*Original article*

Title: Utility of gastric biopsy in diagnosing IgG4-related gastrointestinal disease

Authors:

Kaori Uchino[1,2], Kenji Notohara[2*], Takeshi Uehara[3], Yasuhiro Kuraishi[4], Junya Itakura[2], Akihiro Matsukawa[1*]

Both Kenji Notohara and Akihiro Matsukawa are corresponding authors of this manuscript.

Affiliations:

[1]Department of Pathology and Experimental Medicine, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

[2]Department of Anatomic Pathology, Kurashiki Central Hospital, Kurashiki, Japan

[3]Department of Laboratory Medicine, Shinshu University School of Medicine, Matsumoto, Japan

[4]Department of Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

* These two authors are responsible for correspondence of this work.

Running title:

IgG4-RD diagnosis with gastric biopsy

Abbreviations:

AIP, autoimmune pancreatitis; BHP, bottom-heavy plasmacytosis; GI, gastrointestinal; *HP*, *Helicobacter pylori*; HPF, high-power field; Ig, immunoglobulin; IgG4-GID, IgG4-related gastrointestinal disease; IgG4-RD, IgG4-related disease; MALT lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; MLP, mucosal lamina propria; SMT, submucosal tumor

Correspondence:

Kenji Notohara, MD, PhD, Department of Anatomic Pathology, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama 710-8602, Japan

Email: notohara@kchnet.or.jp

Akihiro Matsukawa, MD, PhD, Department of Pathology and Experimental Medicine, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kitaku, Okayama 700-8558, Japan

Tel.: +81-86-235-7143, Fax: +81-86-235-7148

Email: amatsu@md.okayama-u.ac.jp

ABSTRACT

The utility of gastric biopsy for diagnosing IgG4-related gastrointestinal disease (IgG4-GID) remains unclear. Bottom-heavy plasmacytosis (BHP) is a distinct feature of IgG4-GID. To clarify the feasibility of using gastric biopsies to diagnose BHP in IgG4-GID, we analyzed the histological features and immunostaining of gastric biopsy specimens from 31 known IgG4-related disease (IgG4-RD) patients and we assessed the presence of BHP in 1,696 consecutive routine gastric biopsies. Cases with both >10 IgG4-positive plasma cells per high-power field and an IgG4/IgG-positive ratio >40% were defined as IgG4-high. Ten of the 31 IgG4-RD patients were concluded to have IgG4-GID, in which IgG4-positive plasma cells were notably detected at the deeper part of the mucosa. Six cases displayed BHP whereas the remaining four cases showed transmural infiltration with concomitant *Helicobacter pylori*-associated gastritis. In addition to BHP, we identified two unique histologic features for IgG4-GID: plasmacytic aggregation in the muscularis mucosae and permeative plasmacytic infiltration between fundic glands in the non-atrophic mucosa. Six of the routine cases (0.35%) displayed BHP, including a case with IgG4-RD. IgG4-GID can be suspected by the presence of gastric biopsy specimens with characteristic histological features. Such cases are recommended to undergo further examinations to determine whether IgG4-RD is present.

KEYWORDS

Biopsy, feasibility studies, gastritis, gastric mucosa, IgG4, IgG4-related disease, immunoglobulin G4, immunohistochemistry, plasma cells

## INTRODUCTION

IgG4-related disease (IgG4-RD) is a systemic inflammatory condition of unknown etiology characterized by elevated serum IgG4 levels and the infiltration of numerous IgG4-positive plasma cells in affected organs. IgG4-related gastrointestinal (GI) disease (IgG4-GID) is rare, but it has been reported anecdotally. In fact, various clinical manifestations, such as ulcerations,[1-5] polyps,[6-8] wall thickening,[9-16] submucosal tumors (SMTs),[17-27] GI obstruction,[28-30] vasculitis,[31] fistulas,[32, 33] and the infiltration of IgG4-positive plasma cells without morphologic abnormalities,[34] have been reported in IgG4-GID. As a matter of fact, most cases of IgG4-GID do not exhibit other organ involvement as observed in IgG4-RD cases; thus, it is unlikely that all these cases represent genuine IgG4-GID. Especially, the infiltration of IgG4-positive plasma cells has also been shown in several IgG4-unrelated GI diseases including inflammatory bowel disease, celiac disease, Rosai-Dorfman disease, and Cronkhite-Canada syndrome.[35-37] Storiform fibrosis and obliterative phlebitis are helpful histological features for diagnosing IgG4-RD, but they are not commonly found in reported IgG4-GID cases.

Two histological findings, striated inflammatory lesions in the muscularis propria and bottom-heavy plasmacytosis (BHP) in the mucosal lamina propria (MLP), were recently reported as characteristic features of IgG4-GID in surgically resected specimens of patients with known IgG4-RD.[38] BHP displays a unique inflammatory pattern in which plasma cells primarily infiltrate the bottom to middle portion of the MLP, which is distinct from *Helicobacter pylori* (*HP*)-associated gastritis, which predominantly displays plasmacytic infiltration into the superficial portion of the MLP.

To date, the utility of gastric biopsy for diagnosing IgG4-GID has not been fully studied. Several studies have reported the infiltration of IgG4-positive plasma cells in gastric

biopsy specimens from IgG4-RD patients, mainly those with type 1 autoimmune pancreatitis (AIP).[39-46] However, mere infiltration of IgG4-positive plasma cells is currently considered nonspecific and worthless for the diagnosis of IgG4-GID. We speculate that gastric biopsy may be beneficial for the diagnosis of IgG4-GID in cases where histological (BHP) and immunohistochemical analyses are consistent. Uehara and colleagues reported a study supporting a similar view by observing diffuse or deeper mucosal infiltration of mononuclear cells and IgG4-positive plasma cells in the deeper portion of the MLP in gastric biopsy specimens from AIP patients.[44]

To clarify the feasibility of using gastric biopsies to diagnose BHP in IgG4-GID, we analyzed gastric biopsy specimens from known IgG4-RD patients. We also evaluated consecutive routine cases throughout the year to clarify the frequency and specificity of BHP observed in gastric biopsies.

## MATERIALS AND METHODS

This study was approved by the Ethical Review Boards of Kurashiki Central Hospital (KCH) and Shinshu University and was performed in accordance with the ethical standards of the Declaration of Helsinki. The acquisition of patients' informed consent was waived, but an opt-out policy was used.

### Case selection for retrospective evaluation of gastric biopsy specimens of patients with known IgG4-RD

The pathological and clinical databases from KCH were searched for IgG4-RD patients who visited the hospital between 2009 and 2019. The diagnosis of IgG4-RD was considered definite or probable based on comprehensive diagnostic criteria[47] or organ-

specific diagnostic criteria for AIP, IgG4-related sialadenitis, IgG4-related sclerosing cholangitis, and IgG4-related kidney disease.[48-51] Among the identified patients, we selected those who had undergone gastric biopsy or endoscopic resection procedures. We also included below-mentioned cases which were a part of the prospective serial evaluation as applicable. Clinical data were gathered by chart reviews. Cases from Shinshu University Hospital (SUH) were similarly selected from the clinical records between 2008 and 2014.

IgG4 (mouse monoclonal antibody, MRQ-44, prediluted; Cell Marque corporation, Rocklin, CA, USA; The binding site, Birmingham, UK) and IgG (rabbit polyclonal, prediluted; Cell Marque corporation; Dako, Glostrup, Denmark) were immunostained with autostainer (Ventana BenchMark ULTRA; Ventana Medical Systems, Inc., Tucson, AZ, USA) or manually. The numbers of IgG4-positive plasma cells and IgG-positive plasma cells per high power field (HPF) were counted at a hot spot of IgG4-positive plasma cells. Cases satisfying both >10 IgG4-positive plasma cells/HPF and an IgG4/IgG-positive ratio >40% criteria were defined as IgG4-high. Cases with ≤10 IgG4-positive plasma cells/HPF or an IgG4/IgG-positive ratio of ≤40% were defined as IgG4-low.

**Control case selection**

To serve as a control, we selected gastric biopsy specimens of chronic gastritis and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), both of which often reveal a numerous plasmacytic infiltration in gastric biopsies. Forty consecutive biopsies with chronic gastritis that contained more than 30 plasma cells per HPF were selected from the same routine gastric biopsy series as the

prospective study. Twelve MALT lymphoma cases with marked plasmacytic infiltration among 30 MALT lymphoma cases diagnosed in KCH between 2015 and 2019 were included. The monoclonality of plasma cells was confirmed by immunostaining of kappa (rabbit polyclonal antibody, 1:10,000; Dako) and lambda (rabbit polyclonal antibody, 1:20,000; Dako) in MALT lymphoma cases. IgG4 and IgG-positive cells per HPF were similarly evaluated to the IgG4-RD cases.

**Histological and immunohistochemical analysis of the IgG4-RD and the control cases**

Slides stained with hematoxylin and eosin were reviewed by three pathologists (KU, KN, and JI) and were classified into one of the following four patterns of inflammation: 1) BHP with plasma cells aggregated at the supra-muscularis mucosae region but not at the superficial portion, 2) transmural inflammation with uniform plasmacytic infiltration throughout the MLP, 3) superficial inflammation with plasmacytic infiltration limited in the sub-foveolar mucosal region, and 4) minimal inflammation with low numbers (<20/20,000 $\mu m^2$) of plasma cells. The three pathologists separately determined the inflammation pattern for each case. In cases of disagreement, a consensus was reached by observing the slides together with a multi-headed microscope. The classification of inflammation patterns was not applied to the MALT lymphoma cases. Presence of the aggregation of plasma cells (more than 5 cells) in the muscularis mucosae, presence of the permeation of plasma cells between the non-atrophic fundic glands and eosinophil counts per HPF were recorded. The numbers of IgG4-positive plasma cells and IgG-positive plasma cells per 20,000 $\mu m^2$ were counted separately at the superficial (sub-foveolar regions) and deeper (supra-muscularis mucosae region) parts of the mucosa. Of

note, using an objective lens with an ocular field number of 26.5, the area per HPF is 344,716 $\mu m^2$.

**Prospective evaluation for BHP in consecutive gastric biopsy specimens obtained throughout a one-year period**

All gastric biopsy specimens submitted between June 2018 and May 2019 at KCH were prospectively evaluated by two pathologists, KN and JI, to identify cases with BHP. Specimens with neoplastic diseases were excluded. Clinical chart reviews were performed for cases with BHP. The plasmacytic aggregation in the muscularis mucosae, the permeation of plasma cells between the non-atrophic fundic glands, and eosinophil counts per HPF were recorded. The IgG4-positive plasma cells and IgG-positive plasma cells per HPF were similarly counted to the IgG4-RD cases.

**Statistical analysis**

The Mann-Whitney U-test was used to compare continuous variables between two independent groups. Fisher's exact test was used to test the association between two variables. The statistical analyses were performed using R. Probability (p)-values of $<0.05$ were considered statistically significant.

## RESULTS

**Retrospective evaluation of gastric biopsy specimens of patients with known IgG4-RD**

We collected 51 gastric biopsy specimens and 2 endoscopic resection specimens (42 from KCH and 11 from SUH) from 31 IgG4-RD patients (20 from KCH and 11 from SUH).

Four specimens with only gastric cancer tissue were excluded. The clinical profiles of these patients are summarized in Table 1. One case was a solitary gastric lesion with striated inflammation in the muscularis propria observed in the surgical specimen of gastric cancer; the case was definitively diagnosed with IgG4-RD based on the comprehensive diagnostic criteria. Most of the biopsies were performed to rule out malignancy. In three cases, endoscopy revealed SMTs, but the lesions were not evaluated further nor were they surgically excised. Other lesions, such as thickened muscularis propria or inflammatory pseudotumor, which were previously reported in IgG4-GID cases[38] were not detected.

Six cases were excluded from the immunohistochemical evaluation due to an artificial crushing of plasma cells or background staining (Table 2).[52] Ten of the 25 cases with satisfactory immunohistochemical results were classified as IgG4-high (Table 3).

BHP was identified in nine cases (Fig. 1a). Two of those nine cases partly showed a transmural inflammation pattern as well. Furthermore, a transmural pattern was noted in 14 other cases (Fig. 1c1482, 2a). A superficial inflammation pattern that was consistent with *HP*-associated chronic gastritis was identified in two cases (Fig. 2c, d). The remaining six cases displayed a minimal inflammation pattern. *HP*-negative cases tended to show BHP whereas *HP*-positive cases tended to display a transmural inflammation pattern (Table 2). No storiform fibrosis or obliterative phlebitis were detected in any of the specimens.

**IgG4-high cases**

The average number of IgG4-positive plasma cells was 50.9/HPF (range 13–72/HPF), and the average IgG4/IgG-positive ratio was 80.7% (range 44.8–127.7%). Histologically,

the IgG4-high cases showed BHP (six cases, including one case which partially displayed transmural inflammation) or transmural inflammation pattern (four cases). However, in both groups, IgG4-postive plasma cells infiltrated the deeper mucosa (average 19.16/20,000 $\mu m^2$) rather than the superficial mucosa (average 1.77/20,000 $\mu m^2$) ($p < 0.001$) (Fig. 1b, d). There was marked infiltration of IgG4-positive plasma cells throughout the deeper MLP in nine cases; however, the infiltration was patchy in the remaining case. Corticosteroid therapy had not been administrated in all of the cases.

Seven of the 31 IgG4-RD cases showed plasmacytic aggregation within the muscularis mucosae (Fig. 1e). All of the seven but one case with unsatisfactory immunostaining were classified as IgG4-high, and plasma cells in the muscularis mucosae were IgG4-positive. The permeation of plasma cells between fundic glands (Fig. 1f) was observed in three cases. These three cases were all classified as IgG4-high, and plasma cells permeating the fundic glands were IgG4-positive.

There were significantly more eosinophils (50.6 ± 21.3/HPF, range 15–86/HPF) in the IgG4-high cases (Fig. 1a, e, f) than in the IgG4-low cases (26.8 ± 12/HPF, range 0–67/HPF) ($p < 0.05$), in the control chronic gastric cases (14.1 ± 11.8/HPF, range 0–54/HPF) ($p < 0.001$), or in the MALT lymphoma cases (17.9 ± 16.9/HPF, range 3–55/HPF) ($p < 0.05$).

**IgG4-low cases**

By contrast to the IgG4-high cases, the 15 IgG4-low cases revealed primarily transmural inflammation (eight cases), followed by minimal inflammation (six cases) and BHP (one case, which also partially displayed transmural inflammation) (Supplementary Table 1). There were few IgG4-positive plasma cells in the eight cases with transmural

inflammation (average of 3.75, range 0–9/HPF) (Fig. 2b) and in the six cases with a minimal inflammation pattern (0–6/HPF). IgG4-postive plasma cells infiltrated the deeper mucosa (average 1/20,000 $\mu m^2$) were not significantly different to the superficial mucosa (average 0.53/20,000 $\mu m^2$) ($p = 0.72$). The IgG4-low case with a BHP pattern (case L1, Supplementary Table 1), in which 12 IgG4-positive plasma cells per HPF, and 30.7% of IgG4/IgG-positive ratio were present, was receiving corticosteroid therapy. All three cases that were taken under corticosteroid therapy were classified as IgG4-low.

**Chronic gastritis cases**

All of the 40 cases showed endoscopic features that were compatible with *HP*-associated atrophic gastritis. Twenty-five and 15 cases displayed transmural and superficial inflammation. The average number of IgG4-positive plasma cells was low ($1.7 \pm 7$/HPF, range 0–31). There were more than 10 IgG4-positive plasma cells/HPF in two cases (5.0%), but the IgG4/IgG-positive ratio was low (average 25%). IgG4-postive plasma cells infiltrated the deeper mucosa (average 0.725/20,000 $\mu m^2$) were not significantly different to the superficial mucosa (average 0.725/20,000 $\mu m^2$) ($p = 0.4$). The plasmacytic aggregation in the muscularis mucosae was significantly rare compared with IgG4-high cases (1/40 cases, $p < 0.01$). Non-atrophic fundic gland mucosa was rarely observed (4/40 cases). The permeative infiltration was not detected.

**MALT lymphoma cases**

Five of the 12 MALT lymphoma cases exhibited light-chain restriction of plasma cells. Neoplastic plasma cells showed transmural infiltration that was intermingled with centrocyte-like lymphoma cells, while non-neoplastic plasma cells mainly infiltrated the

superficial portion of the MLP. IgG4-positive plasma cells were rarely observed (average 1.8 ± 1.9/HPF, range 0–7/HPF). IgG4-postive plasma cells infiltrated the deeper mucosa (average 0.83/20,000 $\mu m^2$) were not significantly different to the superficial mucosa (average 0.33/20,000 $\mu m^2$) ($p = 0.44$). The plasmacytic aggregation in the muscularis mucosae was not observed ($p < 0.001$, compared with IgG4-high cases). Fundic glands were atrophic in all the specimens, and the permeative plasmacytic infiltration was absent.

**Prospective evaluation for BHP in consecutive gastric biopsy specimens obtained throughout a one-year period**

Between June 2018 and May 2019, 2,169 endoscopic gastric biopsy examinations were performed in KCH, out of which 473 were excluded due to neoplastic diseases. In total, BHP was found in 6/1,696 (0.35%) examinations.

Our subsequent analyses revealed that 4 of the 1,696 examinations had IgG4-RD, which were included in the retrospective analyses. One of the four cases was determined to exhibit BHP in the prospective study (case 6). One another case (case L1, Supplementary Table 1) was reclassified as BHP during the review of IgG4-RD cases but was not identified in the prospective study because of the lower number of plasma cells. The remaining two cases included superficial inflammation with unsuccessful immunostaining in one case and minimal inflammation in one case, which was classified as an IgG4-low case (case L10).

Finally, five cases were confirmed as BHP without IgG4-RD (Table 4). Two patients had a history of malignant lymphoma, but they were in a remission state when the biopsy was performed. Other two patients had no specific medical history. There were few IgG4-positive plasma cells in these four cases (0–2/HPF). The remaining case with a positive

cytomegalovirus immunostaining had a focus that fulfilled the IgG4-high criteria (41/HPF, IgG4/IgG-positive ratio of 45.5%). Similar to IgG4-RD patients, IgG4-positive plasma cells infiltrated the deeper portion of the MLP, but were localized in a small focus (Fig. 3b, c). This patient had no evidence of immunodeficiency. In addition to BHP, the specimens showed neutrophilic infiltration, granulation tissue, and necrosis, which are features inconsistent with IgG4-RD (Fig. 3a). Plasmacytic aggregation in the muscularis mucosae, storiform fibrosis or obliterative phlebitis were not detected. Non-atrophic fundic glands were absent. Eosinophilic infiltration was not significantly different from that observed in the IgG4-high cases (53.6 ± 22.4/HPF, range 26–80/HPF) ($p = 0.85$).

## DISCUSSION

BHP was recently reported to be characteristic of IgG4-GID based on examinations of surgically resected specimens of patients with known IgG4-RD.[38] This observation prompted us to examine whether a gastric biopsy could identify BHP and contribute to the diagnosis of IgG4-RD. Uehara and colleagues had previously conducted a similar study in patients with AIP and found that mononuclear cells and IgG4-positive plasma cells had infiltrated the deeper portion of the MLP, which might be similar to BHP.[44] In this study, we analyzed histological features in detail by evaluating gastric biopsy specimens of patients with IgG4-RD. We also examined whether there were mimickers of BHP by observing consecutive gastric biopsy series.

We confirmed that BHP was characteristic of IgG4-RD in gastric biopsy specimens in this study. However, it was often difficult to evaluate BHP in biopsy specimens because of disoriented sectioning. Thus, we applied the criteria of the aggregation of plasma cells at the supra-muscularis mucosae region with minimal superficial plasmacytic infiltration

for the identification of BHP. In the retrospective evaluation of IgG4-RD patients, six out of seven cases with BHP fulfilled the criteria for IgG4-high. The only BHP case that fell into the IgG4-low group was receiving steroid therapy.

*HP* infection, which is the most common cause of gastritis and often coexists with IgG4-GID. In fact, *HP* infection was present in half of the IgG4-high cases in this study. Histologically, 4 of these cases displayed a transmural inflammation pattern. However, immunostaining of IgG4 indicated the presence of bottom-heavy IgG4-positive plasmacytosis in those specimens, suggesting that BHP was concealed by coexisting *HP*-associated gastritis. Pure *HP*-associated gastritis may show a transmural inflammation pattern, but the immunostaining was classified as IgG4-low. IgG4-positive plasma cells were rarely found in the 40 control cases of chronic gastritis and 12 cases of MALT lymphoma, and no cases fulfilled the criteria for IgG4-high. Although it is difficult to identify BHP in *HP*-associated gastritis settings, we suggest that immunostaining can be used to highlight BHP and can contribute to the diagnosis of IgG4-RD.

We detected two unique histological features that might be useful for diagnosing IgG4-RD: the plasmacytic aggregation in the intra-muscularis mucosae and the permeation of plasma cells between non-atrophic fundic glands. These two features were observed in cases with BHP or transmural inflammation patterns with IgG4-high immunohistochemistry, while they were rare in the control cases.

Marked eosinophilic infiltration was another frequent and characteristic feature of the IgG4-high cases. However, we emphasize that the presence of eosinophils in the deeper part of the mucosa itself is nonspecific as it was also observed in cases with BHP without the clinical evidence of IgG4-RD.

We only detected one case of BHP representing IgG4-RD among 1,696 consecutive

non-neoplastic gastric biopsies. Although BHP was identified in five other non-IgG4-RD cases, additional features that were inconsistent with IgG4-RD, such as transmural infiltration of neutrophils, granulation, and necrosis, were also evident. Plasma cells did not aggregate in the muscularis mucosae. One of the five cases that was found to have a cytomegalovirus infection was classified as IgG4-high, but the patient revealed localized IgG4-positive cell infiltration. Thus, immunostaining alone is not sufficient to suggest IgG4-RD, and a histological evaluation, including the exclusion criteria, is necessary for diagnosis. In addition, due to the small number of cases, significance of the cut-off value of IgG4-positive cells could not be verified in this study, and further studies are necessary.

MALT lymphoma is included in the differential diagnosis of gastric IgG4-GID due to the presence of numerous plasma cells, which may be monoclonal or polyclonal. Although IgG4-positive cells were rare in our series, IgG4-producing MALT lymphoma has been reported in the ocular adnexa or the cutis,[53, 54, 55] MALT lymphoma must be carefully distinguished even in cases with numerous IgG4-positive cells.

Endoscopic findings of the biopsy sites were variable. We speculate that these findings are simply motivators for biopsy and that IgG4-GID is a bystander, considering that IgG4-GID was detected even by random biopsies. In other words, characteristic wall-thickening and mass-forming lesions were absent in the stomach, and presence of numerous IgG4-positive cells in the deeper part of the mucosa alone may not be sufficient to make the diagnosis of IgG4-GID. Even so, as mentioned above, BHP is useful to identify possible IgG4-RD cases with a gastric biopsy. When such mucosal lesions are incidentally identified in a gastric biopsy, further imaging and clinical evaluations for possible IgG4-RD are recommended. Of note, gastric biopsies should be taken before starting

corticosteroid treatment because all the patients receiving corticosteroid therapy were IgG4-low in our series.

In conclusion, IgG4-GID can be diagnosed using gastric biopsy specimens. The infiltration of plasma cells into the deeper portion of the MLP with IgG4-immunoreactivity is an essential feature of this disease. Plasma cell in the muscularis mucosae and/or permeative plasma cell infiltration between fundic glands is also helpful for diagnosis. There are mimickers of IgG4-related BHP, but they can be distinguished from IgG4-GID by exclusive histological features and IgG4 immunostaining. Although IgG4 immunostaining is important for the diagnosis of IgG4-GID, diagnosing IgG4-GID by immunostaining alone is not recommended.

ACKNOWLEDGEMENTS

This work was supported by MHLW Research Program on Rare and Interactable Disease Grant Number JPMH20FC1040. The authors would like to thank Enago (www.enago.jp) for the English language review.

DISCLOSURE STATEMENT

None declared.

AUTHOR CONTRIBUTIONS

KU designed the study, collected and analyzed data, and drafted the manuscript. KN conceived, designed, and supervised the study and analyzed data. TU and YK contributed the specimens and collected data. JI designed the study and collected and analyzed data. AM generally supervised the study. All of the authors critically reviewed the drafts and

approved the manuscript's final version.

References


1. Fujita T, Ando T, Sakakibara M, Hosoda W, Goto H. Refractory gastric ulcer with abundant IgG4-positive plasma cell infiltration: A case report. World J Gastroenterol 2010; 16: 2183–6.
2. Fujita K, Naganuma M, Saito E. Histologically confirmed IgG4-related small intestinal lesions diagnosed via double balloon enteroscopy. Dig Dis Sci 2012; 57: 3303–6.
3. Wong DD, Pillai SR, Priyanthi KM et al. IgG4-related sclerosing disease of the small bowel presenting as necrotizing mesenteric arteritis and a solitary jejunal ulcer. Am J Surg Pathol 2012; 36: 929–34.
4. Deng X, Fang R, Zhang J, Li R. Multivisceral IgG4-related disease presenting as recurrent massive gastrointestinal bleeding: A case report and literature review. BMC Gastroenterol 2018; 18: 136.
5. He YQ, Fu X, Chen DF. Rare cause of severe hematemesis due to IgG4-related gastric ulcer. Turk J Gastroenterol 2019; 30: 925–7.
6. Kaji R, Okabe Y, Ishida Y et al. Autoimmune pancreatitis presenting with IgG4-positive multiple gastric polyps. Gastrointest Endosc 2010; 71: 420–2.
7. Chetty R, Serra S, Gauchotte G, Märkl B, Agaimy A. Sclerosing nodular lesions of the gastrointestinal tract containing large numbers of IgG4 plasma cells. Pathology 2011; 43: 31–5.
8. Rollins KE, Mehta SP, O'Donovan M, Safranek PM. (2011), Gastric IgG4-related autoimmune fibrosclerosing pseudotumour: A novel location. ISRN Gastroenterol. doi:10.5402/2011/873087.
9. Baez JC, Hamilton MJ, Bellizzi A, Mortelé KJ. Gastric involvement in

autoimmune pancreatitis: MDCT and histopathologic features. J Pancreas 2010; 11: 610–3.

10. Hiyoshi Y, Oki E, Zaitsu Y et al. IgG4-related disease of the ileocecal region mimicking malignancy: A case report. Int J Surg Case Rep 2014; 5: 669–72.
11. Oh JH, Lee TH, Kim HS et al. Esophageal involvement of immunoglobulin G4-related disease: A case report and literature review. Medicine (Baltimore) 2015; 94: e2122.
12. Kawano H, Ishii A, Kimura T et al. IgG4-related disease manifesting the gastric wall thickening. Pathol Int 2016; 66: 23–8.
13. Bulanov D, Arabadzhieva E, Bonev S et al. A rare case of IgG4-related disease: A gastric mass, associated with regional lymphadenopathy. BMC Surg 2016; 16: 37.
14. Inoue K, Okubo T, Kato T et al. IgG4-related stomach muscle lesion with a renal pseudotumor and multiple renal rim-like lesions: A rare manifestation of IgG4-related disease. Mod Rheumatol 2018; 28: 188–92.
15. Lim DY, Cheng LTE, Tan DMY, Al Jajeh I. Isolated IgG4-related gastric disease presenting as diffuse gastric wall thickening with ulcer. J Radiol Case Rep 2018; 12: 9–20.
16. Dias AB, Horvat N, Begnami MD, Abe ES, Viana PCC, Machado MCC. Case report of IgG4-related appendiceal disease: A challenging disease. Medicine (Baltimore) 2020; 99: e20588.
17. Kim DH, Kim J, Park DH et al. Immunoglobulin G4-related inflammatory pseudotumor of the stomach. Gastrointest Endosc 2012; 76: 451–2.
18. Na KY, Sung JY, Jang JY et al. Gastric nodular lesion caused by IgG4-related

disease. Pathol Int 2012; 62: 716–8.

19. Ramakrishna B, Yewale R, Vijayakumar K, Radhakrishna P, Ramakrishna BS. Gastric IgG4-related disease presenting as a mass lesion and masquerading as a gastrointestinal stromal tumor. J Pathol Transl Med 2020; 54: 258–62.

20. Choi SB, Lim CH, Cha MG, Kang WK. IgG4-related disease of the rectum. Ann Surg Treat Res 2016; 90: 292–5.

21. Otsuka R, Kano M, Hayashi H et al. Probable IgG4-related sclerosing disease presenting as a gastric submucosal tumor with an intense tracer uptake on PET/CT: a case report. Surg Case Rep 2016; 2: 33.

22. Woo CG, Yook JH, Kim AY, Kim J. IgG4-related disease presented as a mural mass in the stomach. J Pathol Transl Med 2016; 50: 67–70.

23. Cheong HR, Lee BE, Song GA, Kim GH, An SG, Lim W. Immunoglobulin g4-related inflammatory pseudotumor presenting as a solitary mass in the stomach. Clin Endosc 2016; 49: 197–201.

24. Seo HS, Jung YJ, Park CH, Song KY, Jung ES. IgG4-related disease in the stomach which was confused with Gastrointestinal Stromal Tumor (GIST): Two case reports and review of the literature. J Gastric Cancer 2018; 8: 99–107.

25. Inoue D, Yoneda N, Yoshida K et al. Imaging and pathological features of gastric lesion of immunoglobulin G4-related disease: A case report and review of the recent literature. Mod Rheumatol 2019; 29: 377–82.

26. Mine S, Ozawa E, Ohnita K, Abe K, Nakao K. A case of IgG4-related disease presenting with multiple gastric submucosal tumors. Gastrointest Endosc 2018; 87: 608–10.

27. Yamane T, Eto K, Morinaga T et al. IgG4-related disease presenting as a

submucosal tumor of the stomach resected with laparoscopic endoscopic cooperative surgery: a case report. Surg Case Rep 2020; 6: 93.

28. Coulier B, Montfort L, Beniuga G, Pierard F, Gielen I. Small bowel obstruction caused by peritoneal immunoglobulin G4-related disease mimicking carcinomatosis: Case report. Korean J Radiol 2014; 15: 66–71.

29. Abe A, Manabe T, Takizawa N et al. IgG4-related sclerosing mesenteritis causing bowel obstruction: a case report. Surg Case Reports 2016; 2: 120.

30. Syu KJ, Wang HY, Chang YY. (2020), Immunoglobulin G4-related disease mimicking malignant bowel obstruction. Clin Gastroenterol Hepatol. doi:10.1016/j.cgh.2020.04.065.

31. Comtesse S, Friemel J, Fankhauser R, Weber A. Enterocolic lymphocytic phlebitis of the cecal pole and appendix vermiformis with increase of IgG4-positive plasma cells. Virchows Arch 2014; 464: 113–6.

32. Frydman J, Grunner S, Kluger Y. IgG4-related disease manifesting as an acute gastric-pericardial fistula. World J Gastroenterol 2014; 20: 16782–5.

33. Bohlok A, Khoury M El, Tulelli B et al. A rare presentation of IgG4 related disease as a gastric antral lesion: Case report and review of the literature. Int J Surg Case Rep 2018; 51: 244–7.

34. Li M, Zhou Q, Yang K et al. Rare case of Helicobacter pylori-positive multiorgan IgG4-related disease and gastric cancer. World J Gastroenterol 2015; 21: 3429–34.

35. Faria RJ, Clemente CM, Carneiro FP, Santos-Neto L. Can IgG4 levels identify the ulcerative colitis subtype of inflammatory bowel disease? Gastroenterol Res 2015; 8: 178–85.

36. Zhao M, Li C, Zheng J et al. Case Report Extranodal Rosai-Dorfman disease involving appendix and mesenteric nodes with a protracted course: report of a rare case lacking relationship to IgG4-related disease and review of the literature. Int J Clin Exp Pathol 2013; 6: 2569–77.

37. Fan R-Y, Wang X-W, Xue L-J, An R, Sheng J-Q. Cronkhite-Canada syndrome polyps infiltrated with IgG4-positive plasma cells. World J Clin Cases 2016; 4: 248–52.

38. Notohara K, Kamisawa T, Uchida K et al. Gastrointestinal manifestation of immunoglobulin G4-related disease: clarification through a multicenter survey. J Gastroenterol 2018; 53: 845–53.

39. Kamisawa T, Funata N, Hayashi Y et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 2003; 38: 982–84.

40. Kamisawa T, Nakajima H, Egawa N, Hayashi Y, Funata N. LETTER: Autoimmune pancreatitis can be confirmed with gastroscopy. Dig Dis Sci 2004; 49: 155–56.

41. Shinji A, Sano K, Hamano H et al. Autoimmune pancreatitis is closely associated with gastric ulcer presenting with abundant IgG4-bearing plasma cell infiltration. Gastrointest Endosc 2004; 59: 506–11.

42. Kamisawa T, Egawa N, Nakajima H et al. Gastrointestinal findings in patients with autoimmune pancreatitis. Endoscopy. 2005; 37: 1127–30.

43. Aoki S, Nakazawa T, Ohara H et al. Immunohistochemical study of autoimmune pancreatitis using anti-IgG4 antibody and patients' sera. Histopathology 2005; 47: 147–58.

44. Uehara T, Hamano H, Kawa S et al. Chronic gastritis in the setting of

autoimmune pancreatitis. Am J Surg Pathol 2010; 34: 1241–9.

45. Anjiki H, Kamisawa T, Tabata T et al. Gastric emptying in patients with autoimmune pancreatitis. Pancreas 2011; 40: 1302–6.

46. Yamashita H, Naitoh I, Nakazawa T et al. A comparison of the diagnostic efficacy in type 1 autoimmune pancreatitis based on biopsy specimens from various organs. Pancreatology 2014; 14: 186–92.

47. Umehara H, Okazaki K, Masaki Y et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 2012; 22: 21–30.

48. Shimosegawa T, Chari ST, Frulloni L et al. International consensus diagnostic criteria for autoimmune pancreatitis guidelines of the international association of pancreatology. Pancreas 2011; 40: 352–8.

49. Masaki Y, Sugai S, Umehara H. IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights. J Rheumatol 2010; 37: 1380–5.

50. Ohara H, Okazaki K, Tsubouchi H et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci 2012; 19: 536–42.

51. Kawano M, Saeki T, Nakashima H et al. Proposal for diagnostic criteria for IgG4-related kidney disease. Clin Exp Nephrol 2011; 15: 615–26.

52. Notohara K, Kamisawa T, Fukushima N et al. Guidance for diagnosing autoimmune pancreatitis with biopsy tissues. Pathol Int 2020; 70: 699–711.

53. Cheuk W, Yuen H, Chan A et al. Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. Am J Surg Pathol 2008; 32: 1159–67.

54. Brenner I, Roth S, Puppe B, Wobser M, Rosenwald A, Geissinger E. Primary cutaneous marginal zone lymphomas with plasmacytic differentiation show frequent IgG4 expression. Mod Pathol 2013; 26: 1568–76.

55. Park S, Ahn S, Hong M, Ko YH. Increased plasmacytic differentiation in gastric mucosa-asocciated lymphoid tissue lymphomas: *Helicobacter pylori* eradication response and IgG4+ plasma cell association. Human Pathol 2017; 59: 113–9.