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CASE REPORT

Can colonic inflammatory polyp with numerous immunoglobulin G4-positive plasma cells represent a colonic manifestation of immunoglobulin G4-related disease? A case report

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Abstract

We present an asymptomatic case of a 79-year-old Japanese man who had a 6 mm colonic inflammatory polyp with numerous immunoglobulin G4 (IgG4)-positive plasma cells. No symptoms or abnormal laboratory data, such as changes in serum IgG4 levels, were found at the time of diagnosis or during the 1 year of follow-up thereafter. Additionally, no diffuse/localized swelling or masses were found in organs, except for colonic polyps, by abdominal computed tomography 1 year prior to the polypectomy. Inflammatory myofibroblastic tumor was unlikely from the lack of spindle cell proliferation and ALK immunoreactivity. This is the first case of this colonic polyp in an asymptomatic person. This polyp could be probable for single organ manifestation of IgG4-related disease (IgG4-RD), according to the comprehensive diagnostic criteria for IgG4-RD published in 2012; however, colonic manifestation of IgG4-RD has not been clarified owing to its rarity, and colon-specific criteria for IgG4-RD have not been proposed. Thus, we could not definitively establish the colonic polyp as IgG4-RD. Therefore, careful clinicopathological evaluation is needed to reveal whether this colonic polyp represents a nonspecific inflammatory response or an early manifestation of IgG4-RD.

Keywords Inflammatory polyp · Colon · Immunoglobulin G4-related disease · Autoimmune pancreatitis · Inflammatory myofibroblastic tumor · Plasma cell granuloma

Abbreviations

IgG4	Immunoglobulin G4
HPF	High power field
AIP	Autoimmune pancreatitis
UC	Ulcerative colitis
IMT	Inflammatory myofibroblastic tumor
CT	Computed tomography
IgG4-RD	IgG4-related disease

Introduction

Immunoglobulin G4(IgG4)-positive plasma cells are rare in the colon, because there are very few inflammatory cells (< 1/high power field, HPF) in normal colonic mucosa [1, 2]. Thus, an increased number of IgG4-positive plasma cells in the colon is abnormal. Based on a literature review, increased IgG4-positive plasma cells in the colon have been seen in polypoid lesions in autoimmune pancreatitis (AIP) [3, 4], the inflamed mucosa of ulcerative colitis (UC) [5], and a polyp of Cronkhite-Canada syndrome [6], sclerotic nodular lesions [7], extranodal Rosai-Dorfman disease [8], adenoma [2], plasma cell granuloma [9–12], and inflammatory myofibroblastic tumor (IMT) [13]. IgG4-related disease (IgG4-RD) involving the colon [14] and rectum [15] has been also reported; however, colorectal-involved IgG4-RD has been rarely found. We experienced a case of colonic inflammatory polyp with numerous IgG4-positive plasma cells. To our knowledge, this is the first case report of this colonic polyp. We herein present the colonic polyp clinicopathologically, discuss the differential diagnoses, such as

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IgG4-RD, and demonstrate a possible relationship of this colonic polyp and IgG4-RD.

Case report

An asymptomatic, 79-year-old Japanese man was referred to our hospital to have two colonic polyps endoscopically resected. He had a history of a rectal carcinoid tumor, which had been resected 8 years ago. Following resection, he received endoscopic check-ups and medical check-ups once a year. No asthma or allergic rhinitis was found. Arrhythmia was not found by electrocardiography. Chest X-ray showed no abnormal lesions. No renal dysfunction was found by serum laboratory data and dipstick urinalysis. One year prior to the polypectomy, he felt abdominal discomfort, but there were no abnormalities of physical examination and laboratory tests, including serum amylase and serum carcinoembryonic antigen. Abdominal computed tomography (CT) showed neither nodular lesions nor swelling of organs, including the pancreas and lymph nodes. No retroperitoneal fibrosis was seen. His abdominal symptom disappeared during the course of observation and he was well at follow-up. A recent endoscopic examination revealed two colonic polyps, one in the transverse colon and the other in the sigmoid colon (Fig. 1). No ulcerative lesions indicating the presence of UC were found. The maximum diameter of the transverse colon polyp and sigmoid colon polyp was 3 mm and 6 mm, respectively, and each polyp was a suspected adenoma. Endoscopic mucosal resection was performed.

Pathologically, the transverse colon polyp showed a low-grade tubular adenoma. The sigmoid colon polyp showed granulation tissue with dense lymphoplasmacytic infiltrates (Fig. 2a). Marked infiltration of plasma cells was noted (Fig. 2b). No fibrosis, including storiform type or obstructive phlebitis, was observed. Eosinophilic infiltrate was inconspicuous. Vasculitis and granulomatous inflammation were absent. Histiocytes were inconspicuous and no histiocytes containing lymphocytes or plasma cells were seen. Differential diagnoses of the sigmoid colon polyp included an inflammatory polyp, plasmacytoma, plasma cell granuloma/IMT, and IgG4-related disease (IgG4-RD). Immunohistochemically, the infiltrating plasma cells were diffusely positive for CD79a and CD138 (Fig. 2c), negative for CD56 and cyclin D1, and showed no light chain restriction. Spindle cell proliferation was absent, and no ALK-positive cells were present immunohistochemically. No Epstein–Barr virus-encoded RNA (EBER)1-positive cells were observed by in situ hybridization. According to the consensus statement on counting IgG4-positive cells [16], 296 IgG4-positive plasma cells per HPF were seen (Fig. 2d). The ratio of IgG4 to IgG was 58% (Fig. 2e, f). IgG4-positive cells were scattered near the erosion and were hardly observed in the background mucosa (Fig. 2d). Thus, the sigmoid colon polyp histologically showed an inflammatory polyp with numerous IgG4-positive plasma cells. According to the consensus criteria for the pathology of IgG4-RD [16], the probable histological feature of IgG4-RD was also suggested for the sigmoid colon polyp. After pathological diagnosis, IgG4 serum levels were within normal limits (72.4 mg/dL, normal: 4.5–117.0 mg/dL). No abnormal findings regarding the complete blood cell count or serum laboratory data were found. The patient remained asymptomatic and reported no weight loss, abdominal pain, or diarrhea during the follow-up examination at the end of 1 year after the polypectomy. His average serum IgG4 level was found to be 66.2 mg/dL in the follow-up examination.

Retrospectively, we examined whether the IgG4-positive plasma cells were present in the transverse colon polyp. IgG4-positive plasma cells were present at 20 cells/HPF, and an IgG4/IgG ratio of 61% was observed in the tumor stroma. However, there were no findings of dense lymphoplasmacytic infiltrate, storiform fibrosis, or obliterative phlebitis. IgG4-plasma cells were hardly seen in the background mucosa of the transverse colon polyp.

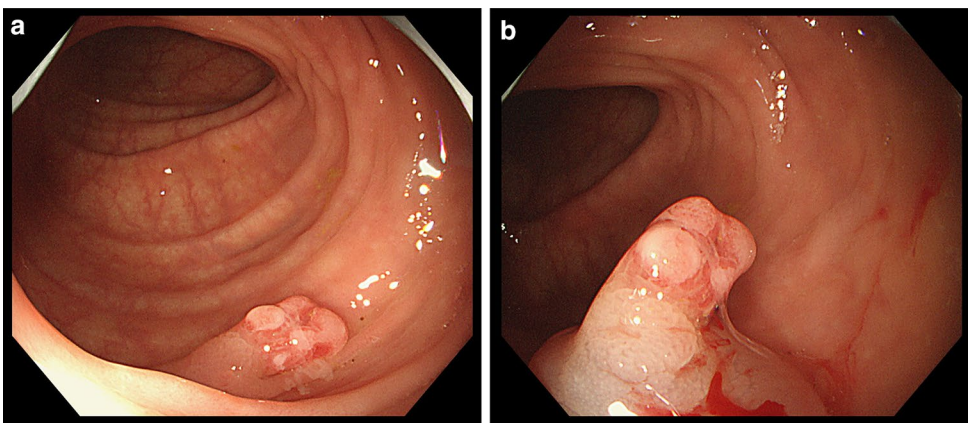

Fig. 1 Endoscopic appearance of the sigmoid colon polyp. **a** A semi-pedunculated polyp is shown. No ulcerative lesions are observed in the background colonic mucosa. **b** When saline is injected into the submucosa, a white and reddish appearance of the polyp is observed

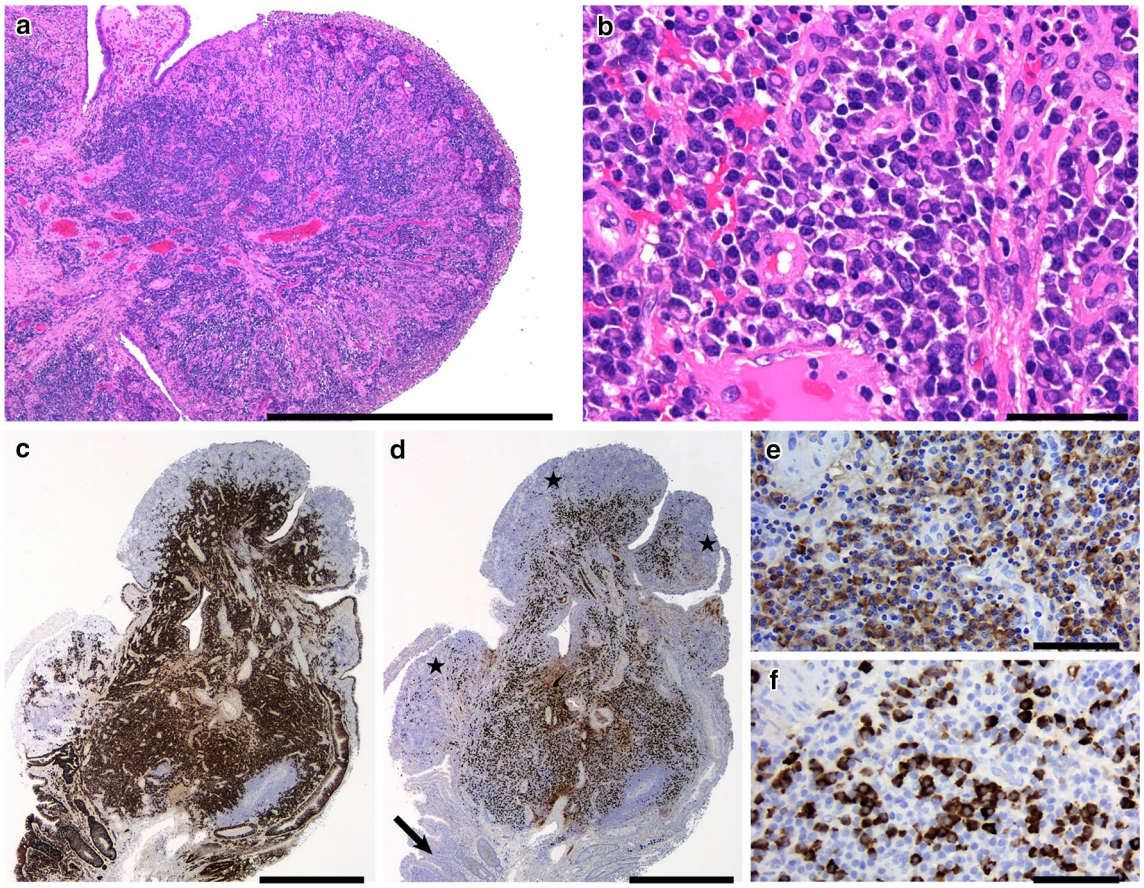

Fig. 2 Pathological appearance of a colonic inflammatory polyp with numerous IgG4-positive plasma cells. **a** The sigmoid colon polyp shows an inflammatory polyp with dense inflammatory infiltrates. Erosion and the absence of crypts are noted. **b** A dense lymphoplasmacytic infiltrate, composed mainly of plasma cells, is seen in the polyp. Spindle cell proliferation is absent. **c–f** Immunohistochemical features of the inflammatory polyp. Diffuse CD138-positive plasma cells are seen (**c** low magnification; **e** high magnification), and IgG4-positive plasma cells accumulate regionally (**d** low magnification; **f** high magnification). IgG4-positive plasma cells are scattered near the erosion (stars) and are hardly seen in the background mucosa in **d** (arrow). Bars in **a, c**, and **d** represent 1 cm, and the bars in **b, e–f** represent 100 μm

Discussion

In our case, increased IgG4-positive plasma cells were observed in the colonic polyps. In particular, the sigmoid colon polyp showed unique histological features with dense infiltration of polyclonal IgG4-positive plasma cells. The pathogenesis and clinical significance of the sigmoid colon polyp in an asymptomatic person remain unknown. Although erosion might increase the number of IgG4-positive plasma cells, this hypothesis was unlikely as they tended to localize away from the erosion.

IgG4-RD should have been examined in our case. Diffuse/localized swelling or masses were not found in organs, including the pancreas and lymph nodes, as visualized by abdominal CT images. In addition to CT, physical examination and laboratory tests confirmed no abnormality. Symptoms or physical findings suggesting a decrease in salivary and lacrimal gland secretion were not found. In addition, serum amylase was normal 1 year prior to and after the polypectomy. In our case, IgG4-RD might not involve organs other than the colon; however, we could not precisely evaluate IgG4-RD for lacrimal and salivary glands because these regions were not tested by radiology.

Additionally, the sigmoid colon polyp with marked infiltration of IgG4-positive plasma cells showed probable diagnosis of single organ involvement of IgG4-RD because this polyp satisfied the following criteria according to the comprehensive diagnostic criteria for IgG4-RD: (1) organ involvement and (2) IgG4-positive cells > 10/high power field and ratio of IgG4-positive cells to IgG-positive cells > 40% [17]. Therefore, patients with probable IgG4-RD could be re-diagnosed based on organ-specific IgG4-RD criteria [18]. To date, colon-specific IgG4-RD criteria has yet to be reported. However, Notohara et al. have recently proposed the concept of IgG4-related gastrointestinal disorders through analysis of eight gastric or esophageal cases [19]. They suggested a gastric case of nodular lymphoid hyperplasia without storiform fibrosis and obliterative phlebitis as a possible case of IgG4-RD [19]. Thus, the

sigmoid colon polyp in our case might indicate possible single organ involvement of IgG4-RD. Unambiguous pathological diagnosis of IgG4-RD mostly requires two of three major histological findings, which are dense lymphoplasmacytic infiltrate, fibrosis (usually storiform in character), and obliterative phlebitis [16]. However, storiform fibrosis and obliterative phlebitis can be absent or inconspicuous in some organs, including the lymph node [20], lacrimal glands [21], and lung [22]. It may be postulated that colonic manifestation of IgG4-RD tends to lack storiform fibrosis and obliterative phlebitis, considering that esophagogastric manifestations of IgG4-RD tend to lack these two pathological findings [19]. Further clinicopathological evaluation of cases similar to our case should be performed to clarify colonic manifestation of IgG4-RD.

The sigmoid colon polyp of our case might be related to another organ involvement of IgG4-RD. The sigmoid colon polyp of our case showed morphological and histological similarities to a colonic polyp reported by Ueno et al. [3]. They reported a patient with AIP, associated with an ascending colon polyp with numerous IgG4-positive plasma cells and an IgG4/IgG ratio of 0.25 [3]. This case also showed significant infiltration of IgG4-positive plasma cells in the background colonic mucosa, which differed from our case. Therefore, clinical follow-up would be required to evaluate AIP/IgG4-RD, considering the case reported by Ueno et al. [3].

According to the comprehensive diagnostic criteria for IgG4-RD [17], diagnosis of IgG4-RD requires exclusion of other diseases mimicking IgG4-RD, such as cancer, lymphoma, Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, granulomatosis with polyangiitis (Wegener's granulomatosis), sarcoidosis, and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome). In our case, cancer, lymphoma, granulomatosis with polyangiitis [23], sarcoidosis [24], and Churg–Strauss syndrome [25] were considered as differential diagnoses because these diseases can involve the colon. No carcinoma was pathologically observed in the sigmoid colon polyp. Aggregates of plasma cells suggested plasmacytoma; however, polyclonal plasma cells were found by immunohistochemistry, and no swollen lymph nodes were detected by abdominal CT. Granulomatosis with polyangiitis was likely excluded because upper airway tract lesions and renal dysfunction were not found, lung-related symptoms were absent, and no abnormal lesions were found on the chest X-ray film. Sarcoidosis was unlikely owing to the lack of granulomatous inflammation. Eosinophilic granulomatosis with polyangiitis was also excluded because there were no findings of asthma, allergic rhinitis, eosinophilia, fever, weight loss, polyneuropathy, gastrointestinal hemorrhage, polyarthralgia, myalgia, or purpura. Thus, mimickers of IgG4-RD appeared to be unlikely in our case. In addition, colonic lesions with a large number of IgG4-positive plasma cells have been seen in UC [5], Cronkhite-Canada syndrome [6], and extranodal Rosai-Dorfman disease [8]. However, our case did not present with UC and Cronkhite-Canada syndrome at the time of diagnosis or after the 1-year follow-up. Pathological study of the sigmoid colon polyp excluded extranodal Rosai-Dorfman disease because of a lack of fibrosis and histiocytes showing emperipolesis.

IMT was also added as a differential diagnosis in our case. Our case grossly or histologically overlapped with plasma cell granuloma [9–12], which can form colonic polyp(s) and includes abundant polyclonal plasma cells. In addition, IgG4-RD can histologically overlap with inflammatory pseudotumor [19]. Plasma cell granuloma and inflammatory pseudotumor have been integrated into an IMT, which is characterized by the proliferation of fibroblastic and myofibroblastic spindle cells and accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and/or eosinophils [26]. *ALK* gene rearrangement can occur in IMTs, which results in overexpression of the *ALK* C-terminal kinase region. Immunohistochemical detection of the *ALK* C-terminal end is useful to detect an *ALK*-rearranged IMT. Our case did not appear to be an IMT, based on the absence of spindle cell proliferation and ALK immunoreactivity. In addition, our case clinically differs from colonic IMTs because colonic IMTs: (1) occur in patients with an age range of 32 to 68 years (median age of approximately 25 years), (2) demonstrate gross features similar to those of carcinomas, and (3) show diameters ranging from 25 to 120 mm, based on literature review [13]. IMT has been acknowledged to fall within the spectrum of IgG4-RD [27]; however, some researchers have suggested that IMT and IgG4-RD are distinct clinicopathological entities [28, 29]. Published cases of colonic plasma cell granuloma [9–12], as well as colonic IMT [13], have not evaluated the possibility of IgG4-RD. Further evaluation may also be needed to determine whether colonic plasma cell granuloma/IMT overlaps with IgG4-RD. An Epstein-Barr virus-associated IMT with abundant plasma cells has been reported as a colonic polyp [30], but our case was negative for EBER1 in in situ hybridization.

We showed a colonic tubular adenoma, accompanied by increased IgG4-positive plasma cells. Uehara et al. reported that colonic adenomas, with or without IgG4-RD, showed increased infiltration of IgG4-positive plasma cells in the tumor stroma compared to the background mucosa; additionally, they showed that 42% (10/24) of colonic adenoma cases without IgG4-RD had > 10 IgG4 plasma cells/HPF [2]. Thus, increased IgG4-positive cells in colonic adenomas may be related to tumor immunity.

In summary, we present a colonic inflammatory polyp with numerous IgG4-positive plasma cells with the IgG4/IgG ratio above 40%. To our knowledge, this is the first case of this colonic polyp in an asymptomatic person. This colonic polyp could be probable for single organ manifestation of IgG4-RD, according to the comprehensive diagnostic criteria for IgG4-RD. However, colonic manifestation of IgG4-RD has not been clarified due to its rarity, and the

colon-specific criteria for IgG4-RD have not been proposed. Thus, we could not definitively establish the sigmoid colon polyp as IgG4-RD. Therefore, careful clinicopathological evaluation will be needed to reveal whether such cases represent merely a nonspecific inflammatory response or an early manifestation of a precursor of IgG4-RD.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for inclusion in this case study.

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