IgG4-Related Sialoadenitis with a Skin Lesion and Multiple Mononeuropathies Suggesting Coexistent Cryoglobulinemic Vasculitis

Mari Kamiya¹, Peter Y. Shane¹, Makoto Soejima¹, Shuji Tohda², Nobuyuki Miyasaka¹ and Hitoshi Kohsaka¹

Abstract

A 68-year-old man was admitted because of weakness of the left leg, dysesthesiae of the extremities and bilateral lower extremity purpura. A neurological examination showed mononeuritis multiplex with laboratory evidence of hypocomplementemia, cryoglobulinemia and leukocytoclastic vasculitis in the biopsy of a skin specimen. The patient also exhibited bilateral submandibular gland swelling, elevated serum IgG4 levels and infiltration of a large number of IgG4-positive plasma cells in the submandibular glands. These findings were consistent with both cryoglobulinemic vasculitis and IgG4-related disease. The administration of oral prednisolone (1 mg/kg/day) resolved the neurological manifestations and the swelling of the submandibular glands and cryoglobulinemia.

Key words: IgG4-related disease, multiple mononeuropathy, cryoglobulinemic vasculitis

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Introduction

After it was first described in the pancreas (1), there have been numerous reports of IgG4-related disease (IgG4-RD), a systemic disorder characterized by high levels of serum IgG4 and massive fibrosis accompanied by IgG4-positive plasma cells infiltrating various organs. Pathologic findings show some variability depending on the site, but common features include a dense lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells and obliterator phlebitis (2, 3). Commonly affected sites include the pancreas, salivary glands, kidneys, lungs, retroperitoneum, aorta, lymph nodes and the orbit (2). However, IgG4-RD rarely involves peripheral nerves. There have been a few reported cases involving the peripheral nervous system, which were characterized by nerve-centered distinct soft tissue masses (4, 5).

Cryoglobulinemia occurs in the serum and involves the presence of one or more types of immunoglobulin that precipitate in the cold and dissolve upon rewarming. Several infectious agents, as well as autoimmune and neoplastic disorders have been associated with the presence of these antibodies (6). Cryoglobulins are classified into three subgroups according to their immunohistochemical composition: type I is defined by the presence of a single monoclonal immunoglobulin (Ig), typically seen in B-lymphoid neoplasms, whereas the mixed cryoglobulinemias are characterized by immune complexes composed of polyclonal IgGs with monoclonal (type II) or polyclonal (type III) IgM (or IgG or IgA) (6). Although most patients with mixed cryoglobulinemia are also infected with hepatitis C virus (HCV), the causes of mixed cryoglobulins is unclear in 5-30% of patients, resulting in the term, “essential cryoglobulinemia” (6). Mixed cryoglobulinemia often leads to systemic vasculitis, which is thought to be caused by the deposition of immune complexes on the walls of the small vessels, and by the subsequent activation of the complement cascade. It is characterized by a typical clinical triad of purpura, weakness and arthralgias. Accompanying multiple organ involve-

¹Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Japan and ²Department of Laboratory Medicine, Tokyo Medical and Dental University (TMDU), Japan

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Correspondence to Dr. Hitoshi Kohsaka, kohsaka.rheu@tmd.ac.jp
ment may include chronic hepatitis, membranoproliferative glomerulonephritis and peripheral neuropathy due to leukocytoclastic vasculitis (6).

In this report, we present the first case of IgG4-RD accompanied by multiple mononeuropathy, which was diagnosed concomitantly with vasculitis accompanying cryoglobulinemia.

Case Report

A 68-year-old man was admitted to our hospital with low-grade fever, purpura and edema in both legs, weakness of the left leg and sensory abnormalities in the extremities that had persisted for a couple of months. Three weeks prior to admission, it had become difficult for him to walk as he had lost the ability to flex and extend his left ankle. He had been diagnosed with asthma 50 years earlier, with Hashimoto’s disease 30 years earlier and with allergic rhinitis 14 years earlier. Three years earlier, he had noticed swelling of the lymph nodes around his neck and was diagnosed with diffuse large B cell lymphoma (clinical stage IIIA, surface IgM+D, λ). He was treated with six cycles of combination chemotherapy of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and the subsequent remission was confirmed by positron emission tomography-computed tomography (PET/CT). On admission, his body temperature was 37.5°C and his blood pressure and heart rate were normal. A physical examination showed enlarged submandibular glands, which were firm and nodular without tenderness or erythema. The patient had been unaware of these findings and was unable to recount their history. Mild edema and non-palpable purpura were seen in both lower extremities. The neurological examination showed 1/5 strength in the left tibialis anterior and the left gastrocnemius, with reduced sensation to touch, heat, pain and vibration as well as dysesthesias involving both lower extremities distal to the knees and all fingers distal to the proximal interphalangeal joints.

Laboratory tests revealed leukocytosis (9,700/μL) with eosinophilia (1,455/μL). The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated (42 mg/L and 109 mm/hr, respectively), with decreased levels of serum complements (CH50: <10 U/mL, C3: 51 mg/dL, C4: 13 mg/dL). Serum immunoglobulin levels were as follows: IgG: 2,564 mg/dL, IgA: 67 mg/dL, IgM: 16 mg/dL, IgE: 746 IU/mL and IgG4 markedly elevated at 1,400 mg/dL. Serum immunoelectrophoresis revealed monoclonal IgG-κ. The serum soluble interleukin-2 receptor level was 1,300 U/mL. Serum creatinine was 0.68 mg/dL, and there were no abnormal findings detected in the urine. Serological tests were negative for anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibody and anti-SS-A/Ro and anti-SS-B/La antibodies. The rheumatoid factor was positive at a low titer (42 U/L). The results for hepatitis B surface antigen, surface antibody, core antibody and hepatitis C antigen were negative. Human immunodeficiency virus tests were negative. Serum cryoglobulins were present with electrophoresis revealing monoclonal IgG-κ and polyclonal IgG including IgG4 (Fig. 1).

A nerve conduction study revealed the presence of multiple mononeuropathies in the left tibial and left peroneal nerves. No abnormal findings were found in the lumbar vertebrae and the lumbar cord by magnetic resonance imaging. An enhanced CT scan of the whole body revealed no significant findings in the lungs, kidneys, pancreas and lymph nodes, but indicated moderate swelling of the bilateral submandibular glands (Fig. 2A). A PET/CT scan showed increased F-18 fluorodeoxyglucose positron (FDG) uptake at the bilateral submandibular glands (Fig. 2B), which was not observed during the diagnosis of malignant lymphoma (Fig. 2C).

A biopsy of the lower extremity lesion showed leukocytoclastic vasculitis in the dermis and infiltration of plasma cells around the dermal and subcutaneous vessels, of which a great majority was found to be IgG4-positive (the ratio of IgG4+ plasmacytes to IgG+ plasmacytes was over 80%) by immunohistostaining (Fig. 3). A biopsy of the submandibular gland showed marked lymphoplasmacytic infiltration with fibrosis, with immunohistostaining revealing that the majority of plasma cells were IgG4-positive (the ratio of IgG4+/IgG+ plasma cells was over 80%) (Fig. 4). Furthermore, a biopsy of the right sural nerve showed a marked reduction of myelinated and unmyelinated fibers (Fig. 5A) accompanied by perineural fibrosis. A slight infiltration of lymphoplasmacytoid cells was found around the vessels inside the epineurium (Fig. 5B, arrowhead) and in the fatty tissue adjacent to the epineurium (Fig. 5B, arrow). There were 27 IgG+ cells and eight IgG4+ cells per high power

![Figure 1. Immunoelectrophoresis of serum cryoglobulins. The main component of the cryoglobulins was monoclonal IgG-κ, revealed by a distorted precipitation line of IgG and a restricted κ/λ ratio. The cryoglobulins also consisted of polyclonal IgG including IgG4. NS: normal human serum, PC: cryoglobulins of the patient, WHS: anti-whole human serum antibody, IgG4: anti-IgG4 antibody, IgG: anti-IgG antibody, IgM: anti-IgM antibody, IgA: anti-IgA antibody, κ: anti-kappa light chain antibody, λ: anti-lambda light chain antibody.](image-url)
field. Destruction of the perineurium or the infiltration of inflammatory cells inside the nerve fascicule were not observed. Atypical cells were not found in any of the specimens and the skewing of the κ/λ light chain ratio could not be determined by means of immunohistostaining.

A clonality analysis of paraffin-embedded lymph node and submandibular gland specimens was performed. The samples were analyzed by polymerase chain reaction (PCR)
Figure 5. Histopathological findings of the right sural nerve. A: Toluidine blue staining showed a marked reduction in the number of myelinated and unmyelinated fibers accompanied with fibrosis around the nerve bundles. B: Hematoxylin and Eosin staining showed infiltration of lymphoplasma-cytoid cells around the vessels surrounding the perineurium (arrowhead) and in the fatty tissue (arrow) adjacent to the nerve bundles.

Figure 6. PCR results for IgH rearrangement in the lymph node sampled during the diagnosis of the lymphoma (top) and submandibular glands (bottom). Both of the samples showed peaks in the analyses of VH (FR3)-JH (A) and DH-JH (B) rearrangements. The sizes of the amplification products were different in both samples, suggesting that the submandibular glands were not clonally related to the lymphoma. The scale indicates the size of the PCR product in base pairs.

using the commercially available Ig heavy chain (IgH) Somatic Hypermutation Assay (InvivoScribe Technologies, San Diego, USA) using established Biomed-2 protocols and capillary electrophoresis (7).

These studies indicated both of the samples had peaks in the variable gene segments (VH) (framework (FR) 3 region)-joining gene segments (JH) (Fig. 6A) and the diversity gene segments (DH)-JH (Fig. 6B). However, the sizes of the amplification products were different in both components, suggesting that the submandibular glands were not clonally related to the lymphoma. The immunohistostaining of the tumor cells of the malignant lymphoma were IgG4-negative
In our patient, salivary gland swelling, a markedly elevated serum IgG4 level (1,400 mg/dL), eosinophilia and infiltration of IgG4-positive plasma cells in the submandibular glands were consistent with IgG4-RD (8, 9). However, multiple mononeuropathy and leukocytoclastic vasculitis of the skin are not common in this disease. The combination of multiple mononeuropathy, leukocytoclastic vasculitis and the presence of mixed cryoglobulins in the serum suggested a diagnosis of cryoglobulinemic vasculitis. Therefore, a diagnosis of IgG4-RD and cryoglobulinemic vasculitis was warranted in this case.

A therapy including high-dose oral prednisolone (1 mg/kg daily) was started. Swelling of the salivary glands resolved within several days and the non-palpable purpura disappeared gradually. The patient’s neurological symptoms slowly improved. Serum complement levels were normalized, serum IgG4 decreased to 447 mg/dL and the cryoglobulinemia disappeared one month after the initiation of the treatment.

Discussion

The present case was diagnosed as IgG4-RD due to the presence of swollen salivary glands, a markedly elevated serum IgG4 level and IgG4-positive lymphoplasmacytic infiltrates in the submandibular glands. However, regarding the skin lesion, the observed leukocytoclastic vasculitis, albeit the infiltration of IgG4-positive plasmacytoid cells, was inconsistent with previous reports of IgG4-RD. Although there have been reports of arteritis in the lungs (9) and the jejun (10) with IgG4-RD, leukocytoclasia has been atypical, not to mention type II mixed cryoglobulinemia being the most frequent cause of vasculitis among the cryoglobulinemias (6). Unfortunately, the lack of biopsy specimens precluded definitive assessments of vessel wall immunoglobulin and complement deposition, and therefore the determination of cryoglobulinemic vasculitis had to be discerned.

IgG4-RD has rarely involved peripheral nerves, with reported cases being associated with a perineural soft tissue mass histologically characterized by a marked inflammatory infiltration including IgG4-positive plasma cells with fibrosis in the epineurium (4, 5). In the case reported herein, these
findings were not observed. Moreover, the nerve biopsy results suggest cryoglobulinemic vasculitis, with mononuclear-predominant perivascular inflammation in the epineurium with perineural thickening/inflammation, which reflects the chronic ischemic state that is sometimes revealed (11).

Since one all-encompassing description was lacking in this case, a diagnosis of IgG4-RD and cryoglobulinemic vasculitis was made. There has been no previous description of the co-occurrence of these diseases.

Regarding the relationship between IgG4-RD and cryoglobulinemic vasculitis, we considered a hypothesis that the patient may have had an underlying malignant lymphoproliferative disorder. Associations between IgG4-RD and malignant lymphoproliferative disorders have been suggested by some case studies (12, 13) and mixed cryoglobulinemia is known to be associated with lymphoproliferative diseases (6). Additionally, our patient had a known history of malignant lymphoma, although no indication of a malignant relapse was found on PET/CT. The increased uptake at the submandibular glands showed no findings suggesting the relapse of the malignant lymphoma. IgH gene rearrangement was detected in the submandibular glands. However, we believed it was oligoclonal or polyclonal and driven by an inflammatory mechanism or benign lymphoproliferative condition rather than monoclonal proliferation driven by a malignant disease because the peaks seemed to be in a polyclonal background compared to that of the lymph node sampled during the diagnosis of lymphoma (Fig. 6). Additionally, it is difficult to discriminate between monoclonal, oligoclonal or polyclonal PCR products because of sensitivity issues (14). Regarding the temporal relationship between cryoglobulinemia and malignant lymphoma, cryoglobulinemia seems to precede the diagnosis of the malignancy by years (15). However, there is a reported case of cryoglobulinemia persisting for nine years after remission of a lymphoma, although the diagnosis of cryoglobulinemia preceded that of the lymphoma by 10 years (16). Because we do not know where the cryoglobulins initially appeared, we could not conclusively rule out the possibility of their association with the malignant lymphoma now in remission.

Another hypothesis is that the cryoprecipitation may have been caused by IgG4, although we could not find any reports of elevated IgG4 in the cryoglobulins. Among all the Ig heavy chain subclasses, IgG3 is the most frequently detected in serum cryoglobulins (17). Because IgG4 does not activate the complement pathway effectively due to its weak or negligible binding to C1q and Fcy receptors (3) (contrary to IgG3), we postulate that the causative component of cold-precipitation is unlikely to be IgG4.

Mixed cryoglobulinemia is known to be associated with systemic autoimmune syndromes such as Sjögren’s syndrome and systemic lupus erythematosus (SLE) (6). The clinical condition of our case appears to be less consistent with a traditional autoimmune disorder such as Sjögren’s syndrome, compared with IgG4-RD.

Although the essential role of the IgG4 antibody in the pathogenesis of IgG4-RD remains unclear, increased serum IgG4 levels and tissue infiltration by IgG4-positive plasma cells are thought to be key events in IgG4-RD (2, 3, 18).

This case may reveal the dysregulation of B lymphocytes, which may be the underlying pathologic cause of both IgG4-RD and cryoglobulinemia; this would be consistent with the past history of lymphoma. An important factor for B lymphocyte survival and proliferation is B cell-activating factor (BAFF). This factor is known to regulate the maturation and survival of B cells and mediate CD40 ligand-independent antibody production and induction of IgG4 class switching in the presence of IL-4 (18, 19). Studies have shown that serum concentrations of BAFF and its homolog APRIL (a proliferation-inducing ligand) were significantly higher in patients with IgG4-RD than in healthy individuals (20, 21) and that serum BAFF levels decrease following therapy (20). Serum BAFF levels have also been associated with the presence of cryoglobulins among HCV infected patients (22) and there have been reports of the effectiveness of a BAFF blockade in patients with cryoglobulinemic vasculitis associated with SLE (23) and Sjögren’s syndrome (24). BAFF is also crucial to the growth of malignant B cells (25). Although BAFF is a common factor with a possible association with both IgG4-RD and cryoglobulinemic vasculitis, we did not determine the serum BAFF levels, and we can only speculate on the underlying B-cell dysregulation.

The differential diagnoses considered in this case included eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), paraneoplastic vasculitis and Sjögren’s syndrome. We considered EGPA because of the history of asthma, mononeuropathy multiplex, eosinophilia and leukocytoclastic vasculitis. Additionally, high levels of serum IgG4 have been reported with EGPA (26). However, a negative result for ANCA and a lack of literature on concomitant cryoglobulinemia eliminated a diagnosis of EGPA. Eosinophilia is a common feature of IgG4-RD (3) and an association between IgG4-RD and conditions like allergic rhinitis or asthma has been reported (12). In EGPA, an increase in IgG4-positive plasma cells is not as prominent (not more than 40% of the infiltrating IgG-positive plasma cells) (26), as it is in IgG4-RD.

A past history of malignant lymphoma led us to consider the possibility of paraneoplastic vasculitis; however, we could not detect a relapse of the malignant lymphoma or any new neoplasia.

Regarding the possibility of Sjögren’s syndrome, although it is known that patients have a significantly higher risk of developing lymphoproliferative disease, mixed cryoglobulinemia and autoimmune thyroiditis, the biopsy specimen from the submandibular gland in this case was consistent with the pathological findings of IgG4-RD, not Sjögren’s syndrome.

This is the first case of IgG4-RD accompanied by cryoglobulinemic vasculitis. The pathogenesis of IgG4-RD is currently being investigated. This case provides suggestions...
regarding the etiology of these two uncommon diseases.

Author’s disclosure of potential Conflicts of Interest (COI).
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References

1. Yoshida K, Toki F, Takeuchi T, Watanebe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci 40: 1561-1568, 1995.

2. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 385: 1460-1471, 2015.

3. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 366: 539-551, 2012.

4. Ohyama K, Koike H, Iijima M, et al. IgG4-related neuropathy: a case report. JAMA Neurol 70: 502-505, 2013.

5. Inoue D, Zen Y, Sato Y, et al. IgG4-related perineural disease. Int J Rheumatol 2012: 401890, 2012.

6. Ferri C. Mixed cryoglobulinemia. Orphanet J Rare Dis 3: 25, 2008.

7. van Dongen JJ, Langerak AW, Brüggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. Leukemia 17: 2257-2317, 2003.

8. Yamada K, Hamaguchi Y, Saeki T, et al. Investigations of IgG4-related disease involving the skin. Mod Rheumatol 23: 986-993, 2013.

9. Yamashita K, Haga H, Kobashi Y, Miyagawa-Hayashino A, Yoshizawa A, Manabe T. Lung involvement in IgG4-related lymphoplasmacytic vasculitis and interstitial fibrosis. Am J Surg Pathol 32: 1620-1626, 2012.

10. Wong DD, Pilla SR, Kumaacsinghe MP, et al. IgG4-related sclerosing disease of the small bowel presenting as necrotizing mesenteric arteritis and a solitary jejunal ulcer. Am J Surg Pathol 36: 929-934, 2012.

11. Collins MP. The vasculitic neuropathies: an update. Curr Opin Neurol 25: 573-585, 2012.

12. Go H, Kim JE, Kin YA, et al. Ocular adnexal IgG4-related disease: comparative analysis with mucosa-associated lymphoid tissue lymphoma and other chronic inflammatory conditions. Histopathology 60: 296-312, 2012.

13. Uehara T, Ikeda S, Hamano H, et al. A case of Mikulicz’s disease complicated by malignant lymphoma: a postmortem histopatological finding. Intern Med 51: 419-423, 2012.

14. Davis TH, Yockey CE, Balk SP. Detection of clonal immunoglobulin gene rearrangements by polymerase chain reaction amplification and single-strand conformational polymorphism analysis. Am J Pathol 142: 1841-1847, 1993.

15. Ferri C, Sebastiani M, Giuggioli D, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum 33: 355-374, 2004.

16. Besuda E, Vik A, Koldingsnes W, Nossent JC. Successful treatment with bortezomib in type-I cryoglobulinemic vasculitis patient after rituximab failure: a case report and literature review. Int J Hematol 97: 800-803, 2013.

17. Karras A, Noël LH, Droz D, et al. Renal involvement in monoclonal (type I) cryoglobulinemia: two cases associated with IgG3 kappa cryoglobulin. Am J Kidney Dis 40: 1091-1096, 2002.

18. Umehara H, Nakajima A, Nakamura T, et al. IgG4-related disease and its pathogenesis-cross-talk between innate and acquired immunity. Int Immunol 26: 585-595, 2013.

19. Masaki Y, Dong L, Kurose N, et al. Proposal for a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis 63: 1310-1315, 2009.

20. Kiyama K, Kawabata D, Hosono Y, et al. Serum BAFF and APRIL levels in patients with IgG4-related disease and their clinical significance. Arthritis Res Ther 14: R86, 2012.

21. Lin W, Jin L, Chen H, et al. B cell subsets and dysfunction of regulatory B cells in IgG4-related diseases and primary Sjögren’s syndrome: the similarities and differences. Arthritis Res Ther 16: R118, 2014.

22. Toubi E, Gordon S, Kessel A, et al. Elevated serum B-Lymphocyte activating factor (BAFF) in chronic hepatitis C virus infection: association with autoimmunity. J Autoimmun 27: 134-139, 2006.

23. De Vita S, Quartuccio L, Salvin S, et al. Sequential therapy with belimumab followed by rituximab in Sjögren’s syndrome associated with B-cell lymphoproliferation and overexpression of BAFF: evidence for long-term efficacy. Clin Exp Rheumatol 32: 490-494, 2014.

24. Golmia AP, Martin R, Hislop C, et al. Disappearance of cryoproteins in the sera of a patient with SLE after treatment with belimumab, a novel subcutaneous anti-B cell therapy. Rheumatology 53: 957-958, 2014.

25. Yang S, Li JY, Xu W. Role of BAFF/BAFF-R axis in B-cell non- Hodgkin lymphoma: demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum 33: 355-374, 2004.