# Eosinophilic granulomatosis with polyangiitis can manifest lacrimal and salivary glands swelling by granulomatous inflammation: a potential mimicker of IgG4-related disease

We read the paper by Vaglio *et al* in your journal with great interest.[1] They reported that patients with eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, showed high serum IgG4 levels, correlating with disease activity and the extent of organ involvement.[1] Since then, the association between EGPA and IgG4-related disease has been discussed by researchers.[2–4] EGPA is one of the systemic vasculitis and is typically preceded by bronchial asthma, allergic rhinitis and/or sinusitis and followed by peripheral blood eosinophilia and eosinophil infiltration into organs. IgG4-related disease is an emerging disease entity characterised by high serum IgG4 levels and marked IgG4-positive plasma cell infiltration at lesions. Mikulicz disease, a prototype of IgG4-related disease, presents with enlarged lacrimal and salivary glands and often has allergic features such as asthma and chronic sinusitis. Pathogenically, T helper type 2-related cytokines, which contributes to IgG4-class switching, is the common immunopathogenic pathway between EGPA and IgG4-related disease.[5–7]

Indeed, several cases of EGPA complicated with Mikulicz disease-like symptoms (lacrimal and salivary glands swelling) along with elevated serum IgG4 have been reported as shown in figure 1A.[8–11] All of those cases showed elevated levels of serum C reactive protein, which are unusual in IgG4-related Mikulicz disease.[12] Then, rheumatologists face with the following questions: 'Are the EGPAs concurrent with IgG4-related disease?' or "Do the EGPAs just mimic IgG4-related disease?'. To address the issue, we reviewed literatures that reported cases with enlarged lacrimal and salivary glands who were diagnosed with EGPA histopathologically with biopsy samples (figure 1B). We regarded the presence of EGPA-specific histopathological findings as the key to answer the question and found that the enlarged lacrimal and salivary glands in patients with EGPA demonstrated eosinophilic granulomas, which is suggestive for EGPA and not consistent with IgG4-related disease (figure 1B).[13–15] Thus, the inflammation of the enlarged lacrimal and salivary glands in patients with EGPA may represent a primary EGPA involvement.

These findings suggest that rheumatologists need to be careful to make the final diagnosis of IgG4-related disease if the patients present with swollen lacrimal and salivary glands and show systemic inflammatory features such as elevated levels of serum C reactive protein, which are uncommon in IgG4-related disease. In addition, it is important to keep it in mind that serum IgG4 elevation and IgG4-positive plasma cell infiltration are not specific findings for IgG4-related disease. It has been widely reported that those findings can be detected in diverse chronic inflammatory diseases, questioning its specificity.[16] Furthermore, the frequency of antineutrophil cytoplasmic antibody (ANCA) positivity in patients with EGPA is low, only up to 30%–40%;[17] therefore, histopathological findings of the swollen lacrimal and salivary glands are the key to discriminate EGPA from IgG4-related disease in such cases. The accurate diagnosis is crucial to initiate the appropriate treatments and to elucidate the precise pathogenesis of both EGPA and IgG4-related disease.

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A

| Authors | Reported year | Age (years) | Sex | Mikulicz disease-like symptoms | Other EGPA symptoms | Blood eosinophil count (cells/μL) | % of blood eosinophil | Serum IgG4 (mg/dL) | Serum IgE (IU/mL) | Serum C-reactive protein (mg/dL) | ANCA serology |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hanioka Y et al. | 2012 | 72 | Male | Enlarged bilateral lacrimal and submandibular glands | Asthma, sinusitis, skin, nerve | 2158 | 32.3 | 343 | 454 | 2.32 | MPO-ANCA |
| Ayuzawa N et al. | 2012 | 68 | Female | Enlarged bilateral salivary glands | Asthma, lungs, kidney, skin, nerve, joint | 13500 | 67.5 | 275 | 5398 | 8.10 | Negative |
| Akiyama K et al. | 2017 | 68 | Male | Enlarged bilateral submandibular glands, enlarged right lacrimal gland, thickening of left extraocular muscles and infraorbital nerve | Fever, asthma, sinusitis, lungs, nerve, joint | 4068 | 39.0 | 1500 | 26.5 | 2.36 | Negative |
| Takahashi K et al. | 2020 | 51 | Female | Enlarged bilateral submandibular glands | Fever, asthma, lungs, skin, joint | 3027 | 32.9 | 261 | 3052 | 2.76 | Negative |

B

| Authors | Reported year | Biopsy site | Histopathological findings |
|---|---|---|---|
| Khandwala MA et al. | 2010 | Enlarged lacrimal gland | Eosinophilic granulomas with giant cells. |
| Ameli F et al. | 2011 | Enlarged lacrimal gland | Eosinophilic granulomas surrounded by eosinophils, lymphocytes, histiocytes, and giant cells. Angiitis with destruction of the vascular architecture along with intense inflammatory cell infiltrates. |
| Tovoli F et al. | 2013 | Enlarged submandibular gland | Eosinophilic granulomas with dendritic cells and histiocytic macrophages. The perivascular and periductal eosinophilic and lymphocytic infiltrates. |

**Figure 1** Characteristics of EGPA complicated with Mikulicz disease-like manifestations. (A) Cases of EGPA complicated with lacrimal and salivary glands swelling along with elevated serum IgG4 levels. (B) Histopathological findings of the enlarged lacrimal and salivary glands of EGPA. EGPA, eosinophilic granulomatosis with polyangiitis.

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