

IgG4-related Skin Lesions in a Patient with IgG4-related Chronic Sclerosing Dacryoadenitis and Sialoadenitis

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Abstract

We describe a 60-year-old man with IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis associated with lymphoplasmacytic and eosinophilic infiltration in erythematous nodules. Physical examination revealed left eye extrusion and small itchy nodules on the scalp and neck. The serum IgG level was 1,570 mg/dL, IgG4 463 mg/dL (29.5%), and IgE 4,554 IU/mL. Lacrimal gland biopsy disclosed prominent infiltrates of IgG4-positive plasma cells and scattered eosinophilic infiltrates with fibrosis, consistent with IgG4-related disease. A skin biopsy of a cutaneous nodule demonstrated that the infiltrated plasma cells around arterioles or venules in the deep dermis and subcutaneous fat tissue were strongly positive for IgG4. Although the swollen lacrimal and parotid gland and itchy subcutaneous erythematous nodules improved rapidly with oral prednisolone at a dose of 20 mg per day, the skin, lacrimal, and parotid lesions deteriorated simultaneously during steroid tapering and improved after increasing the dosage. As skin lesions are easy to biopsy, further study of the skin manifestations of IgG4-related disease will be important in further clarifying the clinical spectrum, pathophysiology and response to therapy of this disorder.

Key words: IgG4-related disease, cutaneous lymphoid infiltrate, IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis

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Introduction

After the establishment of the entity of autoimmune pancreatitis (AIP) (1, 2), a variety of associated extra-pancreatic lesions have been reported including those of the lacrimal glands, salivary glands, lungs, kidneys, liver, bile duct, retroperitoneum, breast, aorta, pituitary gland, and prostate (3-6). In 2003, Kamisawa et al (3) proposed the new clinicopathological entity of "IgG4-related autoimmune disease" based on common pathological features of many IgG4-positive plasma cell infiltrates with fibrosis and increased serum IgG4 levels, which are representative findings of

autoimmune pancreatitis. Since then, many case reports or case series have accumulated, and IgG4-related disease has been accepted as a new clinical entity. IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis are major components of this disease.

However, only a few reports have focused on the skin lesions associated with autoimmune pancreatitis, chronic sclerosing dacryoadenitis and sialoadenitis or systemic IgG4-related lymphadenopathy (7, 8). Here, we describe a case of IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis with nodular skin lesions with marked IgG4-positive plasma cell infiltration and scattered eosinophil infiltration, which appeared in parallel with exacerbation of

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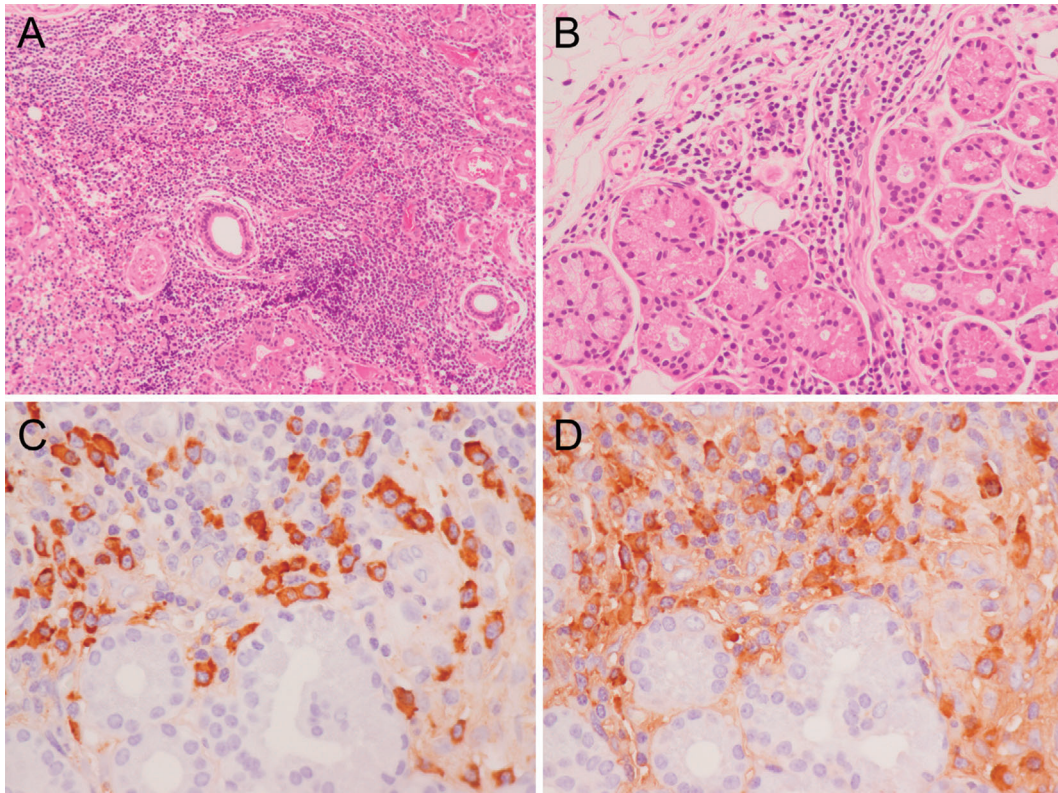


Figure 1. Lacrimal gland biopsy shows marked infiltration of lymphocytes and plasma cells (A) with mild fibrosis (B). Many infiltrating plasma cells are IgG4 positive (C), with an IgG4/IgG ratio of 84.8% (C and D). [(A) lacrimal gland, Hematoxylin and Eosin (HE) staining, $\times 100$, (B) HE staining, $\times 200$, (C) IgG4, $\times 400$, (D) IgG, $\times 400$]

the dacryoadenitis and improved after the corticosteroid dosage was increased.

Case Report

A 60-year-old man was admitted to our hospital for close examination of impaired glucose tolerance and systemic evaluation of IgG4-related disease. One year before entry, a high fasting plasma glucose level had been pointed out for the first time on an annual health checkup and he began treatment for diabetes mellitus. Six months before admission, he noticed protrusion of his left eye, and two months later itchy nodules on his scalp and neck. Magnetic resonance imaging revealed left external eye muscle hypertrophy and multiple mass lesions in the left orbital cavity. As malignant lymphoma was strongly suspected, a left lacrimal gland biopsy was performed. The biopsy specimen was composed of inflammatory tissue with marked infiltrates of IgG4-positive plasma cells and scattered eosinophilic infiltrates with fibrosis suggesting IgG4-related disease (Fig. 1A, 1B). The average ratio of IgG4/IgG positive plasma cells in five different high power fields (hpf) with intense infiltration was 84.8% (Fig. 1C, 1D). On admission to our hospital, physical examination revealed left eye extrusion with obvious lacrimal gland swelling (Fig. 2A). Small itchy nodules were found on the parietal scalp, and 7 little finger tip-sized itchy subcutaneous erythematous nodules on

the neck without any palpable lymph nodes (Fig. 2B). The bilateral parotid glands were swollen, while the submandibular glands were of normal size. He had no history of allergies. Blood eosinophil count was 993/mL accounting for 12.9% of the total white blood cell count. Fasting plasma glucose was 100 mg/dL, and HbA1c 6.4%. Liver function tests, electrolytes, and renal function tests were all within the respective normal ranges. Serum IgG level was 1,570 mg/dL, IgG4 463 mg/dL (29.5%), and IgE 4,554 IU/mL, rheumatoid factor 12 IU/mL, and soluble interleukin 2 receptor 692 U/mL (normal 220-530 U/mL). Antinuclear antibodies were negative. Computed tomography (CT) scans revealed bilateral lacrimal gland and parotid gland swelling without lymphadenopathy. Abdominal CT showed a normalized pancreas without pancreatic duct abnormalities or mass formation. A skin biopsy of a cutaneous nodule was performed. On light microscopy, there was moderate lymphocyte and plasma cell infiltration around arterioles and adnexal structures in the dermis (Fig. 3A). In particular, severe lymphocytic infiltration with plasma cells and eosinophils around arterioles or venules was evident in the deep dermis (Fig. 3B, 3C) and subcutaneous fat tissue, and the majority of infiltrating plasma cells were IgG4 positive (average IgG4 positive cell count in five different hpf with intense infiltration was 47/hpf) (Fig. 3D). A diagnosis of IgG4-related systemic disease was made because of an elevated serum level of IgG4, marked infiltration of IgG4-positive

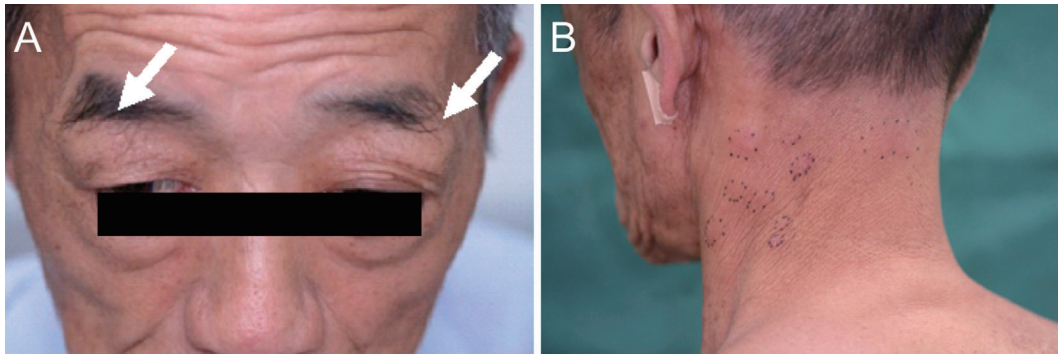


Figure 2. Bilateral swelling of the lacrimal glands is noted (A, arrows). Little finger tip-sized subcutaneous erythematous nodules are present on the neck (B).

plasma cells in the lacrimal glands, and typical features of Mikulicz's disease with symmetrical lacrimal and parotid gland swelling. After the administration of 20 mg of prednisolone, a rapid response was obtained and the multiple nodules in the scalp and neck disappeared. The bilateral parotid swelling was also improved. The prednisolone dose was reduced at the rate of 5 mg every two weeks to 10 mg, which was adopted as the maintenance dose. Six months thereafter, the left eye protrusion, bilateral parotid swelling, and multiple subcutaneous nodules recurred, and the dose of prednisolone was increased to 20 mg after a second skin biopsy. The histopathological findings were similar to those of the previous biopsy with marked IgG4-positive plasma cell infiltration with scattered eosinophils, supporting the recurrence of IgG4-related disease. Twenty days after readministration of 20 mg of prednisolone, ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) was performed. However, no FDG-PET positive lesion was detected, this being consistent with the rapidly improved clinical findings. After that, prednisolone was carefully decreased without recurrence of the eye protrusion, parotid swelling, or appearance of new skin lesions.

Discussion

We report a patient with clinical and histological features of chronic sclerosing dacryoadenitis and sialoadenitis and multiple nodular itchy skin lesions on the scalp and neck. The histological findings of the skin lesions were very similar to those previously reported in IgG4-related disease (3-5, 8), suggesting that the skin lesions of this case should be included as one of the extra-pancreatic manifestations of autoimmune pancreatitis and other IgG4-related disease.

To identify new organ involvement of IgG4-related disease, two approaches to identification exist. One is to find marked IgG4-positive plasma cell infiltration in a suspicious lesion, and to confirm an elevated serum IgG4 level. The other is to find an associated lesion in patients with typical IgG4-related disease, such as autoimmune pancreatitis or IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis, and to prove similar IgG4-positive plasma cell infiltra-

tion in the newly recognized lesion. However, the former approach has not yet been fully accepted because some patients with well established diseases such as Churg-Strauss syndrome (9) and Castleman's disease (6, 10, 11) also have similar IgG4-positive plasma cell infiltration with high serum IgG4 levels.

Kuo et al (12) contended that cutaneous Rosai-Dorfman (RD) disease is an IgG4-related sclerosing disease according to identification by the former approach. They analyzed the skin lesions of 12 patients with RD disease, and noted that all but one of them had more than 30 IgG4 positive cells/hpf. They also found an elevated serum IgG4 level in one patient. Shrestha et al (13) analyzed lung lesions of 8 patients with nodal and extranodal RD disease, and found that 6 of 8 RD cases showed an increased number of IgG4-positive plasma cells in the lung. Although these findings suggest that some relationship may exist between RD disease and IgG4-related disease, the finding of S-100-protein-positive large histiocytes, a histopathological feature of RD disease, is very unusual in IgG4-related disease, making it difficult to regard cutaneous RD disease as a cutaneous manifestation of IgG4-related disease. However, Shrestha et al (13) showed that 2 of 6 patients with lung lesions associated with IgG4-related autoimmune pancreatitis had prominent lymphatic dilatation with emperipolesis and S-100 protein-positive histiocytes in the lung. Therefore, further studies are needed to classify RD disease as an IgG4-related disease.

Miyagawa-Hayashino et al (14) claimed that cutaneous plasmacytosis is a cutaneous manifestation of IgG4-related disease as identified by the former approach. Although hypergammaglobulinemia is common to both cutaneous plasmacytosis and IgG4-related disease, an elevated serum interleukin 6 (IL-6) level, which is a common feature of cutaneous plasmacytosis (15), is very uncommon in IgG4-related disease (7). In addition, an association of pancreatic, lacrimal or salivary gland lesions with cutaneous plasmacytosis has not been reported previously. Therefore, careful judgment is needed to classify cutaneous plasmacytosis as an IgG4-related disease.

In contrast, the present case showed that skin might also be involved in IgG4-related disease as identified by the lat-

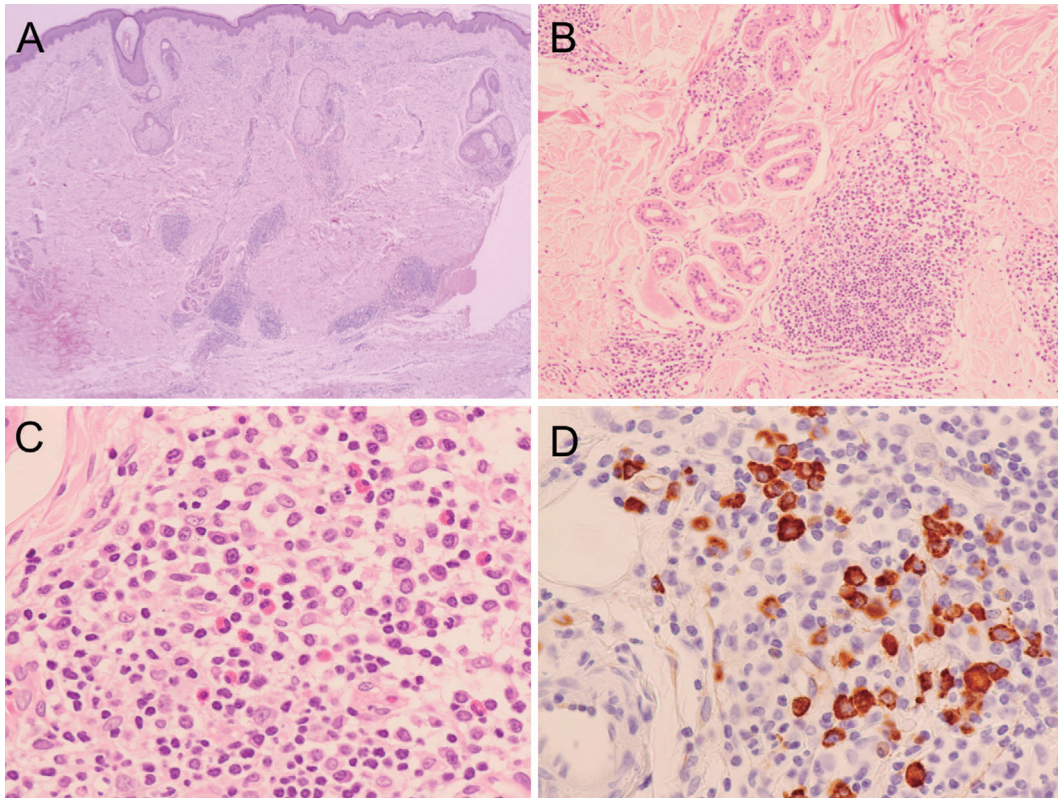


Figure 3. Moderate infiltration of lymphocytes and plasma cells is noted around arterioles or venules in the deep dermis and subcutaneous fat tissue (A). Marked lymphocyte and plasma cell infiltration is noted in the deep dermis without evident fibrosis (B). There are many infiltrating eosinophils (C). Many IgG4-positive plasma cell infiltrates in the skin lesion are seen [average IgG4 positive cell count in five different high power fields (hpf) with intense infiltration: 47/hpf] (D). [(A) skin, Hematoxylin and Eosin (HE) staining, $\times 40$, (B) HE staining, $\times 100$, (C) HE staining, $\times 400$, (D) IgG4, $\times 400$]

ter approach. In our case, the histological findings of the skin lesions with eosinophil infiltration were very similar to those of AIP or IgG4-related chronic sclerosing dacryoadenitis or sialoadenitis (3, 5, 6). Moreover, the skin, lacrimal, and parotid lesions deteriorated simultaneously during steroid tapering and improved after increasing the dosage of corticosteroid, suggesting a similar pathophysiological involvement in these organs.

Only two papers referring to the skin lesions of IgG4-related disease identified by the latter approach are available, but the clinical features of the skin lesions were not fully described and their response to corticosteroid therapy was not mentioned in detail. Sato et al (7) showed that 3 of 9 patients with systemic IgG4-related lymphadenopathy had skin lesions, and demonstrated that one of them had cutaneous pathological findings typical of IgG4-related disease. However, macroscopic findings and the distribution of the skin lesions were not shown in their paper, making it difficult to compare their lesions with those of the present case. Cheuk et al (8) proposed that cutaneous pseudolymphoma might be a skin manifestation of IgG4-related sclerosing disease. Their two cases had lacrimal or salivary gland lesions with markedly elevated serum IgG4 levels. The cutaneous lesions of the present case were itchy and

erythematous, which were consistent with those of their case. The distribution of the skin lesions in the scalp, face and neck was also very similar in their cases and ours. Although the histological findings had many similarities, our patient did not have evident fibrosis with Azan stain (data not shown) and showed less marked lymphocyte and plasma cell infiltration than their cases with pseudolymphoma formation. Therefore, we speculate that the lesion in our case was of an earlier stage than that described by Cheuk et al (8), and that our case if left untreated might also develop a similar pseudolymphoma in the future.

Further study of the skin manifestations of IgG4-related disease is needed so as to enhance our understanding of the clinical spectrum, pathophysiology and response to therapy of this disorder.

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

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