Immunoglobulin G4-Related Disease Manifesting as Isolated, Typical, and Nontypical Gastroesophageal Lesion: A Research of Literature Review

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Keywords

Esophageal immunoglobulin G4-related disease · Gastric immunoglobulin G4-related disease · Isolated lesions · Typical lesions · Nontypical lesions

Abstract

Background: Immunoglobulin G4-related disease (IgG4-RD) is an autoimmune inflammatory and fibrotic condition. The disease is characterized by tissue infiltration with dense lymphoplasmacytes and IgG4-positive plasma cells. **Summary:** The aim of this study was to provide gastroenterologists with novel insights into evaluating the gastroesophageal involvement with IgG4-RD or mimickers of this condition and to give special attention to clinicopathological features. A literature review was performed using the PubMed database. A total of 39 studies presenting cases in the form of isolated, typical, and nontypical gastroesophageal involvement with IgG4-RD published between 2010 and 2018 were included. These studies were thoroughly reviewed for symptoms, lesion location, lesion type, lesion size, immune-histopathology, associated diseases, treatment, and follow-up. Of the 39 studies reviewed, 9 were esophageal IgG4-RD lesions, isolated esophageal IgG4-RD 66.66% (6/9), a typical form of esophageal IgG4-RD 11.11% (1/9), and nontypical form

esophageal IgG4-RD 22.22% (2/9). The 30 gastric IgG4-RD that include isolated gastric IgG4-RD 46.66% (14/30), typical gastric IgG4-RD 40% (12/30), and nontypical gastric IgG4-RD 13.33% (4/30). The majority of lesions were inflammatory tumors, ulceration, nodular lesions, chronic gastritis, and malignant lesions. **Key Messages:** IgG4-RD may be manifested by isolated, typical and nontypical forms of gastroesophageal lesions and should be taken into consideration in the differential diagnosis. Corticosteroids may be the sole diagnostic treatment for this condition.

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an autoimmune systemic disorder that has been defined in various organs. The disease is characterized by chronic inflammatory condition and histologically by tissue infiltration with dense lymphoplasmacytes, and IgG4-positive (IgG4+) plasma cells, variable count of eosinophils, fibrosis (often storiform fibrosis), and obliterative phle-

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bitis within the lesion area [1–4]. The pathogenesis of IgG4-RD remains unclear; however, type 2 T-helper cells, regulatory T-cell cytokines, and B-cell activating factor have been suggested to be linked with the development of IgG4-RD [5]. IgG4-RD can affect multiple organs simultaneously or can present as a solitary, mass-like lesion [2]. The pancreas “autoimmune pancreatitis” (AIP), hepatobiliary system, retroperitoneum, aorta, kidney, orbit, lungs, lymph nodes, and salivary glands are the most commonly affected organs, although, the manifestation of the upper gastrointestinal tract is relatively rare [2, 6–9].

Many experts of IgG4-RD suspect that reported cases of gastroesophageal IgG4-RD are mimickers of this condition. A recent study on 235 consecutive patients with IgG4-RD revealed that 95% of patients have at least one of the top 5 manifestations (pancreatitis, sialadenitis, interstitial nephritis, dacryoadenitis, and periaortitis) [10]. In this study, if any one of the above 5 tissues manifestation coexists with gastroesophageal IgG4+ lesions, it may be signaling IgG4-related typical lesions. IgG4+ lesions with no coexistence of any top 5 typical manifestations “pancreatitis, sialadenitis, interstitial nephritis, dacryoadenitis, and periaortitis” or other associated diseases are called IgG4+ isolated or solitary lesions. However, non-typical IgG4-related lesions are referring to the condition other than that of isolated or typical IgG4-RD, such as associated diseases or the presence of concomitant diseases, including Raynaud’s disease, Henoch-Schonlein purpura, idiopathic thrombocytopenic purpura, autosomal dominant polycystic kidney disease, and so on.

IgG4-RD and/or the mimickers of this condition are relatively rare in the upper gastrointestinal tract, but are known to occur based on anecdotal case reports. The clinical descriptions of IgG4-related GI disease in these presenting reports range widely and include nodules, tumors, ulceration, wall thickening, gastritis, malignant lesions, vasculitis, fistula, and increases in IgG4+ plasmacytes without obvious morphologic abnormalities.

Materials and Methods

The literature search was performed using the PubMed database for studies published in English in years 2010–2018. The following combinations of medical headings were used: “esophageal IgG4-RD,” “gastric IgG4-RD,” “IgG4-related esophageal disease,” “IgG4-related gastric disease,” “gastrointestinal IgG4-RD,” “IgG4-related gastroesophageal disease,” and “IgG4-related gastrointestinal disease.” A total of 39 studies presenting cases of IgG4-RD manifested as isolated, typical, and nontypical gastroesophageal

lesions were included in the analysis. These studies were methodically reviewed for symptoms, lesion location, lesion type, lesion size, immune-histopathology, associated or concomitant diseases, treatment, and follow-up. The method for selecting case studies in tables was based on quantitative methods related isolated, typical, and nontypical IgG4+ gastroesophageal lesion discussed in the introduction section.

Results

The baseline clinical and histopathological characteristics of total 9 cases presenting studies of esophageal IgG4-RD are summarized in Table 1. Dysphagia and weight loss were the 2 most common symptoms in patients with esophageal IgG4-RD lesions. Most patients presented with ulceration and stricture, 6 (66.66%), or mass-like lesions, 2 (22.22%), mainly involved distal and mid-esophagus, 6 isolated lesions (66.66%), 1 typical form of a lesion (11.11%), and 2 nontypical IgG4-related lesions (22.22%). Elevated serum IgG4+ level observed in 3 patients. Moreover, IgG4+ plasmacytic level was determined in only 3 of the 9 cases; however, all lesions were positive for IgG4 plasmacytes.

Regarding gastric IgG4-RD, 30 cases were studied, the majority of them were submucosal inflammatory tumors 15 (50%), nodular lesions 4 (13.33%), ulcerated lesions 7 (23.33%), chronic gastritis 2 (6.66%), malignant lesions 3 (10%), and without data 1 (3.33%).

In isolated gastric IgG4-RD 14 (46.66%), most lesions were located in the gastric body, presented with gastrointestinal symptoms of abdominal pain, anorexia, nausea, loss of appetite, and anemia. Elevated serum IgG4+ level was unremarkable except in 3 patients (9, 12, and 13); however, IgG4+ plasmacytic levels were determined in most of cases which is shown in Table 2.

In typical gastric IgG4-RD 12 (40%), lesions occupied mainly the gastric fundus, body, and antrum with symptoms of abdominal pain, nausea, and vomiting, early satiety, anorexia, weight loss, submandibular salivary glands swelling, decreased visual acuity, renal dysfunction, pruritus, itchy skin lesions, and jaundice. Elevated serum IgG4+ level and increased IgG4+ plasmacytes levels were determined in most of the cases. Moreover, elevated IgG4+/IgG+ ratio was observed in 5 cases (1, 4, 7, 11, and 12) as well as high IgG level in 4 patients (1, 2, 4, and 5) Table 3.

In nontypical gastric IgG4-RD 4 (13.33%), lesions were located in the gastric fundus, body, and antrum presented with epigastric pain, fatigue, and anemia due to the bleeding from chronic mucosal ulceration. Interestingly,

Table 1. List of the cases with isolated, typical, and nontypical esophageal IgG4-RD

Case No. age/ gender [Ref. No.]	Symptoms	Esophageal location	Lesion type	Size, mm	Histopathology and immunohistochemical staining	Serum IgG4	IgG4/ HPF	1. Associated diseases 2. Categorization	Treatment	Follow-up
1. 76/female [14]	Dysphagia, heartburn vomiting weight loss	Thoracic esophagus	Sclerosing esophagitis Strictures	Transmural esophageal wall hypertrophy 50 mm	Lymphoplasmacytic infiltration Scattered lymphoid follicles and eosinophils, inflammatory exudate and granulation tissue. Severe submucosal fibrosis CD-163+ spindle-shaped macrophages IgG4+ plasmacytes IgG4+/IgG+ ratio >40%	No data	>10	None = (isolated IgG4+ lesion)	Esophageal resection	52 months recurrence free
2. 23/male [7]	Dysphagia weight loss	Distal esophagus	GIST like tumor	15 mm extended to muscularis	Lymphoplasmacytic infiltration Venulitis CD4 and CD117+ Scattered spindle cell IgG4+ plasmacytes Fibroblastic spindle cells staining with SMA	No data	75	None = (isolated IgG4+ lesion)	Laparoscopic esophagectomy	4 months recurrence free
3. 63/male [6]	Progressive dysphagia weight loss	Mid- esophagus	Ulceration stricture Wall thickening inflammatory exudates	100	Dense lymphoplasmacytic infiltration Lymphoid follicles Stromal sclerosis Transmural chronic fibrosing inflammatory exudates phlebitis and plexitis were also observed IgG4+ plasmacytes	Elevated	200	None = (isolated IgG4+ lesion)	esophagectomy	No data
4. 63/female [11]	Odynophagia dysphagia heartburn dyspepsia	Distal esophagitis	Ulceration Stricture	NA	Dense lymphoplasmacytic infiltration inflammatory fibrinous exudate with granulation tissue Few IgG4+ plasmacytes noted on autopsy specimen	NA	Unremarkable	Primary biliary cirrhosis, sjogren disease, raynaud disease, asthma, transient cerebral ischemia and osteoporosis = (typical IgG4+ lesion)	PPI, Steroids immunosuppressant immunomodulators	After multiple follow-up for 8 years, the patient was expired
5. 33/male [1]	Progressive dysphagia weight loss	Cervical esophagus	Mass severe stricture	39	Numerous plasmacytes and eosinophils Proliferation of spindle cells IgG4+ plasmacytes	Elevated	12	None = (isolated IgG4+ lesion)	Prednisolone	11 months recurrence free and gradually improved

Table 1. (continued)

Case No. age/ gender [Ref. No.]	Symptoms	Esophageal location	Lesion type	Size, mm	Histopathology and immunohistochemical staining	Serum IgG4	IgG4/ HPF	1.Associated diseases 2.Categorization	Treatment	Follow-up
6. 60/male [12]	Acid reflux	Lower esophagus AND stomach	Fixed mass in the lower esophagus giant gastric ulcer	NA	Gastroesophageal specimens revealed dense lymphoplasmacytic infiltration fibrosis IgG4+ plasmacytes IgG4+IgG+ ratio >30%	Elevated	50	None = (isolated IgG4+ lesion)	steroids and anti-ulcer	3 months, stomach ulcer subsided except esophageal mass
7. 8 patients = (54.7±16.4)/7 male; 1 female [13]	Dysphagia GERD Epigastric pain	NA	3-esophageal strictures 2-postmyotomy treated achalasia, 1-erosive esophagitis 1-esophageal nodule. 1-unremarkable mucosa	NA	All patients had higher lymphoplasmacytic infiltrate 3P- obliterative phlebitis IgG4/IgG ratio 0.76±0.13	Normal	66.9±21.9	None = (isolated IgG4+ lesion)	2 patients- responded to steroid treatment 1 patients- responded to prednisolone 2 patients- with achalasia underwent surgery for dilated thickened esophagus, and one underwent botulinum toxin A 3 patients- NA	No data
8. 29 patients = (43–84)/24.1% male [17]	Dysphagia	Lamina propria Epithelium	Mild fibrostenotic severe fibrostenotic	7 patients ≤40 22 patients ≥40	10/29 patients = IgG4 staining positive, and 3 of them with dense IgG4 deposits IgG4 cells in patients with severe fibrostenotic esophageal lichen planus was 14.6	NA	14.6	Esophageal lichen planus (nontypical IgG4+ lesion)	No data	No data
9. 21 patients = mean age 30 (2–81)/16 male; 5 female [20]	Food impaction Vomiting Asthma eczema, allergic rhinitis Furrows white patches	Lamina propria	EoE >15 intraepithelial eosinophils/HPF	NA	16/21 patients-showed intrascamous extracellular IgG4 deposits Mucosal IgG4-positive plasma cells Intraepithelial deposits of IgG4, submucosal IgG4- positive plasma cells	NA	12.9	EoE (nontypical IgG4+ lesion)	PPI Steroids EoE initial presentation with IgG4+ plasma cells (mean = 22.4) EoE on therapy IgG4+ plasma cells (mean 7.0)	No data

NA, not available; GIST, gastrointestinal stromal tumor; PPI, proton pump inhibitors autoimmune pancreatitis; GERD, gastroesophageal reflux disease; EoE, eosinophilic esophagitis; IgG4-RD, immunoglobulin G4-related disease

Table 2. List of the cases with isolated gastric IgG4-RD

Case No. age/gender [Ref. No.]	Symptoms	Gastric location	Lesion type	Size, mm	Histopathology and immunohistochemical staining	Serum IgG4	IgG4/HPF	Associated disease	Treatment	Follow-up
1. 56/male [25]	Anorexia nusea, abdominal discomfort	Body	Submucosal nodule	8	Abundant lymphoplasmacytes storiform fibrosis IgG4+/IgG ratio 80–90%	No data	102	None	ESD	4 months recurrence free
2. 75/female [30]	Vomiting Weight loss anemia	Body	Polyp/GIST like tumor	56	Abundant lymphoplasmacytes Fibrosis with spindle cells proliferation	Normal	39	None	LWR	2 weeks recurrence free
3. 59/female [36]	No data	Body	GIST like tumor	33	Abundant lymphoplasmacytes storiform fibrosis Numerous lymphoid follicles	Normal	>50	None	LWR	No data
4 54/female [36]	No data	Gastric	GIST like tumor	21	Abundant lymphoplasmacytes storiform fibrosis Numerous lymphoid follicles Numerous psammomatous calcification	Normal	>50	None	LWR	No data
5. 48/female [28]	Asymptomatic	Body	SMT like tumor	36	Abundant lymphoplasmacytes storiform fibrosis Lymphoid nodules with reactive foci Eosinophilic infiltration Obliterative phlebitis IgG4+/IgG+ ratio >85%	No data	210	None	LWR	10 months recurrence free
6. 44/male [39]	Asymptomatic	Body	GIST like tumor	20–22	Abundant lymphoplasmacytic infiltration Fibrosis	Normal	Average	None	Laparoendoscopic surgery	7 weeks recurrence free
7. 57/male [40]	Asymptomatic	Antrum	Oval GIST like tumor	18	Abundant lymphoplasmocytes collagen, anti CD138+ IgG4+ plasmacytes IgG4+/IgG ratio >40%	Normal	>50	None	WR	1 year recurrence free
8. 40/female [5]	Asymptomatic	Antrum	GIST like tumor	40	Abundant lymphoplasmocytes storiform fibrosis Transmural fibrosis Numerous lymphoid follicles IgG4+/IgG+ ratio 0.2–0.4	No data	>57	None	WR	No data

Table 2. (continued)

Case No. age/gender [Ref. No.]	Symptoms	Gastric location	Lesion type	Size, mm	Histopathology and immunohistochemical staining	Serum IgG4	IgG4/HPF	Associated disease	Treatment	Follow-up
9. 77/male [27]	Abdominal pain loss of appetite	Body	Multiple ulcers	No data	Abundant IgG4 plasmacytes serum IgG/IgG4 levels 1,909/203 mg/dL	Elevated	50	None	PPI	11 months recurrence free
10. 73/female [43]	Pale	Body	Ulceration	30	Abundant lymphoplasmacytes storiform fibrosis Formation of lymphoid nodules numerous eosinophils Obliterative phlebitis IgG4+/IgG+ ratio >80%	No data	>100	None	Partial gastrectomy	No data
11. 60/male [12]	Acid reflux	Body	Ulceration	No data	Abundant lymphoplasmacytes Fibrosis IgG4+/IgG+ ratio >30%	Normal	>50	None	Steroid + PPI	3 months recurrence free
12. 63/male [45]	Left epigastric discomfort Anorexia weight loss	Fundus and gastric angle	Dual ulcers	40 and 30	<i>Helicobacter pylori</i> + Abundant lymphoplasmacytes Submucosal fibrosis Multiple lymphoid follicles obliterative phlebitis IgG4+ plasmacytes IgG4+ 50% to IgG+ plasmacytic ratio	Elevated	50–60	None	TG	5 months recurrence free
13. 65/male [42]	Abdominal pain inter- scapular back pain, fever malnourished	Cardia	Necrotic ulceration gastric pericardial fistula	No data	Abundant IgG4+ plasmacytes Storiform fibrosis IgG4:IgG ratio >40%	Elevated	No data	None	Complete gastrectomy	Improved
14. No data [49]	No data	Body and antrum	Atrophic gastritis with pernicious anaemia	No data	17 out of 46 AG+ PA+ cases revealed IgG4+ plasmacytic infiltration 5–16/HPF	Unremarkable	>5	None	No data	No data

WR, wedge resection; LWR, laparoscopic wedge resection; TG, total gastrectomy; ESD, endoscopic submucosal dissection; SMT, submucosal tumor; AG+, atrophic gastritis positive; PA+, pernicious anemia positive; PPI, proton pump inhibitor; IgG4-RD, immunoglobulin G4-related disease.

Table 3. List of the cases with typical gastric IgG4-RD

Case No. age/ gender [Ref. No.]	Symptoms	Gastric location	Lesion type	Size, mm	Histopathology and immunohistochemical staining	Serum IgG4	IgG4/HPF	Associated disease	Treatment	Follow-up
1. 58/male [22]	Abdominal pain early satiety diarrhea weight loss	Body fundus	Nodular thickened wall	14	Dense lymphoplasmacytes Positive mast cells Extensive IgG and IgG4+ immunostaining in the stomach Elevated serum IgG 3,700 mg/dL	Normal	Elevated	AIP, IgG4-related sialadenitis	Prednisone 40 mg/day for 2 months	Improved
2. 74/male [23]	Abdominal pain	Body	Multiple sporadic polyps	No data	Dense IgG4+ plasmacytes Acute inflammatory cell elevated serum IgG 1,849 mg/dL	Elevated	No data	IgG4+ AIP	No data	No data
3. 60/male [24]	Symptoms due to a duodenal bulbar ulcer gastritis	Antrum and pyloro- antral junction	3 Gastric wall lesions 1 nodular lesion of lesser omentum	19–22	Hyalinised fibrous tissue Numerous eosinophils Chronic inflammation with lymphoplasmacytic infiltrates Few lymphoid follicles IgG4+ plasmacytes IgG4/IgG ratio 0.84	No data	298	Autoimmune polyendocrinopathy with hypothyroidism and adrenal insufficiency	DG	No data
4. 64/male [26]	Bilateral submandibular salivary glands swelling	Fundus body	Multiple submucosal tumors like nodules	3–10	Dense IgG4+ plasmacytes Storiform fibrosis Elevated serum IgG 2,817 mg/dL IgG4+/IgG+ ratio >70 and >51%	Elevated	No data	Bilateral submandibular salivary glands swelling	EMR and Prednisolone	4 months recurrence free
5. 67/male [41]	Decreased right visual acuity	Antrum	Malignant lymphoma or GIST like tumor	52	Dense lymphoplasmacytes Eosinophils Fibrosis Obstructive phlebitis Abundant IgG4+ plasmacytes IgG 4,285 mg/dL	Elevated	No data	Optic neuropathy Dacryoadenitis Periaortitis Retroperitoneum fibrosis	DG, prednisolone	9 months recurrence free
6. 61/male [61]	Abdominal distension pruritus jaundice Weight loss	Pyloric	Moderately differentiated adenocarcinoma limited to the mucosa and submucosa	No data	<i>Helicobacter pylori</i> + Dense lymphoplasmacytes Storiform fibrosis IgG4+ and IgG+ plasmacytes in cancer stroma Eosinophilic infiltration Mesenchymal cells	Elevated after 12 months follow-up	No data	IgG4-related AIP and IgG4-related sclerosing cholecystitis <i>H. pylori</i> + multiorgan IgG4-RD	Radical subtotal gastrectomy with cholecystectomy, <i>Hp</i> - eradication therapy steroid	12 months recurrence free
7. 74/male [62]	EGC	Antrum	Adenocarcinoma	15	Dense lymphoplasmacytes Partial fibrosis Lymph follicles and eosinophils IgG4+ plasmacytes IgG4/IgG ratio: 81.5%	Elevated	172	IgG4-RD of pancreas, sclerosing cholangitis, and kidney	DG Prednisolone	2 months gradually improved
8. 81/male [63]	Progressive renal dysfunction anorexia weight loss	Antrum	EGC	25	IgG4+ plasmacytes IgG4/IgG 16.5%, IgE 1,050 IU/mL, IgG4 548 mg/dL	Elevated	No data	IgG4-related multi organ disease of submandibular gland, lymph node, lung, kidney, aortic wall, and prostate lesions	DG Steroid	3 months All lesions improved except recurrent metastatic gastric cancer

Table 3. (continued)

Case No. age/ gender [Ref. No.]	Symptoms	Gastric location	Lesion type	Size, mm	Histopathology and immunohistochemical staining	Serum IgG4	IgG4/HPF	Associated disease	Treatment	Follow-up
9. No data [50]	13 cases-5 patients-chronic gastritis 8 Patients- chronic active gastritis 9 had no symptoms 3 had epigastralgia 1 had nausea and vomiting	Fundus pylorus	Redness Erosion Atrophy	No data	<i>H. pylori</i> + 8 out of 13 cases, Dense lymphoplasmacytes ↑ Mononuclear cell infiltrates in <i>Hp</i> +, 1Mononuclear cell infiltrates in <i>Hp</i> - Scattered eosinophil, Fibrosis, IgG4/IgG ratio ↑ in the lower lamina propria of fundus in both <i>H. pylori</i> (+)(-) groups IgG4/IgG ratio ↑ in the lower lamina propria of pylorus in steroid (-) group IgG4+ plasmacytes ↓ in lower and upper lamina propria in steroid positive group, IgG4/IgG ratios in steroid (+) group was discreet than steroid (-)	Elevated	Elevated	AIP	Steroid Antacid	No data
10. 55,58/male [60]	No data	No data	No data	No data	IgG 1.878 and 1.173 mg/dL IgG4 410 and 220 mg/dL IgE 270 and 134 IU/mL	No data	No data	IgG4-related AIP on steroid therapy prior to gastric cancer development	No data	Early gastric cancer on follow-up screening of 128 and 43 months
11. 55/female [37]	Epigastric pain flatulence	Body	SMT or GIST	20	Lymphoplasmacytic infiltrates Multiple lymphoid follicles Psammomatous calcifications Densely hyalinized, storiform pattern dispersed spindle-shaped cells IgG4+ plasmacytes IgG4/IgG ratio 41%	Normal	62	Hashimoto's thyroiditis, possible PBC	ESD	5 months recurrence free
12. 68/male [38]	Multiple, itchy skin lesions	Antrum	Thickened antrum wall with adjacent ulcer	40	Lymphoplasmacytic infiltration in mucosa, muscularis propria, and subserosa, Numerous eosinophils Dense fibrosis Proliferating oval to spindle-shaped cells (+) and obliterative phlebitis IgG4+ plasmacytes IgG4+/IgG+ ratio >90	Elevated	190	IgG4-RD in lungs, skin, and lymphnodes	DG	No data

DG, distal gastrectomy; EMR, endoscopic mucosal dissection; GIST, gastrointestinal stromal tumor; AIP, autoimmune pancreatitis; PBC, primary biliary cirrhosis; IgG4-RD, Immunoglobulin G4-RD.

Table 4. List of the cases with nontypical gastric IgG4-RD

Case No. age/gender [Ref. No.]	Symptoms	Gastric location	Lesion type	Size, mm	Histopathology and immunohistochemical staining	Serum IgG4	IgG4/HPF	Associated disease	Treatment	Follow-up
1. 45/ female [24]	Anemia	Fundus	Submucosal nodule Surface ulceration	15	Dense lymphoplasmacytes Few lymphoid follicles Hyalinised fibrous tissue Numerous eosinophils Chronic inflammation IgG4+ plasmacytes IgG4/IgG ratio 0.78	Normal	363	Raynaud's disease	WR	6-months recurrence free
2. 62/ female [35]	Fatigue Anemia	Antrum	Ulcerated tumor	80 × 30	Dense lymphoplasmacytes Storiform fibrosis Formation of lymphoid nodules with reactive foci Numerous eosinophils Obliterative phlebitis IgG4+ plasmacytes, postoperative serum IgG4 193 mg/dL	Elevated	50	Henoch-Schonlein purpura	DG	No data
3. 44/ female [5]	Asymptomatic	Body	GIST like tumor	40	Dense lymphoplasmacytes Storiform fibrosis Transmural fibrosis Numerous lymphoid follicles IgG4 and IgG+ with ratio 0.4	No data	>60	ITP	TG	No data
4. 27/ female [34]	Asymptomatic	Fundus	GIST/NET like tumor with surface ulceration	40	Dense lymphoplasmacytes Storiform pattern IgG4+/IgG+ ratio 25.3%	Normal	102	ADPKD	WR	1 year recurrence free

TG, total gastrectomy; WR, wedge resection; DG, distal gastrectomy; ESD, endoscopic submucosal dissection; GIST, gastrointestinal stromal tumor; ITP, idiopathic thrombocytopenic purpura; ADPKD, autosomal dominant polycystic kidney disease; NET, neuroendocrine tumor; IgG4-RD, immunoglobulin G4-RD.

elevated IgG4+ plasmacytic levels were determined in all cases; however, serum IgG4+ level was elevated in only 1 patient, and 3 patients with insignificant IgG4+/IgG+ ratio (0.78, 0.4, 25.3%), respectively Table 4.

The majority of gastroesophageal lesions (66.66%) in the literature review were removed surgically due to suspected malignancy. In all cases, the diagnosis was established on the basis of clinical appearance, histopathological analysis, and immunohistochemical staining. In most of the cases, the findings were characteristic for IgG4-RD. The mean age of patients was 57 years (range of 27–81 years), with the majority being male. The majority of patients respond to steroids treatment, particularly postoperative lesions. The follow-up period of the study group ranged from 2 weeks to 143 months. The recurrence-free cases were 22 (56.41%), except 2 (5.12%) one expired during follow-up another developed early gastric cancer; however, patients without follow-up data were 15 (38.46%), respectively.

Discussions

IGG4-Related Esophageal Disease

IgG4-related esophageal disease is severely uncommon and characterized by dysphagia, odynophagia, and

edematous thickening of the esophageal wall, fibrosis, stromal sclerosis, strictures, sloughing esophagitis, or sometimes on imaging, mimics neoplastic disease, and pathologically by tissue infiltration with dense lymphoplasmacytes and IgG4+ plasma cells [6, 11]. In most isolated cases, increased levels of IgG4+ plasmacytes subsequently normalized following steroid treatment [1, 12].

IgG4-Related Esophageal Ulceration and Stricture

Esophageal ulceration and stricture are very uncommon, however, recently been more frequently reported in the setting of esophageal disorders and IgG4-RD. A study by Obiorah et al. [13] reported 8 patients with IgG4-related esophagitis with strictures who responded well to steroid therapy. However, no other characteristics of infiltration typical for IgG4-RD, particularly fibrosis, stricture, esophageal wall thickening, elevated IgG4/IgG ratio [13, 14], spindle cells infiltration, and phlebitis, were observed in immune-histopathological specimens. Dumas-Campagna et al. [11] reported a patient with severe ulcerative esophagitis that resembled esophagitis dissecans superficialis with a presence of multiple comorbid conditions, in which oral prednisone, infliximab, and immunosuppressant failed to improve the patient symptoms.

IgG4-Related Esophageal Mass-Like Lesions

Polypoid or mass-like lesions are common findings in IgG4-RD involving gastrointestinal tract, which may be mistaken for cancerous lesions. Lopes et al. [7] reported a GIST-like tumor in the distal stomach with significant lymphoplasmacytic infiltration and IgG4+ plasma cells and recurrence free after laparoscopic esophagectomy. Similarly, study by Oh et al. [1] and Yang et al. [12] reported masses like lesions in the cervical and lower esophagus with numerous lymphoplasmacytic infiltrates and IgG4+ plasma cells that responded well to steroids therapy. Yakirevich et al. [15] reported specimens of tumor immunoenvironment of esophageal adenocarcinoma following chemoradiotherapy which showed dense lymphoplasmacytic infiltrates, increased IgG4+ plasma cells, and higher IgG4/IgG ratio. The author also stated that increased IgG4+ plasmacytes might be a reliable factor to predict the prognosis in this entity.

Recent studies have also found dense infiltration of lymphoplasmacytes and IgG4+ plasma cells in lamina propria of severe fibrostenotic esophageal lichen planus [16, 17] and in the deep lamina proprial fibrosis in eosinophilic esophagitis [18], which suggests food-specific eosinophilic esophagitis is IgG4-associated not an IgE [19]. In addition, a study by Zukerberg et al. [20] revealed intrasquamous IgG4 deposits in 16 of 21 eosinophilic esophagitis cases concluded that intrasquamous IgG4 deposit is a valuable marker in the area of differentiation between eosinophilic esophagitis and gastroesophageal reflux disease.

IgG4-related esophageal disease should be kept in mind in the differential diagnosis of dysphagic patients presenting with esophageal stricture, ulcer, tumor, or unexplained esophagitis with strictures.

IGG4-Related Gastric Disease

The possible involvement of the gastrointestinal tract with IgG4-RD is known from published studies presenting case reports, case series, and research papers. There is much argument and concerning, however, as to when the diagnosis of IgG4-related disease can be made in case of upper gastrointestinal involvement. Although some of the reported cases are suspected to be not IgG4-RD but mimickers. Moreover, in this study, *isolated gastric IgG4-RD*, *typical gastric IgG4-RD*, and *nontypical gastric IgG4-RD* are categorized in details in the form of “nodular lesions,” “tumefactive lesions,” “ulcerative lesions,” “chronic gastritis,” and “malignant lesions.”

IgG4-Related Gastric Nodular Lesions

Gastric nodular lesions are commonly found during esophagogastroduodenoscopy. It is most frequently associated with *Helicobacter pylori* infection [21], and rarely, gastric nodular lesions are associated with IgG4+ plasmacytes. Baez et al. [22] reported a patient with sialadenitis and AIP, who showed diffusely thickened gastric nodular mucosa with marked IgG4+ counts and elevated serum IgG level. In 1 AIP patient, numerous sporadic polyps with erosion were also observed in the gastric body, presenting with significant counts of IgG4+ plasmacytes [23]. Two patients with fibrotic nodular lesions in gastric fundus and pyloro-antral junction associated Raynaud's disease and autoimmune polyendocrinopathy showed copious IgG4+ plasmacytes [24]. Moreover, Na et al. [25] reported an endoscopically resected 8 mm gastric nodular lesion with marked submucosal fibrosis, a storiform pattern, multiple lymphoid follicles, dense lymphoplasmacytic infiltrates, and diffusely scattered IgG4+ plasmacytes within the lesion as well as elevated IgG4/IgG ratio about 80–90%. Recently, 1 patient reported with bilateral submandibular salivary glands swelling and multiple submucosal tumor-like nodules in the stomach, which showed severe storiform fibrosis, abundant IgG4+ counts, and elevated serum IgG/IgG4 levels. The patient showed an excellent response to steroid therapy [26].

The abundance of IgG4+ plasmacytic infiltration is not uncommon in the GI tract in the setting of AIP [27]. IgG4+ plasmacytic infiltration may also occur within gastric mucosa in other situations. Serum IgG4 concentration is increased in patients with associated AIP [28].

IgG4-Related Gastric Tumefactive Lesions

IgG4-related tumefactive lesion was first reported to be found at various sites in patients with AIP [29, 30] including the liver [31], lungs [32], and pituitary gland [33]. In this condition, levels of serum IgG4 significantly increased. Recently, it's been reported frequently in the stomach, a novel site for this inflammatory pseudotumor subtype [30, 34]. IgG4-RDs are often misdiagnosed since the lesions can mimic tumors and might be misinterpreted clinically and radiologically as a neoplasm [4, 35].

Eleven case presenting studies with IgG4+ gastric tumefactive lesions were analyzed retrospectively. Four patients had solitary tumefactive mass lesions, presenting with increased IgG4+ plasmacytic counts, storiform pattern, and elevated IgG4/IgG ratio in 1 patient [28, 30, 36]. The 2 patients with IgG4+ gastric tumefactive lesions also had histories of Hashimoto's thyroiditis as well as possible primary biliary cirrhosis and autosomal dominant poly-

cystic kidney disease, respectively [34, 37]. Besides, 2 patients had gastric antral wall thickening, one with an adjacent ulcer presenting characteristic for IgG4-RD with an association of IgG4-related skin and lung disease [38] and another with an ulcer-infiltrative tumor in the antrum showing a storiform pattern, obliterative phlebitis, and increased postoperative serum IgG4 level [35]. Furthermore, 2 patients had GIST-like pseudotumors in the gastric body and antrum, revealed copious infiltration of IgG4+ plasmacytes [39, 40]. Inoue et al. [41] observed a solid lesion within the gastric antrum in a patient previously diagnosed with disease involvement of optic neuropathy, dacryoadenitis, periaortitis, retroperitoneal fibrosis, presenting with dense fibrosis, obliterative phlebitis, and increased IgG4+ plasmacytes. Moreover, Seo et al. [5] reported 2 patients, one with gastric cancer and another with a history of idiopathic thrombocytopenic purpura presenting with GIST-like tumors in the gastric body and antrum with abundant IgG and IgG4+ plasmacytes.

Seven of the 11 cases showing a solitary lesion had no sign of multiorgan involvement. Most cases of gastric IgG4+ tumefactive lesions involved the submucosal layer of the stomach. Muscular propria or mucosa was variably involved. All gastric tumefactive lesions were IgG4+, and serum IgG4 was elevated in only 3 patients.

Histologically, inflammatory tumefactive lesions are characterized by an irregular proliferation of myofibroblasts with a surrounding inflammatory cell infiltrates. The IgG4-related inflammatory pseudotumors are characterized by dense infiltration of lymphoplasmacytes, obliterated veins, storiform fibrosis, and IgG4+ plasmacytes. However, the mechanism by which increased IgG4 levels can induce pseudotumor formation is unclear [30, 34].

IgG4-Related Gastric Ulcerative Lesions

IgG4-related gastric ulcers are very uncommon and by the time these diffuse gastric ulcers make scars, fistula [42], fibrosis, and stricture of the gastric lumen [27, 43]. Gastric involvement [22] of IgG4+ ulcers can be found significantly more frequently in patients with AIP [44]. Fujita et al. [27] reported refractory multiple gastric ulcers that worsened after effective *H. pylori* eradication therapy, and biopsy of the lesions showed increased IgG4+ plasmacytes. In addition, 2 patients, one with intractable gastric ulcer that was suspicious for malignant features after antacids regimen failed to improve the ulcer [43] and another with giant gastric ulceration [12], both lesions showed fibrosis, storiform pattern, and significant counts of IgG4+ plasmacytes. Frydman et al. [42] report-

ed a patient with acute gastric-pericardial fistula secondary to an IgG4-related chronic necrotic gastric ulcer. A pathological specimen of complete gastrectomy showed extensive fibrosis with abundant infiltration of IgG4+ plasmacytes. Furthermore, Li et al. [45] reported *H. pylori*+ dual gastric ulcers with surrounding atrophic tissue and enlarged perigastric lymph nodes. The resected tissue showed submucosal fibrosis, dense lymphoplasmacytes, numerous lymphoid follicles, obliterated veins, and higher counts of IgG4+ plasmacytes.

IgG4-RD is an uncommon but potentially causes chronic gastric ulceration [46], mainly when marked fibrosis and lymphoplasmacytes with lymphoid follicles are present within the ulcer and adjacent tissue [43].

IgG4-RD and Autoimmune Gastritis

Autoimmune gastritis is a type of atrophic gastritis that is restricted to the gastric body which causes impaired absorption of vitamin B12 due to the immune destruction of parietal cells in the setting of atrophic gastritis, and as a result, pernicious anemia occurs. IgG4-RD seems to be still controversial [47]. In the histopathological analysis, histopathology is not the gold standard for the diagnosis of IgG4-RD. Several papers warn of overemphasizing the histopathological findings, in particular, IgG4 immunostaining. Strehl et al. [48] analyzed tissue samples from patients with nonspecific chronic inflammatory conditions and found that in several inflammatory conditions such as rheumatoid arthritis, oral cavity lesions, and some kinds of skin disease, copious IgG4+ plasmacytes infiltration was seen. Bedeir et al. [49] examined gastric biopsy specimens of 17 patients with a medical history of chronic atrophic gastritis and pernicious anemia which revealed 5 or more IgG4+ plasmacytes/HPF, and the control group in the study, which was positive for atrophic gastritis and negative for pernicious anemia or *H. pylori* gastritis without pernicious anemia showed no increase in IgG4+ plasmacytes. Besides, patients with pernicious anemia may have increased IgG4+ plasmacytic infiltration in gastric mucosa [25]. Moreover, IgG4+ plasmacytes may play a key role in the pathogenesis of pernicious anemia and can be a useful marker in recognizing a subset of patients with atrophic gastritis who may have pernicious anemia. Uehara et al. [50] reported 13 cases with IgG4-related chronic gastritis and chronic active gastritis-associated AIP. Endoscopic findings of the gastric fundus and pyloric region were remarkable for redness, erosion, atrophy, and thickening of the gastric wall. The IgG4/IgG ratio in the lower lamina propria of the fundic mucosa was significantly higher than

that in the upper lamina propria in patients with both *H. pylori*+ and negative groups, and IgG4/IgG ratio in the lower lamina propria of the pyloric mucosa was significantly higher than that in the upper lamina propria in steroid negative patients. In contrast, Culver et al. [51], examined gastric biopsy specimens in patients with AIP and chronic active gastritis, which contained lymphocytes, neutrophils, macrophages, and mast cells, without other histological characteristics of IgG4-RD. Furthermore, the author also stated that *H. pylori* plasminogen-binding protein has no role as a microbial antigen in IgG4-RD.

IgG4-RD and Gastric Malignancy

IgG4-RD was considered to be a benign disease in previous studies. However, recently, IgG4-RD with concomitant malignancies at different anatomical sites has potentiated growing attention of clinician [46, 52]. IgG4-related gastric malignancy is, however, potentially dangerous mimickers and obviously not a disease that belongs in the spectrum of IgG4-RD. Several researchers have documented that peritumoral IgG4+ plasmacytes infiltration is sometimes present in a variety of cancers, which is called IgG4-reaction [53]. According to Yamamoto et al. [54], malignancies are the possible complication in patients with IgG4-RD, such as gastric signet ring cell carcinoma concurrent with morphologically verified IgG4-RD [55]. Smoking history has found to be a risk factor for IgG4-related concomitant malignancy [56].

Whether IgG4-RD can increase the risk of malignancy remains controversial [10]. Speculation exists that IgG4-RD and AIP represent a premalignant state or paraneoplastic condition [57]. However, no vigorous study has proven these hypotheses [57, 58]. Serum IgG4 levels at the diagnosis of AIP are significantly higher in AIP patients with cancer than in those without cancer [57]. An active IgG4-RD state is supposed to be a strong risk factor for malignancy formation, particularly during the first year after the diagnosis of IgG4-RD [56, 59]. Hirano et al. [60] examined 2 patients with IgG4-related AIP on steroid therapy prior to gastric cancer development. In these patients, the earlier episode of the gastric cancer was counted. Li et al. [61] reported an *H. pylori*+ IgG4-related AIP, as well as *H. pylori*+ early moderately differentiated adenocarcinoma of gastric pylorus with dense lymphoplasmacytes, elevated serum IgG4, and patchy distribution of IgG4+ plasmacytes in the cancer stroma. Inoue et al. [62] reported a patient with a long history of sclerosing cholangitis presented with adenocarcinoma of the gastric antrum, bile duct, pancreas, and kidney lesions. The resect-

ed tissue revealed dense lymphoplasmacytic infiltrates with lymph follicles, increased IgG4+ plasmacytes, and elevated IgG4/IgG ratio: 81.5%. However, typical storiform fibrosis and obliterative phlebitis, which are characteristic histological findings of IgG4-RD, were not noticed. Horita et al. [63] reported a patient with IgG4-related submandibular gland, lymph node, lung, kidney, aortic wall, and prostate lesions with concomitant gastric cancer. The distal gastrectomy showed significant IgG4+ plasmacytes and high serum IgG and IgG4 level. This suggests that the stomach can also be a site of involvement of IgG4-RD. Although a study by Shiokawa et al. [57] showed 2 patients with gastric cancer and IgG4-RD who had many IgG4+ plasmacytes infiltrates around the tumor cells, they do not consider the stomach to be one of the affected organs of IgG4-RD in these patients.

Moreover, malignancies as complications to IgG4-RD are categorized as lymphoma and nonlymphoid tumors. Lymphoma presents a background of chronic inflammation and includes mucosa-associated lymphoid tissue lymphoma and non-Hodgkin lymphoma [54, 63]. The overall incidence of malignancy in patients with IgG4-RD is 23 times higher than that in the general population [64]. Lymphadenopathy commonly exists in IgG4-RD; it can appear before, concurrent with, or after the diagnosis of this disease, which is characterized by tumefactive lesions mainly affecting extranodal sites [65]. According to Ahn et al. [64], lymphoma is the most common malignancy associated with IgG4-RD. The risk and incidence of malignancy in patients with non-Hodgkin lymphoma are severely high for all periods of diagnosis of IgG4-RD [64]. Moreover, long-term chemotherapy for B cell lymphoma may cause IgG4-RD [66].

Diagnostic Criteria

The diagnostic guideline for IgG4-RD and IgG4-related other organ involvement is complex and usually requires a combination of clinicopathological correlation, imaging, and serological analyses [46]. Difficult preoperative diagnosis of gastroesophageal IgG4-RD may require a full thickness biopsy and review biopsy samples that obtained earlier to prevent unwarranted surgeries. IgG4-RDs are often misdiagnosed; any undiagnosed mass concerning symptoms should be verified with the biopsy; however, tissue diagnosis is still mandatory. The IgG4 levels alone are actually not as beneficial as its elevation observed in the list of other diseases. Moreover, magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography have shown usefulness for detecting multiorgan involvement [47, 63, 67]. Based on the con-

Fig. 1. IgG4-related disease diagnostic criteria. IgG4-RD, immunoglobulin G4-related disease; EGD, esophagogastroduodenoscopy.

sensus statement [68], 4 minimal criteria were proposed for IgG4-RD involvements of new organs: (1) characteristic histologic findings (particularly storiform fibrosis and obliterative phlebitis), increased IgG4+ plasmacytes and IgG4/IgG+ ratio; (2) high serum IgG4 level; (3) an effective response to corticosteroid; (4) coexistence of other organ involvements with IgG4-RD. A definite diagnosis of IgG4-RD can be made by a combination of comprehensive diagnostic criteria and organ-specific criteria – *Possible diagnostic criteria* and *Probable diagnostic criteria* [69] (Fig. 1). However, these criteria did not include the concept of IgG4-RD restricted to the gastrointestinal tract.

Treatment

The treatment approaches for gastroesophageal involvements of IgG4-RD are either medicinal or surgical. Thus, appropriate treatment strategies for gastroesophageal IgG4-RD are mandatory by the physicians, especially gastroenterologists.

In 2015, International Consensus Guidelines for therapeutic purposes of IgG4-RD was published. The first-line treatment strategy for IgG4-RD management consists of corticosteroids administration. If persistently active disease other immunosuppressants such as azathioprine or mycophenolate mofetil may be administered [70]. The effect of corticosteroids is so overwhelming that it has been suggested as one diagnostic criterion for the disease [4]. However, patients with mild disease or without the involvement of significant organs may remain under observation. Biologics, such as rituximab, may be an appropriate choice for patients contraindicated with corticosteroids [70]. Besides, biologics are effective for the relapses of IgG4-RD [47].

However, due to solid lesions and ulcerations raising suspicions of malignant conditions, the majority of patients underwent surgery. High-incidence of IgG4-RD manifested by inflammatory tumors was observed in the review, awareness of doctors should be raised to avoid unnecessary surgical treatment [25, 30, 34].

In relation to most of the gastroesophageal lesions, cases of patients were reported with esophageal ulceration and stricture, gastric mucosal ulceration, inflammatory pseudotumors, and gastroesophageal wall thickening developing in the course of IgG4-RD and respond excellently to corticosteroids treatment.

In this aspect, however, further studies are required.

A careful observation of patients over time is also required because the characteristics of IgG4-RD may develop further lesions in other organs in later years [2, 3].

Conclusions

IgG4-RD is a recently recognized clinical entity characterized by inflammatory and fibrotic courses. IgG4-RD with gastroesophageal involvement may be manifested by isolated, typical, and nontypical lesions; however, some lesions are suspected to be not IgG4-RD but mimickers and should be taken into consideration in differential diagnosis. Making an ultimate diagnosis without clinicopathological and serological examination appears to be difficult and can lead to misdiagnosis. Moreover, deep mucosal biopsy and evaluation of previously obtained biopsy samples are crucial to avoid inappropriate treatment. IgG4-RD responds well to steroid therapy and suggested as one diagnostic criterion for the disease. However, on this matter, further studies are required.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

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Author Contributions

All the persons who have made substantial contributions to the work reported in the manuscript, their names declared in the author list. The author S.K.: contributed to the paper in writing, data collection, data analysis, and manuscript preparation.” L.P.Z., K.J., and W.L.: contributed in literature search and in the definition of intellectual content. X.C. and B.M.W.: contributed to the study concept, design, manuscript editing, and manuscript review. All authors read and approved the final manuscript.

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