colon. Chetty et al. described a 56-year-old woman with a 12-mm caecal polyp and a 47-year-old man with a 17-mm polyp in the sigmoid tract which were detected during routine endoscopy; both had an increased number of IgG4+

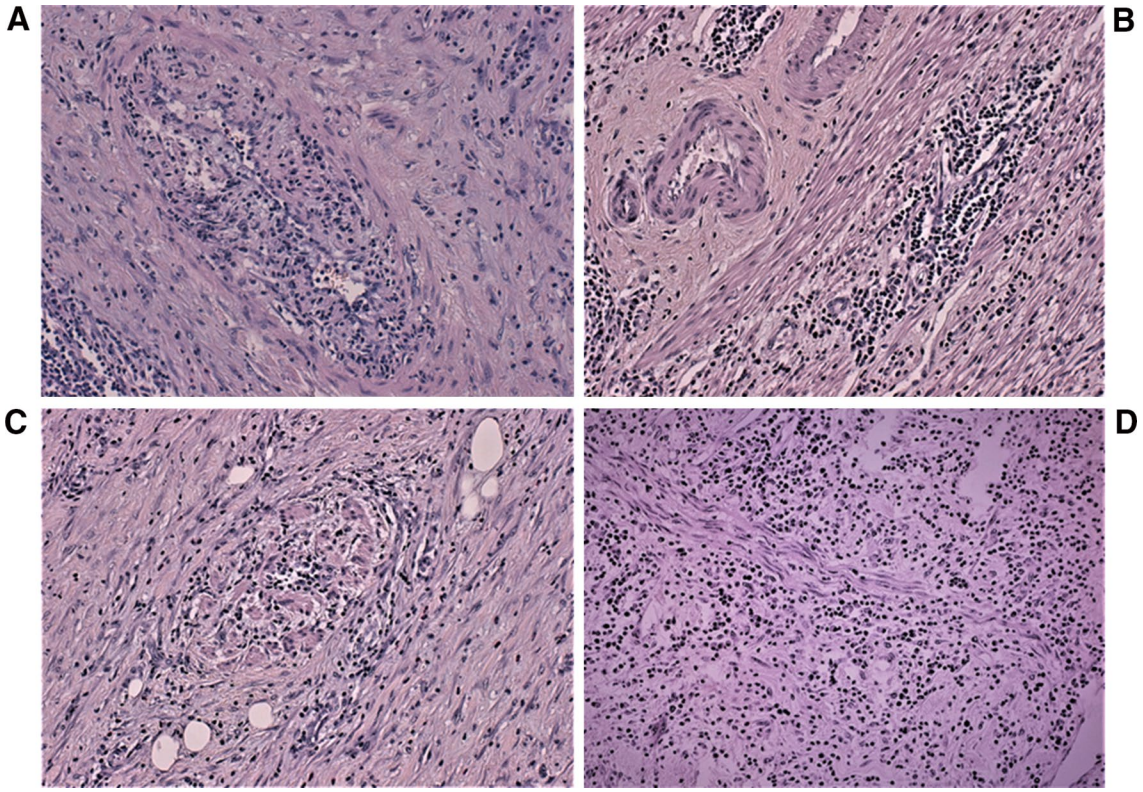

Fig. 2 Haematoxylin–eosin staining, original magnification ×20. Inflammatory infiltrate involving some venous structures (**a**) with diffuse periphlebitis but no arterial involvement (**b**). Inflammatory infiltrate with partial destruction of some nerve fibres of the myenteric plexus (**c**) and diffuse perineuritis (**d**)

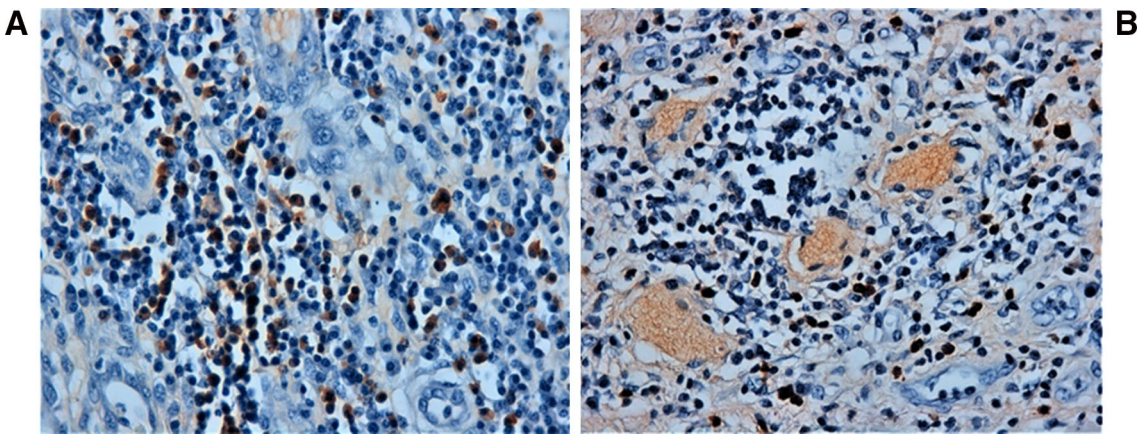

Fig. 3 Immunohistochemical staining, original magnification ×40. The inflammatory infiltrate is rich in plasma cells of which 50% are IgG4-positive (**a**); diffuse IgG4 positivity is also seen in the capillary lumen (**b**)

plasma cells (respectively, 202/3 HPF and 55/3 HPF) and an abnormal IgG4+/IgG ratio (0.72 and 0.29) [29]. Neither had concomitant pancreatic disease, and serum IgG4 levels were not assessed.

Hiyoshy et al. reported the case of a 74-year-old woman with oedematous wall thickening of the terminal ileum involving the lower ascending colon, who underwent right hemicolectomy for suspected malignant lymphoma. Histopathological examination of the surgical specimen found an increased number of IgG4+ cells (150/HPF) and an elevated IgG4+/IgG ratio (50%), leading to a diagnosis of IgG4-RD [40].

Table 1 Case reports of upper gastrointestinal tract IgG4-related disease

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Lopes et al. [19]	23-year-old male	Distal oesophagus	1.5-cm mass	Dysphagia, weight loss, strictures	No	EUS, FNAB	75/HPF	n.a.	n.a.	Surgery	Neither symptom nor disease recurrence 4 months after surgery
Lee et al. [20]	63-year-old male	Middle oesophagus	10-cm stricture with ulcer	Dysphagia, weight loss	No	X-rays, thoracic CT, upper endoscopy with biopsy	200/HPF	n.a.	n.a.	Surgery	n.a.
Campagna et al. [21]	63-year-old female	Upper and middle oesophagus	Multiple strictures and ulcers	Dysphagia, odynophagia	PBC, Sjogren's syndrome, Raynaud's disease, asthma	Upper endoscopy with biopsy	30/HPF	n.a.	n.a.	Mycophenolate mofetil, cyclosporine, corticosteroids, adalimumab, rituximab (fatal outcome)	No symptom regression, death 7 years into follow-up (cause of death not identified at autopsy)
Nada et al. [22]	60-year-old male	Distal oesophagus	Stricture	Dysphagia, weight loss	No	EUS, PET, barium swallow, upper endoscopy with biopsy	Positive	n.a.	n.a.	Surgery, endoscopic dilatation	Symptom-free at 8 months
Fujita et al. [30]	77-year-old male	Stomach	Multiple ulcers	Abdominal discomfort, loss of appetite	No	MRI, upper endoscopy with biopsy, abdominal CT scan	50/HPF	10%	203 mg/dL	PPIs	At 64 months the patient is well and stable under maintenance therapy with PPIs; persistence of multiple ulcers and ulcer scars at endoscopy

Table 1 (continued)

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Kaji et al. [31]	74-year-old male	Gastric body	Multiple polyps with erosions	Upper abdominal pain	Autoimmune pancreatitis and cholangitis	US, CT scan, upper endoscopy with biopsy	n.a.	32%	595 mg/dL	Prednisone	n.a.
Baez et al. [32]	58-year-old male	Gastric fundus and body	1.4-cm nodule, wall thickening	Weight loss, early satiety, diarrhoea, abdominal pain	Autoimmune pancreatitis	Abdominal CT scan, EUS, FNAB	n.a.	1.6%	58 mg/dL	Prednisone	2-Month course of prednisone (40 mg/day) tapered upon symptom improvement
Chetty et al. [29]	45-year-old female	Gastric fundus	1.5-cm nodule	Anaemia	Raynaud's disease	Upper endoscopy with biopsy	363/HPF	78%	n.a.	Surgery	No symptoms 6 months from surgery
Chetty et al. [29]	60-year-old male	Gastric antrum	Ulcer and multiple nodules up to 2.2 cm	Heartburn	Autoimmune polyendocrinopathies	CT scan, post-operative histology	298/HPF	84%	n.a.	Surgery	n.a.
Rollins et al. [33]	75-year-old female	Gastric body	5-cm polypoid lesion	Weight loss, vomiting	No	CT scan, upper endoscopy with biopsy	39/HPF	n.a.	n.a.	Surgery	Well 2 weeks after surgery
Na et al. [34]	56-year-old male	Gastric body	0.8-cm nodule	Anorexia, nausea, abdominal discomfort	DM2	CT scan, upper endoscopy with biopsy	102/HPF	85%	n.a.	ESD	n.a.
Kim et al. [35]	59-year-old female	Stomach	3-cm mass	No symptomatic incidental finding	No	EUS, CT scan, post-operative histology	> 50/HPF	n.a.	Normal	Surgery	n.a.
Kim et al. [35]	54-year-old female	Stomach	2-cm mass	No symptomatic incidental finding	No	EUS, CT scan, post-operative histology	> 50/HPF	n.a.	Normal	Surgery	n.a.
Bateman et al. [15]	73-year-old female	Stomach	3-cm ulcer	Anaemia	DM2, ischaemic heart disease	CT scan, upper endoscopy with biopsy	> 100/HPF	> 90%	n.a.	Surgery	n.a.

Table 1 (continued)

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Frydman et al. [23]	65-year-old male	Stomach	Large necrotic ulcer from the cardia with fistulization towards the pericardium	Bleeding	No	CT scan, upper endoscopy with biopsy	n.a.	> 40%	620 mg/dL	Surgery	Post-operative lung complications, corticosteroid therapy and rehabilitation, progressive improvement and return to normal activities. Follow-up duration not reported
Woo et al. [24]	48-year-old female	Gastric body	3.6-cm mass	No symptomatic incidental finding	Breast cancer	CT scan, upper endoscopy, post-operative histology	210/HPF	85%	n.a.	Surgery	No disease recurrence at 10 months
Zhang et al. [25]	55-year-old female	Gastric body	Mass/polyp	Epigastric pain, flatulence	No	EUS, upper endoscopy with biopsy	62/HPF	41%	169 mg/L	ESD	No signs of recurrence at 5 months
Cheong et al. [26]	27-year-old female	Gastric fundus	3.5-cm mass	No symptoms	High blood pressure, autosomal dominant polycystic kidney disease	CT scan, upper endoscopy, post-operative biopsies	102/HPF	25.3%	295 mg/dL	Surgery	No evidence of disease recurrence at 1 year
Otsuka et al. [27]	44-year-old male	Gastric body	2.2-cm mass	No symptoms incidental finding	No	Upper endoscopy with biopsy, EUS, PET-CT	Positive	n.a.	n.a.	ESD	Well 7 weeks from surgery
Bulanov et al. [28]	62-year-old female	Lesser gastric curvature	0.8-cm ulcer, wall thickening	Severe weakness, fatigue, anaemia	Henoch–Schonlein purpura	CT scan, upper endoscopy with biopsy	> 50/HPF	n.a.	193 mg/dL	Surgery	n.a.

Table 1 (continued)

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Kawano et al. [3]	68-year-old male	Gastric antrum	Tumour-like lesion adjacent to ulcer, 1.5-cm wall thickening	Skin lesions, episode of pneumonia	No	CT scan, upper endoscopy with biopsy	> 190/HPF	> 90%	> 2500 mg/dL	Surgery	Uneventful post-operative course. Follow-up duration not reported
Matsunaga et al. [36]	72-year-old male	Duodenal bulb	Redness and oedematous lesions	Urine discoloration	No	CT scan, ERCP and upper endoscopy with biopsy	n.a.	n.a.	608 mg/dL	Steroids	n.a.

IgG4+, IgG4-positive; n.a., not available; n.r., normal range; PBC, primary biliary cholangitis; DM2, diabetes mellitus type 2; EUS, endoscopic ultrasound; FNAB, fine needle aspiration biopsy; CT, computed tomography scan; US, ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; HPF, high-power field; ESD, endoscopic submucosal dissection.; a.i., autoimmune; MRCP, magnetic resonance cholangiopancreatography; PPIs, proton-pump inhibitors; PET, positron emission tomography

Tsuchiya et al. reported the case of a 67-year-old man with ulcerative mass of the rectum, who underwent laparoscopic low anterior resection of the rectum with creation of ileostomy for suspected malignant neoplasm. Histopathological examination of the surgical specimen found an infiltrating moderately differentiated rectal adenocarcinoma (T3N2bM0), with a preoperative IgG4 serum level of 1140 mg/dL, and a post-operative level of 597 mg/dL [53].

The clinical and histological features of our patient had initially suggested a diagnosis of CD. The diagnosis was then changed to IgG4-RD, when histopathological and immunohistochemical re-evaluation of the surgical specimen identified features consistent with this condition. Endoscopic examination 6 months after the right hemicolectomy had found no macroscopic GI lesions. The only notable finding of the histological examination of the endoscopic biopsies from the jejunum, duodenum, ileum and colon was several IgG4+ cells in the lumen of mucosal capillaries, whose pathogenic significance is unclear.

In all reported cases, follow-up was of short duration without local GI recurrence of the disease. A patient with multiple stomach ulcers, who refused corticosteroid therapy, was well and stable under maintenance therapy with proton-pump inhibitors, but upper endoscopy showed the persistence of the gastric ulcers [30]. In another patient, computed tomography (CT) scanning and magnetic resonance imaging (MRI) 5 months after surgery detected an 11-cm mass with hydronephrosis involving the left ureter; prednisolone (30 mg/day) was started, and 10 months later the mass had almost disappeared on MRI [48].

Since the risk of IgG4-RD recurrence in the GI tract is unknown, there are insufficient data to determine whether endoscopic follow-up should be envisaged.

The majority of patients were treated with surgical or endoscopic resection, whereas a minority received steroids and/or immunosuppressants. In four cases a maintenance treatment with immunosuppressants (mycophenolate, cyclosporine, azathioprine) was carried out [21, 45–47].

Conclusions

Gastrointestinal IgG4-RD often mimics malignancy and is difficult to diagnose clinically. To avoid unnecessary surgery, this entity should be included in the differential diagnosis when marked wall thickening or a lesion resembling a pseudotumour is detected in the GI tract. However, surgical resection may still be necessary in patients with suspected fibrosis or intractable neoplastic GI obstruction mimicking these conditions. A multidisciplinary approach is clearly required.

It is still to be determined whether endoscopic follow-up should be envisaged, or whether it should be done only in

Table 2 Case reports of lower gastrointestinal tract IgG4-related disease

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/ other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Chen et al. [41]	46-year-old male	Mesentery	7-cm mass	Abdominal pain	History of Hodgkin's lymphoma in childhood	Post-operative histology	> 100/HPF	30%	n.a.	Surgery	Death from pneumonia and bacteraemia 4 months after surgery: patient on TPN due to short gut syndrome
Salvarani et al. [42]	42-year-old male	Mesentery, above the bladder and in contiguity with ileum loops	3-cm mass	No symptomatic incidental finding at abdomen-US	No	Abdomen and pelvic US and CT scan, post-operative histology	60/HPF	40%	119 mg/dL (n.r. 8-140) (only post-operative)	Surgery	n.a.
Nomura et al. [43]	82-year-old female	Mesentery of small bowel	11.7-cm mass	Abdominal pain	Previous appendicectomy and cholecystectomy	CT scan, post-operative histology	130/HPF	75.9%	171 mg/dL (n.r. 8-140) (only post-operative)	Surgery	Disease-free without medications Follow-up duration not reported
Minato et al. [44]	53-year-old male	Mesentery of ileocaecal region	7-cm mass	Abdominal pain	Previous appendicectomy and right orchiectomy	CT scan, post-operative histology	75/HPF	64%	127 mg/dL (n.r. 8-140) (only post-operative)	Surgery	Disease-free without medications Follow-up duration not reported
Wong et al. [45]	46-year-old female	Mesentery and jejunum	2.3-cm stenotic ulcer	Subacute small bowel obstruction, vomiting, 2-year abdominal pain	History of 2 spontaneous abortions	Abdominal X-rays and CT scan, enteroscopy with biopsy	n.a.	50%	> 800 mg/dL (n.r. 8-140) (only post-operative)	Surgery, mycophenolate, prednisone	Symptom-free over first 4 months from surgery, then abdominal pain and successful management with mycophenolate and prednisone

Table 2 (continued)

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/ other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Hasosah et al. [46]	7-year-old female	Mesentery	4-cm stenotic mass	Abdominal pain, vomiting, diarrhoea, and fever	No	CT scan, upper enteroscopy with biopsy	n.a.	52%	149 mg/dL (pre-treatment), normal (post-treatment, n.a. value)	Prednisone, azathioprine	Symptom-free with reduction in mesenteric mass 6 months into treatment; maintenance therapy with prednisone (5 mg/day) without symptom recurrence at 24 months
Coulier et al. [47]	57-year-old female	Ileum, mesentery, uterus and ovaries	3–4-cm masses and nodules	Intestinal obstruction	No	Abdominal CT scan, post-operative histology	Reported numerous IgG4+ plasma cells (without specific value)	n.a.	Reported normal (only post-operative, n.a. value)	Surgery, methylprednisolone and azathioprine	Methylprednisolone 32 mg/day and stepwise. Azathioprine 100 mg/day added due to persistence of 2 peritoneal nodules; no disease progression over 1 year

Table 2 (continued)

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/ other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Mori et al. [48]	64-year-old male	Right lower mesentery	6-cm mass	Abdominal pain	Retroperitoneal fibrosis, DM2	Abdominal CT scan, post-operative histology	38/HPF	80%	81 mg/dL (n.r. 8-140) (only post-operative)	Surgery, steroids	CT and MRI detection of an 11-cm mass with hydronephrosis involving the left ureter 5 months after surgery. Almost disappeared on MRI 10 months later after management with prednisolone (30 mg/day)
Lee et al. [49]	70-year-old female	Mesentery	8-cm mass	Abdominal pain	Total hysterectomy 10 years earlier	PET-CT scan, post-operative histology	n.a.	> 90%	2130 mg/L (n.r. 8-140) (only post-operative)	Surgery, steroids	Symptom-free Steroid dosage and follow-up duration not reported
Harvin et al. [50]	66-year-old female	Mesentery and terminal ileum	Wall thickening, dilated loops of small bowel and moderate ascites	Intermittent periumbilical abdominal pain, nausea, vomiting and diarrhoea	Chronic obstructive pulmonary disease and history of mild reflux	Abdominal CT scan, post-operative histology	Reported positive (without specific value)	n.a.	n.a.	Surgery	No symptoms without medications; normal small bowel at MRI enterography Follow-up duration not reported
Ko et al. [52]	43-year-old male	Small bowel (ileum)	4 × 3 cm mass	One-year history of intermittent abdominal pain	History of acute myocardial infarction 10 years previously and benign prostatic hyperplasia	Abdominal CT scan, post-operative histology	> 50/HPF	n.a.	n.a.	Surgery	No post-operative complications Follow-up duration not reported

Table 2 (continued)

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/ other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Abe et al. [37]	77-year-old female	Distal ileum mesentery	3-cm mass	Intestinal obstruction	No	Abdominal CT scan, double-balloon enteroscopy, post-operative histology	n.a.	50%	114 mg/dL (only post-operative) (n.r. 4.8-105)	Surgery	No evidence of disease recurrence and no symptoms at 4 years
Higashioka et al. [51]	67-year-old male	Jejunum	Oedema and wall thickening	Swelling of submandibular glands, pancytopenia	Swelling of lymph nodes and salivary and lacrimal glands, a.i. pancreatitis, interstitial nephritis, retroperitoneal fibrosis, periaortitis, pulmonary lesions, splenomegaly	Chest X-rays, CT scan, renal and lymph node biopsy	300/HPF	90%	n.a.	Prednisolone	Oral prednisolone (0.6 mg/kg/day); no disease recurrence at 4 months
Comtesse et al. [39]	20-year-old female	Appendix, extending to caecal pole	10.5-cm mass	Acute abdomen	n.a.	Laparoscopic appendectomy changed to open appendectomy, post-operative histology	n.a.	> 40%	n.a.	Surgery	Disease-free without medications Follow-up duration not reported
Kim Soo et al. [38]	51-year-old male	Appendix	3.6-cm mass	Right lower abdominal pain	No	Abdominal CT scan, post-operative histology	n.a.	> 50%	n.a.	Surgery	Disease-free without medications Follow-up duration not reported

Table 2 (continued)

Reference	Age and gender	GI tract organ(s) involved	Type of lesions	Clinical features	Other organs involved/ other diseases	Diagnostic workup	IgG4+/HPF	IgG4/IgG ratio	Serum IgG4 (mg/dL)	Treatment	Follow-up and outcome
Chetty et al. [29]	56-year-old female	Caecum	1.2-cm polyp	No symptoms	History of uterine endometrioid carcinoma, goitre, chronic renal insufficiency, unspecified thyroid disease	Colonoscopy with polypectomy	202/HPF	72%	n.a.	Polypectomy	Disease-free without medications Follow-up duration not reported
Chetty et al. [29]	47-year-old male	Sigmoid flexure	1.7-cm polyp	No symptoms	No	Colonoscopy with polypectomy	55/HPF	29%	n.a.	Polypectomy	Disease-free without medications Follow-up duration not reported
Hiyoshi et al. [40]	74-year-old female	Terminal ileum, lower ascending colon	10-cm mass	Abdominal pain, slight fever	n.a.	Abdominal US, colonoscopy with biopsy	150/HPF	50%	102 mg/dL (only postoperative) (n.r. 6-121)	Surgery	Disease-free without medications Follow-up duration not reported
Tsuchiya et al. [53]	67-year-old male	Rectum	2–4-cm intermittent nodular lesions (T3N2bM0, stage IIIC, infiltrating rectal cancer)	Increased CEA and CA19-9, no symptoms	Biliary tree narrowing, retroperitoneal fibrosis, lymph node involvement, DM2	ERCP, MRCP, CT scan, PET scan, lower enteroscopy with biopsy	n.a.	n.a.	1140 md/dl (preoperative), 597 mg/dL (postoperative)	Surgery	Treated with modified FOLFOX6 as adjuvant therapy Outcome and follow-up duration not reported

IgG4+, IgG4-positive; n.a., not available; n.r., normal range; PBC, primary biliary cholangitis; DM2, diabetes mellitus type 2; EUS, endoscopic ultrasound; FNAB, fine needle aspiration biopsy; CT, computed tomography; US, ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; HPF, high-power field; ESD, endoscopic submucosal dissection.; a.i., autoimmune; MRCP, magnetic resonance cholangiopancreatography, PET, positron emission tomography; TPN, total parenteral nutrition

patients with a post-operative clinical recurrence. No pharmacological maintenance treatment appears to be indicated.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare, and they did not use any outside assistance in preparing the manuscript.

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