

[ CASE REPORT ]

## Punctate Purpura Complicated with Immunoglobulin G4-related Disease

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### Abstract:

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition affecting multiple organs; however, the involvement of skin lesions is rare. We herein report a 65-year-old man who presented with pruritic punctate purpura on both legs and elevated liver enzyme levels. Computed tomography showed enlargement of the pancreas and thickening of the bile duct wall. Magnetic resonance cholangiopancreatography showed diffuse irregular constriction of the main pancreatic duct, stricture of the lower common bile duct, and dilation after confluent stricture. A histopathologic examination of the pancreas and his enlarged salivary gland showed infiltration of IgG4-positive plasma cells. Ultimately, the patient was diagnosed with IgG4-RD.

**Key words:** IgG4-RD, skin lesions, liver damage

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### Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by the dense lymphoplasmacytic infiltration of created IgG4-positive plasma cells and an elevated serum IgG4 level (1). It usually occurs in middle-aged or older patients with male predominance and can synchronously or metachronously affect multiple organs, such as when manifesting as type 1 autoimmune pancreatitis, sclerosing cholangitis, salivary gland disease, orbital disease or retroperitoneal fibrosis (2). In 2011, comprehensive diagnostic criteria for IgG4-RD including the involvement of various organ were published. These comprehensive diagnostic criteria were as follows: 1) swelling or masses; 2) serum IgG4 levels >135 mg/dL; and 3) histology showing marked lymphocyte and plasmacyte infiltration and fibrosis, >10 IgG4+ plasma cells/high-power field, and percentage of IgG4+ plasma cells/IgG+ plasma cells >40%. The diagnosis is definite when criteria 1), 2), and 3) are fulfilled, probable when criteria 1) and 3) are fulfilled, and

possible when criteria 1) and 2) are fulfilled (3). However, IgG4-RD involving cutaneous lesions is rare, with only 6.3% of cases reported in a study 80 Japanese patients (4) and only 4.2% of cases in a study 118 Chinese patients (5).

We herein report a rare case of secondary eruption associated with IgG4-RD, along with its clinical and histological features.

### Case Report

A 65-year-old man presented to our hospital due to pruritic punctate purpura on both legs for about 10 days (Fig. 1). His laboratory tests showed elevated liver enzyme levels as follows: total bilirubin (TBIL) was 2.3 mg/dL, aspartate aminotransaminase (AST) was 233 U/L, alanine aminotransaminase (ALT) was 426 U/L, alkaline phosphatase (ALP) was 2,846 U/L, and  $\gamma$ -glutamyl transpeptidase ( $\gamma$ GTP) was 1,053 U/L. His other laboratory test findings are shown in Table. The serum IgG4 level was elevated at 794 mg/dL.

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**Figure 1.** Clinical appearance. Purpura of several millimeters in size were noted on the legs.



**Figure 2.** Computed tomography (CT) image of the abdomen. Thickening of the bile duct wall are visible.

### Imaging findings

Computed tomography (CT) showed thickening of the bile duct wall (Fig. 2). Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) showed diffuse irregular constriction of the main pancreatic duct, stricture of the lower common bile duct, and dilation after confluent stricture

**Table.** Laboratory Blood Test Findings on Admission.

Variable	
White blood cells, / $\mu$ L	7,000
Red blood cells, $\times 10^4$ / $\mu$ L	404
Hemoglobin, g/dL	12.8
Platelets, $\times 10^4$ / $\mu$ L	25.3
Aspartate aminotransferase, U/L	233
Alanine aminotransferase, U/L	426
Lactate dehydrogenase, U/L	256
Alkaline phosphatase, U/L	2,846
Gamma-glutamyl transpeptidase, U/L	1,053
Total bilirubin, mg/dL	2.3
Amylase, U/L	45
Blood urea nitrogen, mg/dL	10
Serum creatinine, mg/dL	0.91
HbA1c, %	5.7
Fasting blood sugar, mg/dL	90
IgG, mg/dL	2,114
IgG4, mg/dL	794
IgM, mg/dL	94
IgA, mg/dL	123
IgE, mg/dL	183
Ana antinuclear antibody (ANA)	negative
Anti-mitochondrial antibody (AMA)	negative
Anti-Sjogren's syndrome A antibody	negative
Anti-Sjogren's syndrome B antibody	negative

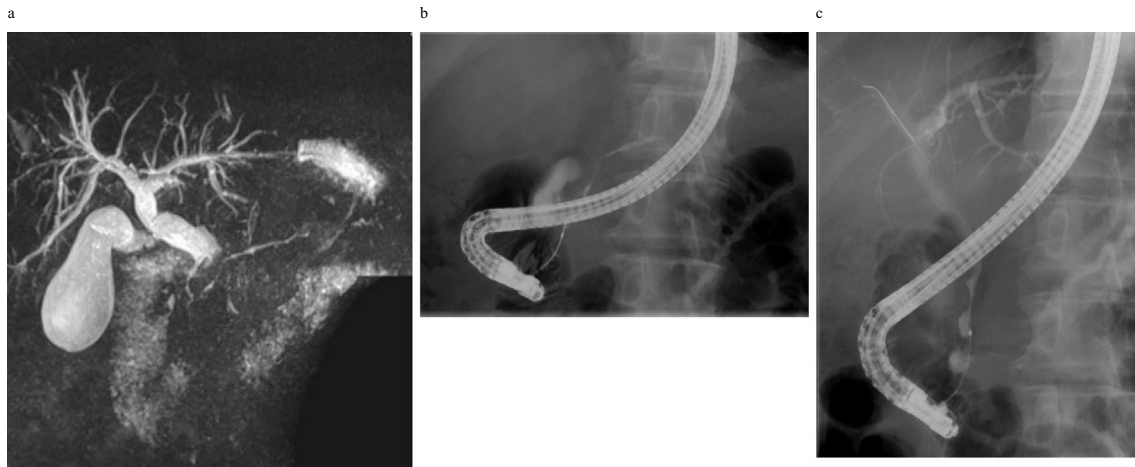
(Fig. 3). Biliary stent placement was not performed during ERCP because the findings of ERCP did not reveal any bile duct obstruction.

### Histopathology

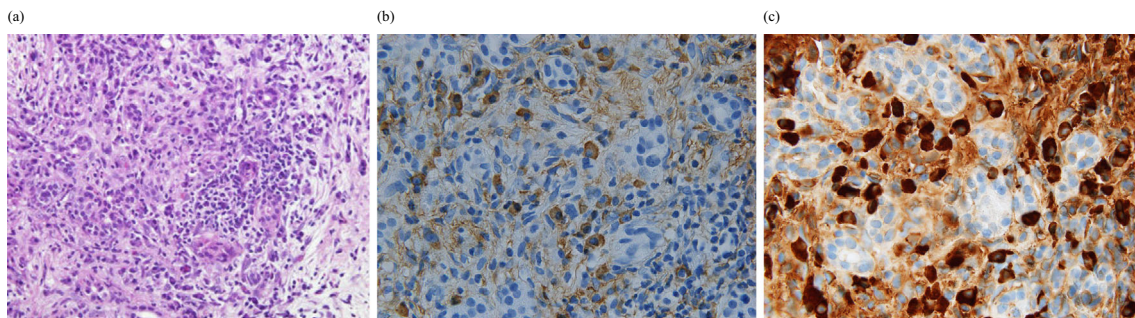
A histopathologic examination of an aspiration biopsy sample from the pancreas obtained by an endoscopic ultrasound-guided fine-needle aspiration biopsy showed prominent infiltration of lymphocytes and plasma cells along with fibrosis of more than 10 IgG4 plasma cells/high-power microscopic field (Fig. 4).

He also had left submaxillary gland enlargement. A histopathologic examination of his enlarged submaxillary gland also showed infiltration of IgG4-positive plasma cells, and the rate of IgG4-positive plasma cells/IgG-positive plasma cells/5 high-power microscopic fields was more than 50% (Fig. 5). Ultimately, the patient was diagnosed with IgG4-related disease. In addition, he underwent a skin biopsy. A histopathologic examination of the leg purpura skin showed perivascular infiltration of neutrophils, eosinophils, lymphocytes (Hematoxylin-eosin), and IgG4-positive deposition along the small vessel wall in the dermis, although IgG4 plasma cells were not detected (Fig. 6).

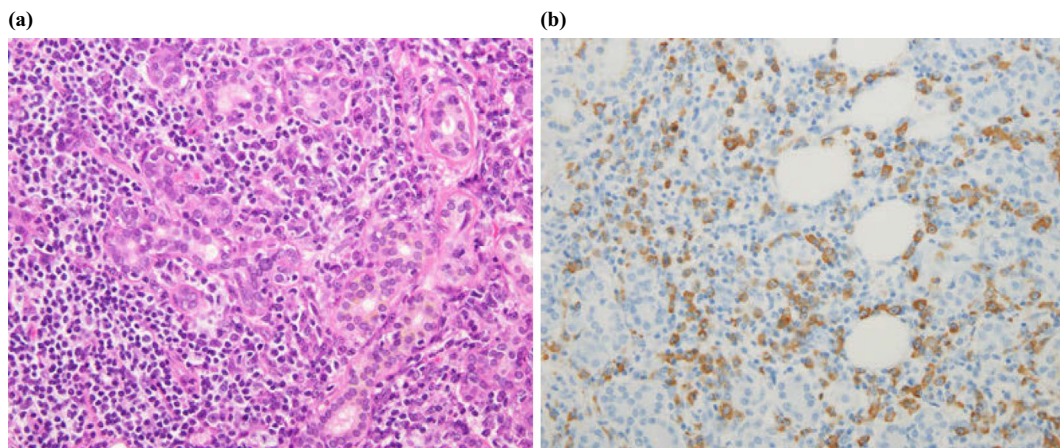
Our case met the criteria of the International Consensus Diagnostic Criteria for AIP 2018, which include irregular narrowing of the main pancreatic duct, elevated serum IgG4 levels (more than 135 mg/dL), extra-pancreatic lesions (e.g., sclerosing cholangitis, sclerosing sialadenitis, prominent in-



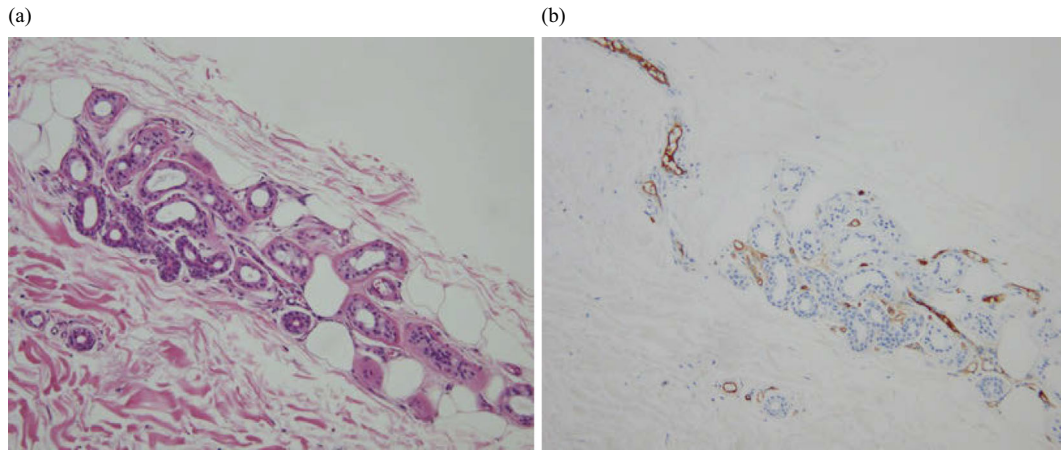
**Figure 3.** Magnetic resonance cholangiopancreatography (MRCP) (a) and endoscopic retrograde cholangiopancreatography (ERCP) (b, c) show diffuse irregular constriction of the main pancreatic duct, stricture of the lower common bile duct, and dilation after confluent stricture.



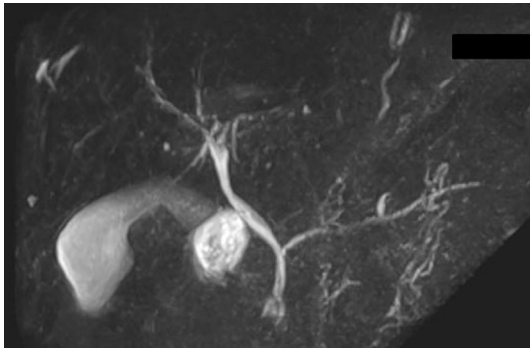
**Figure 4.** Histopathological findings of endoscopic ultrasound-guided fine-needle aspiration from the pancreas. (a) Inprominent infiltration of lymphocytes and plasma cells along with fibrosis (Hematoxylin and Eosin staining, original magnification  $\times 400$ ), (b) 23 IgG4 plasma cells per high-power microscopic field (immunostaining for IgG4,  $\times 600$ ). (c) the rate of IgG4-positive plasma cells/IgG-positive plasma cells/5 high-power microscopic fields was 57.5% (23/40). (immunostaining for IgG,  $\times 600$ ).



**Figure 5.** Histopathological findings of the enlarged submaxillary gland. (a) Inflammatory cells, which consist of lymphocytes and plasma cells with fibrosis. (Hematoxylin and Eosin staining, original magnification  $\times 400$ ) (b) 80 IgG4-positive plasma cells per high-power microscopic field (immunostaining for IgG4,  $\times 400$ ).



**Figure 6.** Histopathological findings of the leg lesion. (a) Perivascular infiltration of neutrophils, eosinophils, lymphocytes (Hematoxylin and Eosin staining, original magnification  $\times 200$ ). (b) IgG4-positive deposition along the small vessel wall in the dermis, but IgG4 plasma cells were not detected (immunostaining for IgG4,  $\times 200$ ).



**Figure 7.** The stricture of the common bile duct was improved on Magnetic resonance cholangiopancreatography after the patient was treated with only ursodeoxycholic acid

filtration of lymphocytes and plasma cells along with fibrosis), and more than 10 IgG4-positive plasma cells per high-power microscopic field on pathological findings (6). Furthermore, the case met the clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012, showing diffuse or segmental narrowing of the intra- and/or extra-hepatic bile duct associated with the thickening of the bile duct wall, elevated serum IgG4 levels (more than 135 mg/dL), coexistence of autoimmune pancreatitis, and IgG4 sialoadenitis (7).

### Treatment

He was successfully treated with ursodeoxycholic acid without steroid administration after we confirmed that he did not have obstructive jaundice.

His transaminase level subsequently normalized within about 30 days. The stricture of the common bile duct was improved, and his skin lesions also disappeared. Following discontinuation of ursodeoxycholic acid, his transaminase level remained normal, and stricture of the common bile duct was noted on MRCP (Fig. 7).

### Discussion

IgG4-RD can affect one or multiple organs, so the clinical symptoms are varied, but 60% to 90% of patients show effects on multiple organs (8). The most common symptom of IgG4-RD at the onset is lacrimal gland swelling (32.2%) followed by submandibular gland swelling (23.7%), abdominal pain (19.5%), parotid gland swelling (9.3%), enlarged lymph nodes (8.5%), jaundice (7.6%), low back pain (7.6%), nasal congestion (2.5%), and nausea and vomiting (1.7%). Throughout the disease course, salivary gland swelling, lacrimal gland swelling, lymphadenopathy, abdominal pain, parotid gland swelling, nausea and vomiting, cough, jaundice, and low back pain have been reported as clinical manifestations (5). Symptoms of asthma or allergy are present in about 40% of patients (5, 8). In cases of autoimmune pancreatitis (AIP), the most commonly reported symptoms are jaundice (48.6%) followed by abdominal pain (25.6%), extra-pancreatic lesions (12.0%), body weight loss (3.0%), back pain (2.3%), acute pancreatitis (0.9%), and others (7.5%) (9). In patients with IgG4-RD skin disease, the most common extracutaneous organ systems are the salivary glands (53.3%) followed by the lymph nodes (46.7%), lacrimal glands (33.3%), and orbit (30%). Systemic involvement preceded cutaneous involvement in 76% of cases. The mean latency period until the development of skin disease after systematic involvement was 20 months (10).

Some patients with IgG4-RD have skin lesions. IgG4-related skin lesions are reportedly typically erythematous and itchy plaques, subcutaneous nodules, or papules like prurigo nodularis. Cutaneous lesions are predominantly located on the head and neck (11, 12). Many patients with IgG4-related skin symptoms are reported to be Asian middle-aged and older men. Some investigators have reported that skin lesions were unresponsive to topical corticosteroids (13, 14). These features fit the present case.

Tokura et al. classified cutaneous lesions in IgG4-RD into seven subtypes based on documented cases (16):

1. Cutaneous plasmacytosis: Symptoms of multiple circular or ellipsoid patches with pigmentation.
2. Pseudolymphoma and angiolymphoid hyperplasia with eosinophilia: Symptoms of plaques and papulonodules mainly in the periauricular and facial areas.
3. Mikulicz disease of IgG4-related dacryoadenitis and sialadenitis: Symptoms of palpebral swelling, sicca syndrome, and exophthalmos.
4. Psoriasis-like eruptions: Symptoms of scaly erythematous plaques.
5. Unspecified maculopapular or erythematous eruptions: Symptoms of multiple maculopapular or exudative erythematous lesions.
6. Hypergammaglobulinemia, purpura and urticarial vasculitis: Symptoms of bilateral palpable purpuric lesions or prolonged urticarial lesions.
7. Ischemic digit: Symptoms of Raynaud phenomenon and digital gangrene.

In addition, they considered subtypes 1-3 to be primary lesions and 4-7 to be secondary non-specific lesions. Pathologically, in primary lesions, IgG4-positive plasma cells directly infiltrate the skin tissue. Based on the comprehensive criteria of IgG4-RD, the primary lesion can be defined by marked lymphoplasmacytic infiltration with a ratio of IgG4/IgG plasma cells exceeding 40% and more than 10 IgG4 plasma cells/high-power field, with fibrosis not necessarily required. Secondary lesions are accompanied by IgG4-RD and can be defined as slight plasma cell infiltration or perivascular IgG4 deposition (11, 15). Another report suggested that the appropriate cut-off point may vary among organs, depending on the predominance of fibrosis at the time the diagnosis is made. They also suggested that the diagnosis of IgG4-RD is made based on the combined presence of a characteristic histopathological appearance and increased number of IgG4 plasma cells. The critical histopathological features are a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis, with the presence of >200 IgG4 plasma cells in the primary skin lesion also proposed as necessary (16).

Accordingly, the present case seemed to be one of a secondary skin lesion, and the skin lesion improved with the improvement in the liver damage. Among them, the present case was categorized as having hypergammaglobulinemia, purpura and urticarial vasculitis.

Previous studies have shown that corticosteroid treatment is effective for patients with IgG4-RD, at least in the short term (1, 2, 17). Ise et al. reported a 55-year-old IgG4-RD patient with AIP and skin lesions in whom AIP was treated by corticosteroid at 5 mg/day, although this therapy failed to control the skin lesions (13). Sato et al. reported six patients with IgG4-RD skin disease who were treated with systemic corticosteroid, which reduced the size of the lesions. However, in five of these patients, the lesion size increased again once corticosteroid administration was tapered (14). In the

present case, the liver damage improved with ursodeoxycholic acid without corticosteroid administration. Furthermore, the stricture of the common bile duct was improved on CT (18). Tsubakio et al. reported that a 51-year-old woman with AIP had been successfully treated with ursodeoxycholic acid (18). Our patient was reluctant to receive steroids due to the associated side effects. Therefore, we initiated ursodeoxycholic acid at first. Eventually, our patient was treated without steroids because his liver dysfunction showed an improving trend. In contrast, spontaneous remissions of IgG4-RD or at least temporary remission without corticosteroid administration has been reported (16, 19, 20). Kubota et al. reported that spontaneous remission of IgG4-RD was associated with female sex, the absence of jaundice, a low level of serum IgG4, and negative staining of duodenal papilla for IgG4 (20, 21). Clinical factors predictive of relapse were reported to be an elevated serum IgG level, the presence of diffuse pancreatic swelling, and the presence of stricture in the lower part of the bile duct (20). The present case had none of the features of spontaneous remission but did have a relapse-related factor. Therefore, we need to carefully monitor his condition by a blood examination and imaging findings, such as MRCP or CT, over time.

In conclusion, skin findings can be useful for diagnosing IgG4-related disease.

**The authors state that they have no Conflict of Interest (COI).**

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