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Case Report

Coincidence of Mixed Connective Tissue Disease with Immunoglobulin G4–Related Disease: A Case Report

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Abstract

Immunoglobulin G4–related disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder characterized by mass-forming lesions that can result in irreversible organ damage and mortality if ignored. Mixed connective tissue disease (MCTD) is characterized as an overlap of systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myopathy, and rheumatoid arthritis (RA). While cases of IgG4-RD linked to SLE and RA have been documented, to the authors' knowledge, there has not been a recorded instance of a patient with IgG4-RD related with MCTD. A patient diagnosed with both MCTD and IgG4-RD is presented.

Keywords: IgG4-RD, immunoglobulin G4–related disease, MCTD, mixed connective tissue disease

Case Presentation

A 45-year-old female patient visited the rheumatology outpatient clinic in 2018 with a complaint of edema in her left eye. She denied having ever experienced Raynaud's phenomenon, xerostomia, xerophthalmia, arthralgia/arthritis, serositis, photosensitivity, dermatitis, or alopecia at that time.

Laboratory examination revealed a C-reactive protein (CRP) level of 0.2 mg/L and an erythrocyte sedimentation rate (ESR) of 67 mm/h. The antinuclear antibody test was positive in 1/1000 titers with a granular pattern, the extractable nuclear antigen panel showed +++ positive U1 ribonucleoprotein (U1-RNP) antibodies, and MPO-ANCA was also positive. Additionally, RF (rheumatoid factor) Anti-dsDNA, Scl70, SSA/Ro, SSB/La, and centromere-B were negative. Her urine analysis and pulmonary imaging were unremarkable. A serum level of IgG4 was ordered and resulted in 7.26 g/L (normal <1.25 g/L), and a lacrimal gland biopsy was performed and revealed dense lymphoplasmacytic cell infiltration rich in plasma cells in the lobules, follicles containing germinal centers, and the vein is obliterated by aggregated inflammatory cell infiltration (obliterative phlebitis). In addition to the presence of $IgG4^+$ cell infiltration in the histopathological examination, an IgG4+/IgG+ plasma cell ratio of >40% was demonstrated. The diagnosis of orbital inflammatory disease due to immunoglobulin G4–related disease (IgG4-RD) is made by detecting immunopositive plasma cells with IgG4 (40%) (Figure 1).

She received methylprednisolone and azathioprine and did not attend the clinic for the previous 4 years. Still, she returned in September 2022 with complaints of fatigue, arthralgia, pain, and rigidity in the muscles surrounding her neck, shoulders, and hips. Her muscle pain was exacerbated during physical activity and alleviated with rest. She also expressed her dissatisfaction with the Raynaud phenomenon at that time. In order to conduct additional diagnostic testing, she was admitted to the hospital. Physical examination revealed swelling in the left eye, finger edema, sclerodactyly distal to proximal interphalangeal joints, pitting scars in the fingertips, and livedo reticularis in both upper and lower extremities (Figure 2). Nailfold capillaroscopic examination demonstrated enlarged (giant) capillaries with multiple hemorrhages. The patient was evaluated for dry eye by an ophthalmologist; Schirmer's test was positive (Schirmer-1: 2 in the right eye and 1 mm in the left eye). Laboratory evaluation revealed a CRP level of 78 mg/L, an ESR of 69 mm/h, and a serum IgG4 level of 3.37 g/L (normal value: 0-1.25 g/L). Minor salivary gland biopsy was unremarkable, and an orbital magnetic resonance imaging (MRI) indicated disease recurrence with bilateral lacrimal gland involvement and an increase in lesion sizes relative to 2018 scans (Image 1).

The patient was diagnosed with mixed connective tissue disease (MCTD) and IgG4-RD based on Raynaud phenomenon, sclerodactyly, high titer anti-U1-RNP positivity, capillaroscopic findings, serum IgG4 level,

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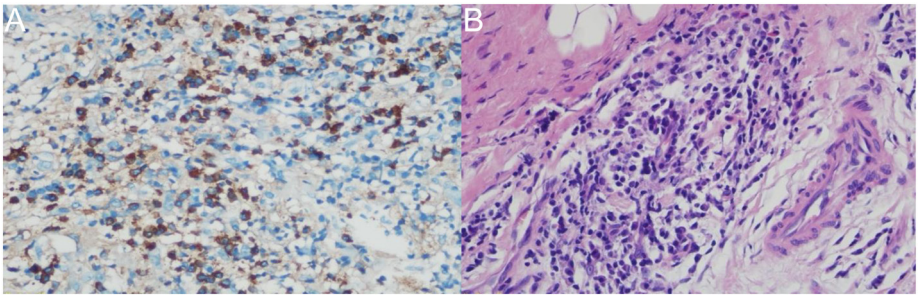

Figure 1. Histopathological evaluation of the lacrimal gland. (A) Immunohistochemical staining shows immunoglobulin G4–positive plasma cell infiltration (>40%) in the lobules. (B) Hematoxylin-eosin stain reveals obliterative phlebitis and dense lymphoplasmacytic infiltrates (H&E, ×400).

and orbital MRI, and put on acetylsalicylic acid, nifedipine, methylprednisolone, hydroxychloroquine, and azathioprine.

By the third month of medication, her problems were completely alleviated, and the acute phase reaction had retreated (an ESR value of 28 mm/h and a CRP level of 6.6 mg/L). The patient's laboratory results are shown in Table 1.

Discussion

We presented a patient with IgG4-related disease who was concurrently diagnosed with MCTD, exhibiting cumulative clinical symptoms. Symptoms may develop years after antibody positivity occurs in MCTD patients. It has been shown that symptoms such as swollen edematous hands, Raynaud's phenomenon, sclerodactyly, livedo reticularis, and telangiectasia may develop in the patients' follow-up.[1] The findings that emerged during the follow-up demonstrate the significance of patient history and physical examinations at regular intervals in these patients.

Immunoglobulin G4–related disease is an immune-mediated fibro-inflammatory condition characterized by mass-forming lesions that can lead to permanent organ damage. Abundant IgG4-positive plasma cells in affected tissues and fibrosis represent hallmark pathological features of this disorder. Although the disease was initially described in its pancreatic form, it is now understood that IgG4-RD is a systemic disease with a broad spectrum of clinical manifestations.[2]

Mixed connective tissue disease (MCTD) has been reported as an overlap of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory myopathy, and rheumatoid arthritis (RA). The overlap of these conditions typically occurs sequentially over time rather than simultaneously.[3] Early in the course of the disease, patients may have somewhat nonspecific symptoms such as fatigue, fever, myalgia, arthralgia, Raynaud's phenomenon, and puffy digits. The diagnosis of MCTD should be suspected in a patient presenting with the above-mentioned clinical manifestations, mainly when found in association with a high titer of anti-U1-RNP antibody and/or with abnormal nail fold capillaroscopy.[4]

Immunoglobulin G4–related disease cases associated with SLE and RA have been previously reported.[5] Nevertheless, to the best of the authors' knowledge, no patient with IgG4-RD associated with MCTD has been reported. In this section, a patient with IgG4-RD and MCTD is presented.

Anti-U1-RNP positivity is an essential diagnostic test, and the presence of Raynaud's phenomenon, capillaroscopic findings, swollen hands, telangiectasia, sclerodactyly, and pitting scars are noted in the patient. Mixed connective tissue disease often overlaps with or might have the features of Sjogren's syndrome. Sicca symptoms, which include dry eyes, parched mouth, and inflammation of the salivary or lacrimal glands, are present in 40%-95% of patients with MCTD. A significant number of those patients are positive for anti-Ro/SSA, and a few are also positive for anti-La/SSB.[6] The patient exhibited objective signs of xerophthalmia; however, a minor salivary gland biopsy revealed normal histology. In the current patient, dry eye may result from lacrimal gland involvement in an IgG4-related disease.

Both MCTD and IgG4-RD involve complex immune dysregulation. A common mechanism includes Th2-driven immune responses and dysfunction in regulatory T cells (Tregs). Cytokines such as interleukin (IL)-4, IL-10, and TGF-β, which are predominant in IgG4-RD, also play a role in modulating the autoimmune responses seen in MCTD. Additionally, increased B cell activation and autoantibody production—hallmarks of both conditions—suggest a potential immunopathogenic link between them.[7]

Interestingly, the patient tested positive for MPO-ANCA, which is typically associated with ANCA-associated vasculitides. Although MPO-ANCA positivity is rare in IgG4-RD, several case reports and literature reviews have documented overlap between IgG4-RD and ANCA-positive vasculitis, including hypertrophic

Main Points

- To the authors' knowledge, this is the first reported case illustrating the coexistence of mixed connective tissue disease (MCTD) and immunoglobulin G4–related disease (IgG4-RD), expanding the clinical spectrum of IgG4-RD and highlighting the importance of differential diagnosis in autoimmune conditions.
- This case underscores the necessity for continuous monitoring of patients with IgG4-RD, particularly when new systemic symptoms and specific autoantibodies such as anti-U1 ribonucleoprotein emerge, as they may indicate evolving overlap syndromes like MCTD.

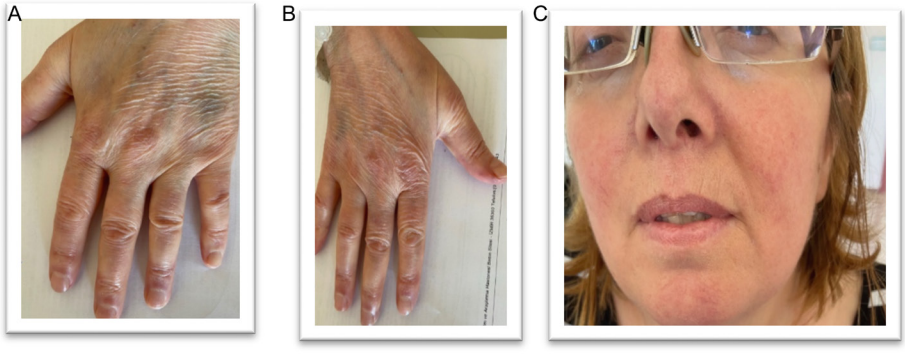

Figure 2. Physical findings. (A) Puffy fingers with edematous swelling and tight skin. (B) Sclerodactyly extending to the proximal interphalangeal joints. (C) Facial telangiectasia on cheeks and perioral area.

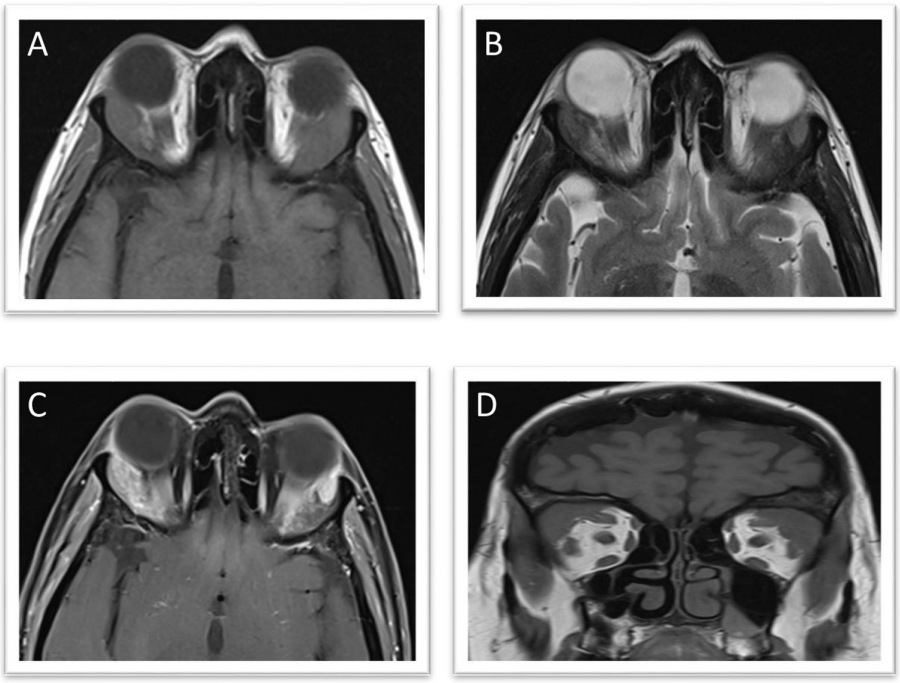

Image 1. Orbital magnetic resonance imaging findings from the 2022 recurrence. (A) Axial T1-weighted image showing hypointense infiltrative lesions in both orbits. (B) Axial T2-weighted image indicating lesion expansion compared to the prior scan. (C) Axial T1 with fat-suppressed contrast showing diffuse enhancement. (D) Coronal T1 with fat-suppressed contrast indicating bilateral proptosis due to space-occupying effect.

pachymeningitis and renal involvement. These observations raise the possibility of a shared or mimicking inflammatory pathway in some patients. The pathogenic relevance of MPO-ANCA in IgG4-RD remains unclear, but it may reflect broader immune dysregulation that warrants further investigation.[8]

In conclusion, it should be kept in mind that patients with an autoimmune disease may have more than 1 organ or system involved, as well as multiple types of diseases. The primary clinical takeaway from this case is that individuals with unexplained autoantibody-positive and/or test results should be closely monitored for the development of alternative diseases.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

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Author Contributions: Concept – H.K., S.A.; Design – H.K.; Supervision – S.A.; Resources – H.K.; Materials – H.K., I.A.; Data Collection and/or Processing – H.K.; Analysis and/or Interpretation – H.K., N.E.; Literature Search – E.E.; Writing Manuscript – H.K., S.A.; Critical Review – H.K., E.E.

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Table 1. Summary of Laboratory Findings During Initial Presentation (2018) and Relapse (2022)

Test	2018	2022	Reference Range
C-reactive protein (CRP) (mg/L)	0.2	78	0-5
Erythrocyte sedimentation rate (ESR) (mm/h)	67	69	0-20
Serum IgG4 (g/L)	7.26	3.37	<1.25
Antinuclear antibody (ANA)	1:1000, granular	1:1000, granular	Negative
Anti-U1-RNP	+++	+++	Negative
MPO-ANCA	Positive	Positive	Negative

Anti-U1-RNP, anti-U1 ribonucleoprotein; IgG4, immunoglobulin G4.