

IgG4-Related Disease Presenting as Generalized Itchy Papules: A Case Report

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ABSTRACT:

IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory disease characterized by increased serum IgG4 and IgG4⁺ cell infiltrated tissues. Affected organs usually include the pancreas, biliary tract, retroperitoneum, aorta, salivary, and lacrimal glands. Cutaneous lesions are uncommon. IgG4-RD is treatable and highly responsive to glucocorticoids. This case report concerns a rare case of IgG4-RD presenting with generalized erythematous to brownish itchy papules and bilateral lacrimal gland masses with lung involvement including mediastinal lymphadenopathy, multiple lung nodules, and ground glass opacities in both lungs that responded to prednisolone and ciclosporin.

Key words: IgG4-related disease, Cutaneous plasmacytosis

Case report

A 40-year-old Myanmar male presented with generalized indurated erythematous to brownish papules and plaques on the trunk and all extremities, which he had experienced for 2 years (Figure 1). The lesions were persistent and itchy. He went to the hospital and was given antihistamine drugs and topical treatment, but his symptoms did not improve. Subsequent to initial treatment, he developed bilateral lacrimal

gland masses for a month. He did not suffer from a fever, weight loss, arthralgia, abdominal pain, or dyspnea. He went to see an ophthalmologist and got a biopsy of the right lacrimal gland. Histology showed reactive lymphoid proliferation with numerous plasma cell infiltrations. Immunostaining of IgG4 showed more than 200 IgG4⁺ plasma cells per high-power field, and the ratio of IgG4⁺/IgG⁺ was approximately 60%.

The laboratory disclosed a normal complete blood count, as well as normal renal and liver function. Serological tests for HIV, syphilis, anti-nuclear antibodies, anti-Ro/SSA, anti-La/SSB, pANCA, and cANCA were negative. ESR was high, and C3 level was a little low. Computed tomography (CT) scans showed mediastinal lymphadenopathy, multiple lung nodules, and ground glass opacities in both lungs (Figure 2). There was neither pancreatic

nor retroperitoneal involvement. Lung with lymph node biopsy and bronchoalveolar lavage were carried out to exclude infection and malignancy. Lung biopsy also revealed lymphoplasmacytic infiltration. According to the 2019 ACR/EULAR classification criteria for IgG4-RD (Table 1)¹, the patient was diagnosed with IgG4-RD based on histopathology and lacrimal gland involvement.



Figure 1 (A) Multiple indurated erythematous to brownish papules and plaques on the back. The lesions exhibited generalized distribution; (B) Close-up view of skin lesions

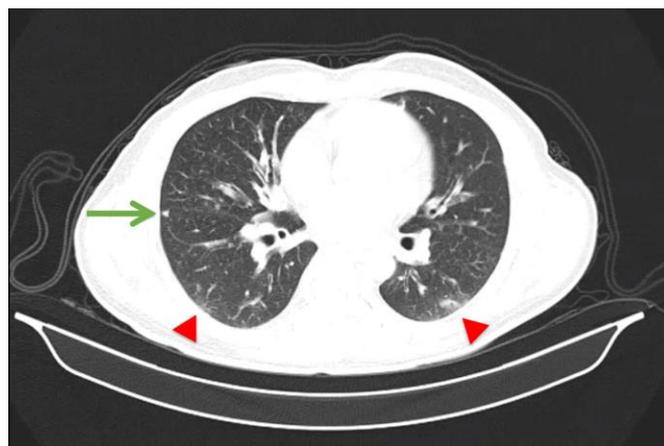


Figure 2 Computed tomography scan showing multiple lung nodules (green arrow) and ground glass opacities (red arrow) in both lungs

Table 1. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease¹

Step	Categorical assessment or numeric weight
<p>Step 1. Entry criteria Characteristic clinical or radiologic involvement of a typical organ (e.g., pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges, or thyroid gland [Riedel's thyroiditis]) OR pathologic evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain etiology in one of these same organs</p>	<p>Yes or No</p>
<p>Step 2. Exclusion criteria: domains and items</p> <p><i>Clinical</i> Fever No objective response to glucocorticoids</p> <p><i>Serologic</i> Leukopenia and thrombocytopenia with no explanation Peripheral eosinophilia Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase) Positive SSA/Ro or SSB/La antibody Positive double-stranded DNA, RNP, or Sm antibody Other disease-specific autoantibody Cryoglobulinemia</p> <p><i>Radiologic</i> Known radiologic findings suspicious for malignancy or infection that have not been sufficiently investigated Rapid radiologic progression Long bone abnormalities consistent with Erdheim-Chester disease Splenomegaly</p> <p><i>Pathologic</i> Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated Markers consistent with inflammatory myofibroblastic tumor Prominent neutrophilic inflammation Necrotizing vasculitis Prominent necrosis Primarily granulomatous inflammation Pathologic features of macrophage/histiocytic disorder</p> <p><i>Known diagnosis of the following:</i> Multicentric Castleman's disease Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present) Hashimoto thyroiditis (if only the thyroid is affected)</p>	<p>Yes or No</p>
<p>If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3.</p>	

Table 1. (Cont'd)

Step	Categorical assessment or numeric weight
Step 3. Inclusion criteria: domains and items	
<i>Histopathology</i>	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
<i>Immunostaining#</i>	
0–16, as follows: Assigned weight is 0 if the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is 0–9. Assigned weight is 7 if 1) the IgG4+:IgG+ ratio is ≥41% and the number of IgG4+ cells/hpf is 0–9 or indeterminate; or 2) the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is ≥10 or indeterminate. Assigned weight is 14 if 1) the IgG4+:IgG+ ratio is 41–70% and the number of IgG4+ cells/hpf is ≥10; or 2) the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is 10–50. Assigned weight is 16 if the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is ≥51.	
<i>Serum IgG4 concentration</i>	
Normal or not checked	0
> Normal but <2× upper limit of normal	+4
2–5× upper limit of normal	+6
>5× upper limit of normal	+11
<i>Bilateral lacrimal, parotid, sublingual, and submandibular glands</i>	
No set of glands involved	
One set of glands involved	0
Two or more sets of glands involved	+6
<i>Chest</i>	+14
Not checked or neither of the items listed is present	
Peribronchovascular and septal thickening	0
Paravertebral band-like soft tissue in the thorax	+4
<i>Pancreas and biliary tree</i>	+10
Not checked or none of the items listed is present	
Diffuse pancreas enlargement (loss of lobulations)	0
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+8
Pancreas (either of above) and biliary tree involvement	+11
<i>Kidney</i>	+19
Not checked or none of the items listed is present	
Hypocomplementemia	0
Renal pelvis thickening/soft tissue	+6
Bilateral renal cortex low-density areas	+8
<i>Retroperitoneum</i>	+10
Not checked or neither of the items listed is present	
Diffuse thickening of the abdominal aortic wall	0
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+4
	+8
Step 4: Total inclusion points	
A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20.	

Dermatologists were consulted about the skin lesions, and a skin biopsy was carried out on the left arm. Histological examination revealed dense perivascular and periadnexal infiltration of lymphocytes and plasma cells (Figure 3). Immunostaining for IgG4 was also positive (Figure 4). The patient was given

prednisolone 40 mg/day for induction and prednisolone 5 mg/day combined with ciclosporin 100 mg/day for maintenance. The lacrimal glands were completely resolved in 3 months, and pulmonary lesions and rashes improved in a year.

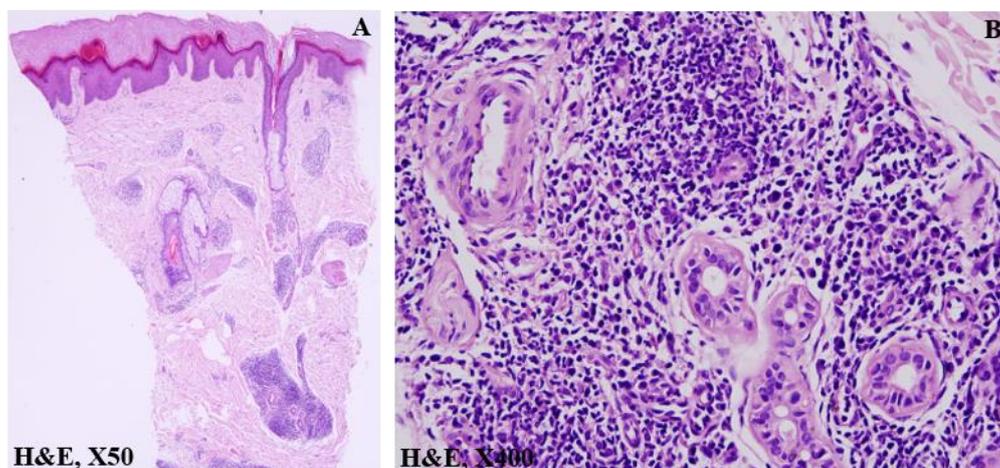


Figure 3 Histological examination showing (A) dense perivascular and periadnexal infiltration; (B) There were many lymphocytes, plasma cells, and few eosinophils.

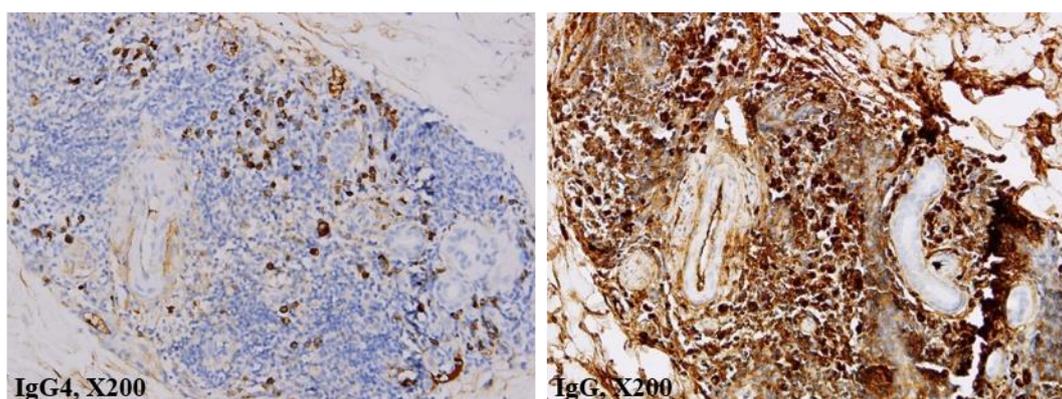


Figure 4 Immunostaining showed IgG4⁺ cells > 50 cells/HPF and infiltration of IgG4⁺/IgG⁺ plasma cells ratio > 40%.

Discussion

IgG4-related disease is a chronic inflammatory and fibrosing disease characterized by high levels of circulating IgG4 and tissue infiltration of IgG4⁺ plasma cells². IgG4-RD was first described in 2003³. The prevalence of IgG4-RD in Japan is estimated to be 62 per 1 million subjects. Prevalence in Japan is higher than in Western countries. Onset is most often seen around 50–70 years old, and male predominance is evident⁴.

The pathophysiology of IgG4-RD remains unclear. Aberrant innate and adaptive immunity has been recognized to be key role players. Macrophages, mast cells, basophils, complement, and plasmacytoid dendritic cells are activated to produce various kinds of cytokines. Type 2 helper T lymphocytes produced cytokines such as IL-4, IL-5, and IL-13, and regulatory T lymphocytes secreted IL-10 and TGF- β . These cytokines can induce

inflammation and increase IgG4 production by B cells, which leads to fibrosis⁵.

The clinical manifestations of IgG4-RD are variable and depend on the organs involved. Constitutional symptoms are rare⁶. Cutaneous IgG4-RD is uncommon. The lesions are pruritus⁷. Cutaneous IgG4-RD can be categorized into primary and secondary eruptions. Primary eruptions include cutaneous plasmacytosis, pseudolymphoma, and angiolymphoid hyperplasia with eosinophilia, as well as Mikulicz disease, which are induced by the direct infiltration of IgG4⁺ plasma cells. Cutaneous plasmacytosis manifests as multiple red-brown, indurated, papules and nodules with circular or oval shapes on the trunk. The lesions usually exhibit prominent pigmentation. A biopsy revealed dermal lymphoplasmacytic infiltration which was positive for IgG4⁺ plasma cells⁸. Based on the characteristics of the skin lesions and histopathology, the patient in this case was consistent with cutaneous plasmacytosis-type.

The secondary eruptions consist of the following four types of skin manifestations: psoriasis-like eruption, unspecified maculopapular or erythematous eruptions, hypergammaglobulinaemic purpura and urticarial vasculitis, and ischemic digit, which also found IgG4⁺ plasma cells infiltration in histology⁸.

In extracutaneous manifestation, autoimmune pancreatitis is the most common presentation, occurring in 20-60% of cases². The salivary glands, lacrimal glands, and retroperitoneum are usually involved. The frequency of involvement of salivary glands, lacrimal glands, and retroperitoneum ranges between 20-30% in Europe and 60-80% in Asia at 10-50% and 10-27%, respectively². Lung involvement has been found in 10-30% of cases². Imaging study typically shows peribronchovascular and septal thickening, as well as paravertebral band-like soft tissue in the thorax¹. Here, the patient's CT scan revealed

mediastinal lymphadenopathy, multiple lung nodules, and ground glass opacities in both lungs. Although the results were not typical, the lung biopsy showed lymphoplasmacytic infiltration. A pulmonologist also mentioned that the symptoms could be caused by IgG4-RD from the infiltration of plasma cells in histology and imaging response after therapy. Life-threatening conditions of IgG4-RD are aortitis and coronary arteries⁷.

Diagnosis was based on the 2019 ACR/EULAR classification criteria for IgG4-RD¹. According to step 1, the patient showed typical organ involvement with lymphoplasmacytic infiltration in the orbit and lungs. The patient did not meet any exclusion criteria in step 2. In step 3 of the inclusion criteria, immunostaining of the lacrimal gland revealed that the IgG4⁺:IgG⁺ ratio was 60% and the number of IgG4⁺ cells/hpf was 200 (14 points). The involvement of both lacrimal glands was rated at 6 points. Skin lesions and CT scan results of the lungs were not considered part of the inclusion criteria. The patient's total points added up to 20, which led to the diagnosis of IgG4-RD. The specificity was 97.8%, and sensitivity was 82.0%¹.

The treatment for IgG4-RD is often based on clinical experience and retrospective studies. Early treatment is important, as it can help prevent fibrosis and organ dysfunction.

In the induction phase of treatment, glucocorticoids are the first-line therapy. The starting dose is 0.6 mg/kg/day of prednisolone⁹. Tapering or after withdrawal of glucocorticoids resulted in a relapse of skin lesions in 93.3% of cases, and 85.6% reported a relapse of systemic involvement⁷. If patients are resistant to glucocorticoids, rituximab is considered. In the maintenance phase, low-dose glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) such as azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, leflunomide, and ciclosporin, or rituximab are

suggested. The prognosis of the disease is a slow and gradually progressive course⁹.

In summary, the patient was diagnosed with IgG4-RD alongside cutaneous and lacrimal gland involvement. Cutaneous lesions were compatible with cutaneous plasmacytosis. Although pulmonary lesions are not a typical finding, they may be caused by IgG4-RD due to the infiltration of plasma cells. Here, the patient was given prednisolone and ciclosporin. The lacrimal glands were completely resolved, and pulmonary lesions as well as rashes gradually improved.

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