IgG4-positive multi-organ lymphoproliferative syndrome manifesting as chronic symmetrical sclerosing dacryo-sialadenitis with subsequent secondary portal hypertension and remarkable IgG4-linked IL-4 elevation

Sirs, Immunoglobulin G (IgG) 4-positive multi-organ lymphoproliferative syndrome (IgG4 + MOLPS), also known as IgG4-related systemic disease [1–3] and others, is an emerging clinical entity [2, 3] that exhibits a variety of clinical manifestations, including autoimmune pancreatitis, inflammatory pseudotumour and chronic symmetrical sclerosing dacryo-sialadenitis [CSSD; or Mikulicz disease (MD)] [2–8]. We report a patient initially diagnosed with SS, but subsequently recognized with CSSD-manifesting IgG4 + MOLPS after re-presenting with symptoms of secondary portal hypertension (SPH).

A 55-year-old female was admitted in September 2004 with a 2-month history of abdominal distention against a 18-month background of SS satisfying the 2002 Revised American–European Classification Criteria [9], with dryness of the eyes and mouth, bilateral lacrimal and salivary gland enlargement, lymphocyte infiltration on salivary gland biopsy, positive Schirmer’s test and decreased salivary gland function on 99mTc scintigraphy. Abdominal findings confirmed ascites, and lacrimal and salivary glands were enlarged bilaterally. Serum autoantibodies including anti-Ro or SSA and anti-La or SSB were negative and abdominal CT showed multiple abdominal masses in the hepatic hilar and mesenteric regions. Pathological findings are shown in Figure 1A–C.

Discharging against medical advice, she subsequently re-presented in December 2005 and August 2006 for upper gastrointestinal variceal bleeding. Imaging results are shown in Figure 1F–I. Further literature search revealed a histopathological similarity with IgG4-related autoimmune pancreatitis, and a then-recent case series describing raised serum IgG4 levels and infiltration of lacrimal and salivary glands and lymphoid tissue by IgG4-expressing cells in 7 so-called MD patients but not 14 SS patients [1]. Subsequent investigation showed elevated serum IgG4 (1100 mg/dl; normal range 4.8–105 mg/dl). Immunohistochemistry of the biopsied lesions for IgG4 is shown in Figure 1D and E. We consequently diagnosed CSSD-manifesting IgG4 + MOLPS rather than SS [2].

Corticosteroid (CS) therapy was started with oral prednisolone [60 mg/day (= 1 mg/kg/day)]. The glandular swelling showed complete resolution at 2 weeks, whereas the abdominal distention, abdominal masses and varices showed partial but significant regression on CT and endoscopy at 3 months. Serum IgG4 decreased, but remained elevated at 4 weeks (530 mg/dl). Further, immune complexes involving all IgG subtypes, including IgG4, were also decreased at 4 weeks. Among proinflammatory cytokines measured at the start of treatment, two were significantly elevated, with IL-4 at 51.9 pg/ml (normal range 6.0) and IL-6 at 12.5 pg/ml (normal range 4.0). While IL-6 quickly decreased to normal (0.7 pg/ml), IL-4 also decreased but remained high (31.7 pg/ml) at 2 weeks. This decrease in IL-4 was largely consistent with the decreased but still elevated levels of IgG4 at 4 weeks. CS was tapered to 6 mg/day of oral methylprednisolone (mPSL) at 6 months. Subsequent serology showed a declining but still elevated IgG4 (386 mg/dl) and continued elevation of IL-4 (32.5 pg/ml). Presently, a mild, persistent elevation of IgG4 (282 mg/dl) remains. Lacrimal and salivary gland size and function are normal, and the patient is well on maintenance mPSL at 4 mg/day.

This case fulfilled the proposed diagnostic criteria for both MD [1] and IgG4 + MOLPS [2], strengthening the validity of the diagnosis, but also fulfilled the diagnostic criteria for SS [9]. This case therefore highlights the need for comprehensive diagnostic criteria that provide both high sensitivity for this emerging clinical syndrome and specificity from potentially clinically similar entities such as SS.

Establishing an early diagnosis of IgG4 + MOLPS lessens unnecessary investigations and offers the possibility of an effective treatment. Consistent with previous reports, IgG4 appeared to be a useful serological marker in both diagnosis and monitoring [2, 4, 5]. PET-CT was more informative [8] than conventional CT or 67Ga scintigraphy, providing valuable information on sites that were not suitable for biopsy, although this is still required to exclude malignancy. Further, CS had a significant effect on the lacrimal and salivary gland lesions, but only a partial effect on the mesenteric and hepatic hilar masses. Other studies have reported significant and often complete normalization of glandular size and function with CS, further emphasizing the importance of timely diagnosis [2, 4–6, 10]. Concerning the extra-glandular...
lesions, the differing histopathological patterns of lymphocyte: plasma cell ratios and accompanying fibrosis and differing response levels to CS may suggest a specific window of therapeutic opportunity and CS sensitivity [3]. Importantly, by demonstrating analogous immunohistochemical findings in both glandular and extra-glandular lesions, our case provides a clear illustration of the systemic nature of IgG4+ MOLPS [2, 3, 6, 7]. Further, the role of IgG4 in IgG4+ MOLPS remains unclear [3, 5] and a finding of hyper-IgG4 may not necessarily indicate a central aetiological role for IgG4. Interestingly, the elevated IL-4 in the active phase decreased with CS, largely consistent with changes in IgG4 levels.

FIG. 1 Investigational findings on initial and subsequent presentations leading to a diagnosis of CSSD-manifesting IgG4+ MOLPS. Initial pathological examination on haematoxylin and eosin staining of minor salivary gland [(A) Low magnification and (B) High magnification], hepatic hilar (C) and mesenteric lesion (not shown) biopsies shows significant plasma cell infiltration with fibrosis in all specimens, with lymphocytes predominating over plasma cells in the glandular lesions, whereas the reverse is seen in the extra-glandular lesions, accompanied by an increase in fibrosis. No evidence of malignancy was detected in any specimen, and the initial pathological diagnosis was inflammatory pseudotumour. Co-registered [(18F)fluorodeoxyglucose PET (FDG-PET) and CT images on first re-admission show the clear persistence of the bilateral lacrimal and salivary gland, hepatic hilar and multiple mesenteric masses in coronal (F) and sagittal (G) views of the whole body and axial views at two levels (H and I). Immunohistochemical examination shows IgG4-expressing plasma cells in salivary gland (D) and hepatic hilar (E) lesions.

Letters to the Editor
This case highlights the systemic nature of IgG4 + MOLPS and the importance of distinguishing it from clinically similar entities such as SS. Clinical recognition of IgG4 + MOLPS is important, as CS may provide complete relief from symptoms and reduce morbidity, particularly if instigated early in the course of the disease. Comprehensive, validated diagnostic criteria and a greater understanding of the pathogenesis of IgG4 + MOLPS are required.

**Rheumatology key message**

- CSSD-manifesting IgG4+MOLPS can present with SPH and remarkable IgG4-linked IL-4 elevation.

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## References


