

Just Another Case of Sjögren's Syndrome?

To the Editor:

A 60-year-old woman was seen at the outpatient clinic of the Department of Rheumatology because of increased complaints of xerophthalmia. In 1997, she had already been diagnosed with Sjögren's syndrome (SS) based on xerophthalmia, xerostomia, bilateral salivary gland swelling, and positive sialography showing chronic inflammation without local obstruction. Antinuclear antibodies (ANA) and anti-SSA/SSB were negative. Because of persistent progressive salivary gland swelling at that time, a total bilateral submandibular gland excision was performed as development of non-Hodgkin lymphoma as a complication of SS was suspected. Histology showed sialoadenitis as seen in SS without signs of lymphoma. In 2002, a renal biopsy performed because of increased creatinine level without proteinuria revealed focal global glomerulosclerosis with interstitial nephritis due to SS or chronic ischemia. In an attempt to treat possible active interstitial nephritis due to SS, she was treated with 30 mg of prednisone and azathioprine. Prednisone was stopped after 6 months and azathioprine after one year, however, there was no effect on renal function.

A current physical examination revealed no serious abnormalities. Blood pressure was 150/90 mmHg. There were no signs of arthritis. The Schirmer test (without eye drops) revealed normal results with 15 mm and 12 mm wetting on the right and left side, respectively, after 5 minutes.

Laboratory tests showed a normal complete blood count, erythrocyte sedimentation rate (ESR) of 39 mm/h, C-reactive protein level of 7 mg/l, and stable creatinine level of 158 μ mol/l. Rheumatoid factor, ANA, and anti-SSA/SSB were negative. The protein spectrum showing an elevated gamma fraction of 24.8 g/l. Immunoelectrophoresis revealed an elevated total IgG of 29 g/l (normal range < 16 g/l). Further analysis of the IgG showed mainly enhanced level of IgG4 of 19.9 g/l (normal range < 1.4 g/l). Unfortunately, we were not able to perform IgG4 staining on the former tissue samples of the salivary gland and kidney because of technical issues.

At this point, we considered that the patient did not have SS but most probably Mikulicz's disease (MD)/IgG4-positive multiorgan lymphoproliferative syndrome (IgG4+ MOLPS) based on the exceptionally elevated IgG4 levels¹. As this patient only had mild complaints of xerophthalmia with no major organ involvement at this time, no immunosuppressive therapy was indicated.

MD is a disease that involves bilateral enlargement of the salivary and lacrimal glands associated with prominent mononuclear infiltration. Since patients with MD often have complaints of xerophthalmia, xerostomia, and bilateral salivary gland swelling, but no SSA/SSB autoantibodies, this disease has been characterized in the past as a seronegative subtype of primary SS. It has been reported that MD patients frequently have increased serum IgG4 concentrations and abundant infiltration of IgG4-positive plasma cells in the salivary and lacrimal glands². The ratio of serum IgG4 to total IgG is 34.85%, while in healthy controls the ratio is about 4%³. In SS patients serum IgG4 is not elevated and no infiltration of IgG4-positive plasmacytes is observed⁴. High serum IgG4 concentrations have also been found in a small number of pathological conditions, such as autoimmune pancreatitis, atopic dermatitis, pemphigus vulgaris, and even interstitial nephritis^{1,5,6}. Therefore, recent reports proposed a new clinical entity called the IgG4+ MOLPS for the above mentioned diseases including MD⁷.

The histopathological characteristics are similar showing degeneration and disappearance of normal tissue by severe mononuclear infiltration, proliferation of ductal epithelial cells and duct stenosis, formation of myoepithelial islands, and cystic dilatation of peripheral ducts⁸. A high frequency of apoptosis has been seen in SS, however, Tsubota, *et al*^{9,10} reported that the frequency of apoptosis in gland cells is significantly decreased in IgG4+ MOLPS. Moreover, it has been reported that sialography in patients with IgG4+ MOLPS did not show a punctuate sialectasis. This

seems to indicate a lack of glandular destruction in IgG4+ MOLPS. This could explain why salivary function can improve significantly in IgG4+ MOLPS after steroid therapy, whereas SS is considered unable to improve using corticosteroids due to irreversible damage of the glands³. These findings strongly suggest that IgG4+ MOLPS represents both a clinical and histopathological separate entity from SS.

Our patient was eventually diagnosed as having IgG4+ MOLPS. In retrospect, an adequate treatment with corticosteroids in the past might have spared her from a bilateral submandibular gland excision. In 2002, the nephrologist treated her with prednisone (30 mg daily) for suspected interstitial nephritis without improvement. Interstitial nephritis has also been described in the IgG4-related diseases. However, the lack of response on prednisone at that time might suggest either a late chronic stage of renal disease or insufficient immunosuppressive treatment since other case studies described successful treatment of interstitial nephritis with high dose methylprednisolone pulse therapy followed by 60 mg/day prednisone^{5,6}.

IgG4+ MOLPS should be considered in patients with sicca complaints and negative SSA/SSB antibodies.

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