INTERNAL MEDICINE

□ CASE REPORT □

Overlap of IgG4-related Disease and Multicentric Castleman's Disease in a Patient with Skin Lesions

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Abstract

A 59-year-old man presented with multiple dark red erythemas with induration, anemia, and polyclonal hypergammaglobulinemia. A skin biopsy revealed the infiltration of lymphocytes and plasma cells and he was initially diagnosed with multicentric Castleman's disease (MCD). Glucocorticoid treatment was only partially effective. Four years later, the patient's bilateral lacrimal glands gradually became enlarged and a biopsy revealed dense lymphocyte and plasma cell infiltration with an IgG4+/IgG+ plasma cell ratio of 70%. The patient was diagnosed with IgG4-related disease (RD). Rituximab only had a slight effect. This case demonstrates that overlapping features of IgG4-RD and MCD may present in a single patient, which suggests a shared pathogenesis.

Key words: IgG4-related disease, multicentric Castleman's disease, skin lesion, rituximab

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Introduction

Immunoglobulin (Ig) G4-related disease (RD) is an immune-mediated fibroinflammatory disease characterized by infiltration with IgG4-positive plasma cells and an elevated serum IgG4 level, which affects various organs and tissues leading to tumefactive and tissue destructive lesions (1-3). In addition to the characteristic histological features such as dense lymphoplasmacytic infiltration, a storiform pattern of fibrosis, and obliterative phlebitis, an IgG4+/IgG+ plasma cell ratio of >40% is mandatory for the histological diagnosis of IgG4-RD (2). IgG4-RD can affect virtually every organ; however, IgG4-related skin lesions are uncommon and are rarely the initial manifestation of IgG4-RD (4-7).

Castleman's disease (CD) is a benign lymphoproliferative disorder mediated by deregulated cytokines, particularly interleukin (IL)-6. Two distinct presentations of CD are recognized: unicentric CD and multicentric CD (MCD) (8). Unicentric CD is confined to a single lymph node area and a histological examination reveals features that correspond to the hyaline vascular type. MCD involves multiple lymphoid regions and frequently shows systemic manifestations and abnormal laboratory findings; a histological examination reveals plasma cell type (8). MCD patients sometimes have an elevated serum IgG4 level and an IgG4+/IgG+ plasma cell ratio of >40% in the affected tissues (2, 9-11) and it is sometimes difficult to make a histological diagnosis of MCD (12).

We herein report a case of IgG4-RD in a patient who presented with skin lesions which did not meet the diagnostic criteria for IgG4-RD. The laboratory findings were highly suggestive of MCD, and the patient was initially diagnosed with MCD. The patient subsequently developed typical IgG4-RD lesions in other regions. His clinical presentation, response to therapy, and immunohistological findings suggested that he had overlapping features of IgG4-RD and MCD. The differential diagnosis between IgG4-RD and MCD is sometimes difficult (2, 9-12), and this case demonstrates that these two conditions may share a common pathogenesis and that overlapping features can be present in a single patient. This notion appears to have important therapeutic implications. IgG4-RD and MCD patients respond

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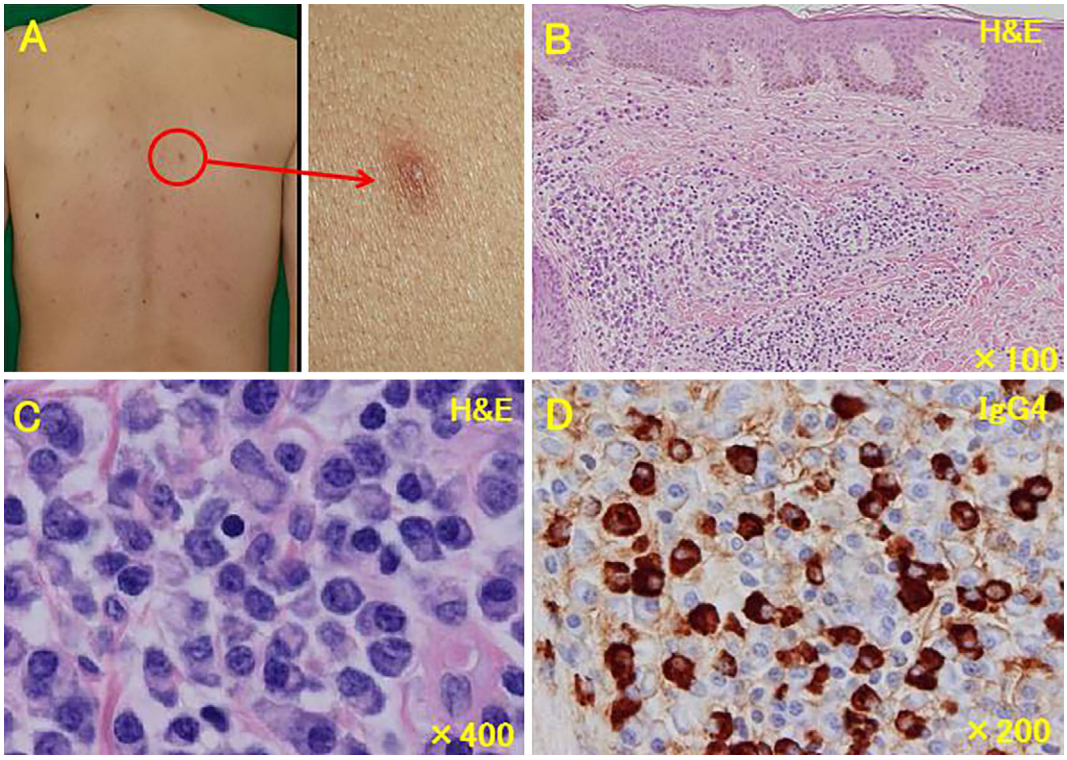

Figure 1. **The appearance and histological findings of the skin lesions. (A) The left panel shows multiple dark red erythemas of 3-4 mm in diameter with induration scattered on the trunk. The right panel shows a close view of the circled erythema, which was biopsied for a histological examination. (B and C) The examination of the biopsy specimen revealed inflammatory cell infiltration, consisting of lymphocytes and plasma cells, in the pereivascular areas and around the skin adnexa (Hematoxylin and Eosin staining). (D) Immunostaining showed an increase in the number of IgG4+ plasma cells with an IgG4+/IgG+ plasma cell ratio of 36%.**

differently to different treatment modalities such as glucocorticoids or rituximab (3, 8, 13-17); however, the expected responses may not be achieved in patients with overlapping features.

Case Report

A 59-year-old man was referred to our hospital due to anemia and hypergammaglobulinemia. Three years previously, an elevated total protein (TP) level had been detected in a regular health-check and polyclonal hypergammaglobulinemia with a TP level of 9.1 mg/dL with 30.2% γ-globulin was noted; however, in the absence of other significant findings, no further evaluations were performed. Shortly thereafter, the patient noticed non-pruritic erythemas on his face, which gradually extended to his trunk. His medical history included acute hepatitis of unknown etiology at 32 years of age. He smoked one pack of cigarettes and drank 350 mL of beer per day.

On referral, multiple dark red erythemas of 3-4 mm in diameter with induration were scattered on the patient's face and trunk (Fig. 1A). The superficial lymph nodes were not enlarged. The patient's heart and respiratory sounds were normal and the liver and the spleen were not palpable.

The laboratory data were as follows: white blood cell count, 8.4×10^{9}/L (with normal differentials); red blood cell count, 3.86×10^{12}/L (1.23% reticulocytes); hemoglobin, 11.2 g/dL; hematocrit, 33.5%; and platelet count, 235×10^{9}/L. The patient's coagulation test results were within reference ranges. The erythrocyte sedimentation rate was 119 mm/hr. The blood chemistry results were as follows: TP, 10.5 g/dL (γ-globulin 47.8%); albumin, 3.1 g/dL; creatinine, 0.70 mg/dL; total bilirubin, 0.3 mg/dL; aspartate aminotransferase, 11 U/L; alanine aminotransferase, 7 U/L; and lactate dehydrogenase, 103 U/L. The patient's C-reactive protein level was 6.20 mg/dL. Immunoelectrophoresis of the serum protein revealed a polyclonal increase in the patient's immunoglobulin levels: IgG, 5,511 mg/dL; IgG4, 692 mg/dL (reference range, 4.8-105.0); IgA, 859 mg/dL; and IgM, 462 mg/dL. The patient's serum interleukin (IL)-6 level was 19.5 pg/mL (reference range, <2.41) and he was negative for hepatitis B surface antigen, anti-hepatitis C virus and anti-human immunodeficiency virus antibodies. The chest computed tomography (CT) revealed diffuse, faint, and centrilobular granular shadows and ground glass opacities with the thickening of the interlobular septa. Several enlarged mediastinal and hilar lymph nodes were detected; however, a lymph node biopsy was not performed due to their small size (the largest was < 1 cm in diameter).

A skin biopsy of an erythema on the patient's back re-

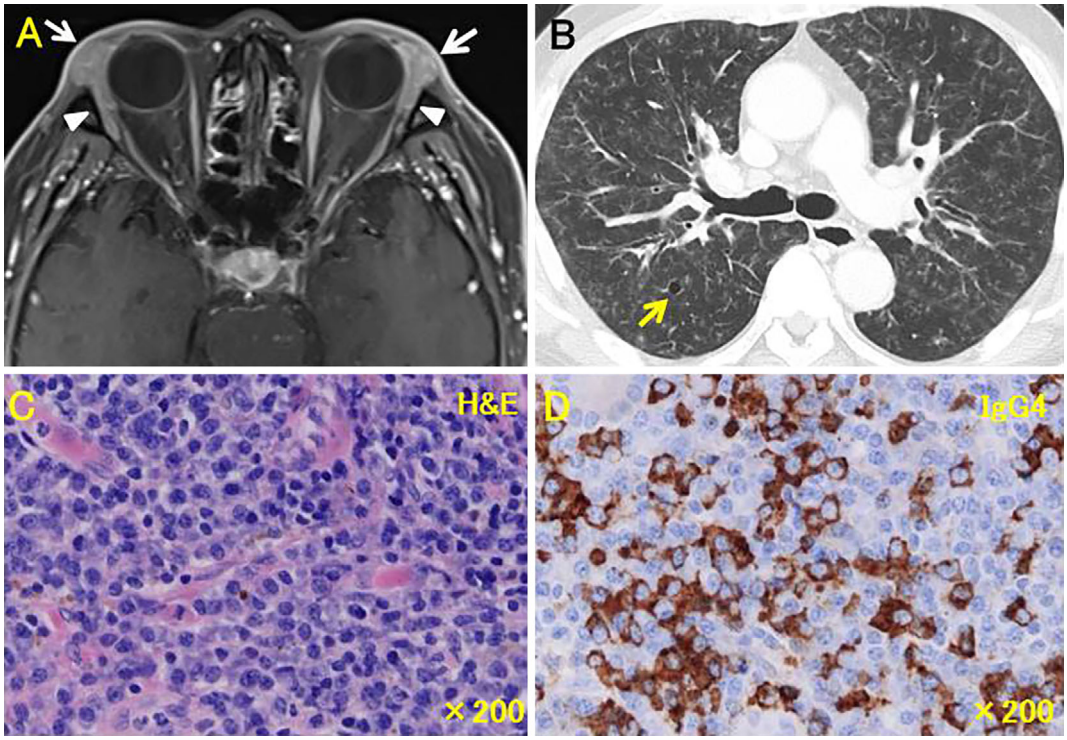

Figure 2. **Magnetic resonance imaging (MRI) of the orbits, computed tomography (CT) of the chest, and the histology of the lacrimal gland. (A) Gadolinium-enhanced T1-weighted MRI shows the diffusely enhanced bilateral enlargement of the lacrimal glands (arrows) which had a slightly high-intensity on T2-weighted images and extended along the rectus muscles (triangles). (B) Chest CT reveals diffuse, faint, and centrilobular granular shadows, ground glass opacities with the thickening of the interlobular septa along the bronchovascular bundles, and multiple small air cysts with a thin wall (arrow). (C) A biopsy specimen from the lacrimal gland showed that the structure of the lacrimal gland was destroyed and replaced by dense lymphocyte and plasma cell infiltration (Hematoxylin and Eosin staining). (D) Immunostaining showed increased numbers of IgG4+ plasma cells and an IgG4+/IgG+ plasma cell ratio of 70%.**

vealed inflammatory cell infiltration consisting of lymphocytes and plasma cells in the perivascular areas and around skin adnexa (Fig. 1B and C). The IgG4+/IgG+ plasma cell ratio was 36% (Fig. 1D). Although this ratio was considered to be elevated, MCD was diagnosed based on other histological findings in the skin and the clinical and laboratory findings — especially elevated C-reactive protein (CRP) and IL-6 levels. Two months later, the patient developed shortness of breath on exercise and night sweats and treatment with oral prednisolone (PSL) was initiated at 0.5 mg/kg. Although this led to the resolution of the patient's symptoms, the laboratory data did not improve and PSL was continued at a reduced dose of 0.25 mg/kg.

Four years later, he noticed gradual swelling of the bilateral eye lids and salivary glands. Magnetic resonance imaging (MRI) revealed enlargement of the bilateral lacrimal glands, which extended along the rectus muscles (Fig. 2A). A biopsy of the enlarged lacrimal gland was performed, which revealed dense infiltration with lymphocytes and plasma cells, without atypia, and destruction of the lacrimal structure (Fig. 2C). The IgG4+/IgG+ plasma cell ratio was 70%; these findings were considered to be compatible with IgG4-RD (Fig. 2D). The patient's serum IgG4 and IL-6 levels were 981 mg/dL and 28.8 pg/mL, respectively. Chest CT showed the progression of the previously observed findings and the emergence of multiple small thin-walled air cysts (Fig. 2B). No change was observed in the number or appearance of the mediastinal and hilar lymph nodes. Rituximab was administered weekly at a dose of 375 mg/m^2 (four times) with the approval of the Institutional Review Board. This resulted in only a slight reduction of the enlarged lacrimal glands; however, the other clinical and laboratory features showed no improvement.

At two years after rituximab treatment, the patient's disease is stable. He is currently being treated with PSL (0.2 mg/kg).

Discussion

IgG4-RD is a multisystem disorder and affects virtually every organ; however, IgG4-related skin lesions are rare and develop in less than 2% of IgG4-RD patients (4, 5). While cutaneous IgG4-RD lesions are mostly present with other extracutaneous lesions, skin involvement rarely precedes other lesions as the first manifestation (6, 7, 18). IgG4-related skin lesions usually present as erythematous and

itchy plaques or subcutaneous nodules (19, 20). The critical diagnostic histopathological features of IgG4-RD include dense lymhoplasmacytic infiltration, a storiform pattern of fibrosis, and obliterative phlebitis. The present case was initially suspected to have IgG4-related skin lesions; however, as the histological findings did not fulfil these diagnostic features and the IgG4-/IgG+ plasma cell ratio was below 40%, we did not diagnose the patient with IgG4-RD at that time. On the other hand, because MCD patients can have elevated serum IgG4 levels and a high tissue IgG4+/IgG+ plasma cell ratio (18) and due to the presence of laboratory findings that are frequently observed in MCD patients, such as anemia, hypergammaglobulinemia and, importantly, elevated CRP and IL-6 levels, he was initially diagnosed with MCD. Patients with IgG4-RD do not usually have constitutional symptoms and have only modestly abnormal inflammatory marker levels with a normal IL-6 level. These findings are useful for making a differential diagnosis between IgG4-RD and MCD (10-12, 21). The frequency of MCD patients who have a tissue IgG4+/IgG+ plasma cell ratio of > 40%, which fulfills the immunohistochemical criteria for IgG4-RD, is not known. However, the average IgG4+/IgG+ plasma cell ratio of the MCD patients who fulfil the criteria is 52%; this is comparable to the average IgG4+/IgG+ plasma cell ratio in IgG4-RD patients, which is 58% (9, 10, 12). Thus, the distinction between IgG4-RD and MCD cannot be made based on the IgG4+/IgG+ plasma cell ratio alone. However, the patient was diagnosed with IgG4-RD and not with MCD based on the high IgG4+/IgG+ plasma cell ratio and the other histological findings of the lacrimal mass which were compatible with IgG4-RD. Moreover, CD involving the lacrimal glands is very rare. To the best of our knowledge, only three cases of lacrimal CD have been reported in the literature. Lacrimal gland biopsies in two of these three cases revealed that they corresponded to the hyaline vascular type, while a salivary gland biopsy of the third case revealed that the patient corresponded to the plasma cell type (22-24). Thus, it appeared unlikely that the lacrimal lesions were manifestations of MCD. In retrospect, it appears reasonable and justified to consider that the initial skin lesions were representative of the early stage of IgG4-related skin disease as the three critical diagnostic histological features of IgG4-RD are often not observed in patients with IgG4-related skin disease (19). However, the possibility that they were cutaneous manifestations of MCD cannot be completely excluded. Nonetheless, we consider the present case to represent an example of an overlap of IgG4-RD and MCD rather than a case of IgG4-RD or MCD in a patient with features of the other disease.

Other features also indicated the overlap of IgG4-RD and MCD in the present case. The pulmonary lesions of IgG4-RD basically show diffuse lymphoplasmacytic infiltration (25) and present as the thickening of the bronchovascular bundles, solid nodular lesions, round-shaped ground-glass opacities, alveolar interstitial disease, the thickening of the interlobular septa, or a mixed pattern of these findings (25-28). MCD is associated with lymphatic interstitial pneumonitis and the radiological findings may resemble those of the bronchovascular disease seen in IgG4-RD (26, 29). With the exception of nodular lesions, these findings were observed in the present case. The specific characteristic CT finding of MCD is thin-walled cysts, which are caused by the peribronchial and peribronchiolar distribution of lymphatic interstitial pneumonitis (29). The development of thin-walled cysts during the course of the disease in the present case suggests that his pulmonary lesions were associated with MCD either alone or in combination with IgG4-RD; however, a lung biopsy has not been performed thus far.

Glucocorticoid is the first-line therapy for IgG4-RD and the initial response to corticosteroids is generally very favorable (3, 14). Rituximab is a humanized monoclonal antibody against CD20 and is effective in more than 90% of IgG4-RD patients who are refractory to glucocorticoid treatment (13, 15, 16). Although the response of MCD patients to glucocorticoid has not been fully evaluated, glucocorticoid is sometimes effective in improving symptoms of MCD; however, the effects are not consistent (8, 17). Rituximab has been administered to patients with MCD and is only partially effective (17). The present case showed only a marginal response to glucocorticoid and almost no response to rituximab; these responses appear to be in line with the characteristics of MCD rather than Ig4G-RD.

IgG4-RD is a relatively new disease entity and its nature and clinical characteristics have not been clearly defined. The present case demonstrates that a clear overlap of clinical and histological features of IgG4-RD and MCD may present in a single patient and suggests a shared pathogenesis. The accumulation of cases will be necessary to elucidate the association between these two rare disorders.

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

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