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IgA nephropathy, non-cirrhotic portal fibrosis, and POEMS syndrome: A rare combination in the long-term follow-up of Sjögren's syndrome

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Abstract

Sjögren's syndrome is a heterogeneous autoimmune disorder that may be associated with systemic manifestations involving multiple organs. We herein reported a rare combination of immunoglobulin A nephropathy; non-cirrhotic portal fibrosis; and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome in a 15-year follow-up of a female patient initially diagnosed with Sjögren's syndrome. The patient had excessive lymphoproliferation featured by lymphadenopathy and hyperglobulinemia. The diagnoses of immunoglobulin A nephropathy and non-cirrhotic portal fibrosis were confirmed by renal and liver biopsies. She received prolonged corticosteroids and immunosuppressive drugs, which improved immunoglobulin A nephropathy but did not hinder the progression of portal fibrosis, leading to intractable variceal bleeding. The patient died of repeated hematemesis despite endoscopic variceal ligation. Valuable pathological information of multi-organ involvement as well as detailed clinical course were presented to facilitate further understanding of this rare

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entity. Excessive lymphoproliferation might play an important role in the progression of systemic complications in Sjögren's syndrome, which requires prolonged immunosuppression and organ-specific treatment.

Keywords
Sjögren's syndrome, IgA nephropathy, non-cirrhotic portal fibrosis, POEMS syndrome, lymphoproliferations

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Introduction

Sjögren's syndrome (SS) is a heterogeneous autoimmune disorder that may be associated with systemic manifestations involving other organs including the skin, lung, heart, and kidneys, as well as the neural and hematopoietic systems.[1] In 2018, we reported a clinical image describing a combination of non-cirrhotic portal hypertension and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome in a patient initially diagnosed with SS.[2] The patient was followed up afterwards, who presented with a rare constellation of comorbidities composed of immunoglobulin A (IgA) nephropathy, non-cirrhotic portal fibrosis (NCPF), and POEMS syndrome, and finally died of hematemesis secondary to NCPF. We herein gathered valuable pathological information of multi-organ involvement, as well as the details of the clinical course to facilitate further understanding of this rare entity. The possible contribution of excessive lymphoproliferation to the development of systemic involvement was discussed in the present case.

Case presentation

In 2006, a 58-year female patient presented with xerostomia and xerophthalmia. Laboratory findings showed elevated levels of immunoglobulin G (IgG) and IgA and positivity for antinuclear and anti-SSA antibodies. Labial salivary gland biopsy showed a focus score >1 (more than 50 lymphocytes per 4 mm^2 of tissue). She was diagnosed with SS and was treated with low-dose prednisolone and hydroxychloroquine. In 2011, she developed interstitial lung disease (Figure 1(a)) and began taking cyclosporine A (CsA); the disease remained stable after suspending CsA in 2012. In June 2016, the patient presented with lymphadenopathy, edema, ascites (Figure 1(b)), and 3.5 g/24 h proteinuria. She was admitted to Peking University International Hospital. Renal biopsy revealed IgA glomerulonephritis (Figure 1 (c) and (d)), a rare finding in SS.[3] IgG subclass staining was performed on the renal biopsy, which revealed negative results. Laboratory findings were remarkable for an increased serum IgA of 6.39 g/L with elevated levels of interleukin-6 (61.0 pg/mL, [normal, <3.4]), and vascular endothelial growth factor (VEGF; 249 pg/mL, [normal, <66]). The test for serum cryoglobulin was negative. Biopsy of the inguinal lymph node showed lymphoid hyperplasia and diffuse plasma cell infiltration (Figure 1(e) and (f)). Prednisolone of 40 mg/d was administered due to hyperglobulinemia and nephrotic-range proteinuria. Her proteinuria greatly improved, and her lymphadenopathy and hyperglobulinemia subsequently resolved. Prednisolone was tapered quickly to a maintenance dose of 7.5 mg within 8 weeks.

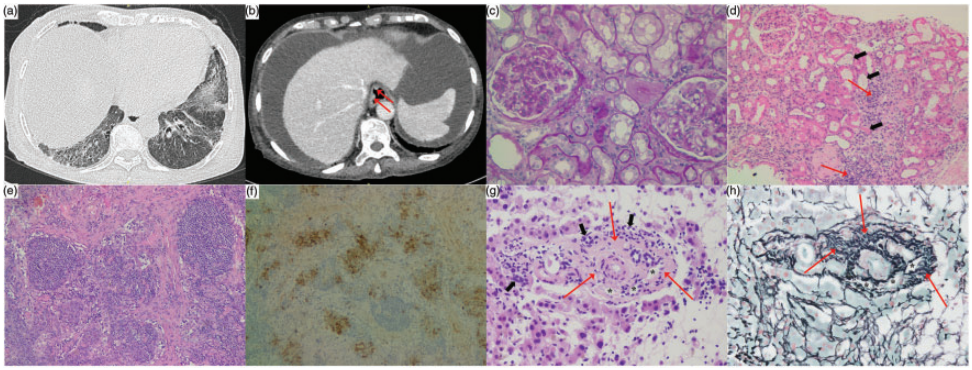

Figure 1. Radiological and histological findings of the patient. (a) Reticular opacities in both lungs and subpleural honeycombing. (b) Ascites and esophageal varices (arrow). (c) Mild increase in mesangial matrix and cellularity with segmental endocapillary hypercellularity (PAS 200×). (d) Lymphocytic interstitial infiltrates (long arrow) and tubular atrophy (short arrow) (H&E 100×). (e, f) Lymphoid hyperplasia with plasma cell infiltration in the lymph node (H&E 100× and CD138 stain 100×, respectively) and (g, h) liver biopsy revealed lymphocytic infiltrates in the portal tract (short arrow), portal fibrosis (long arrow), and narrowed portal vein lumen (*) (H&E 200× and Reticulin + Masson stain 200×, respectively). H&E: hematoxylin and eosin; PAS: periodic acid–Schiff.

However, her ascites became intractable despite that the albumin levels returned to normal as nephrotic syndrome improved. Abdominal paracentesis revealed elevated serum ascites-albumin gradient (SAAG, 1.8 g/dL), indicating portal hypertension. The results of liver biopsy were consistent with obliterative portal venopathy, which is also called NCPF (Figure 1(g) and (h)). Prednisolone was started at an initial dose of 50 mg/d and tapered gradually, which steadily improved her ascites. Significantly decreased levels of interleukin-6 (10.7 pg/mL) and VEGF (70.2 pg/mL) were observed 3 months after treatment. Cyclophosphamide was prescribed but refused by the patient. She remained free of ascites for 1 year with a minimal maintenance dose of prednisolone (7.5 mg/d).

In 2018, she presented with another relapse of ascites with elevated levels of IgG and IgA (Figure 2). Upon physical examination skin pigmentation, painful swollen joints, and lymphadenopathy were found. Her liver function was normal. Anti-mitochondrial and anti-smooth muscle antibodies were negative. Infectious disease testing was unremarkable. Laboratory tests showed elevated levels of serum prolactin (94 ng/mL), interleukin-6 (30.6 pg/mL), and VEGF (263 pg/mL). POEMS syndrome (characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin alterations) was suspected; however, serum immunofixation revealed polyclonal hyperglobulinemia rather than monoclonal M-protein. The patient was thus diagnosed with Castleman disease variant of POEMS syndrome, which had no clonal M-protein and typically little or no peripheral neuropathy but had several of the minor diagnostic criteria for POEMS syndrome.[4] Bortezomib and dexamethasone (BD) regimen comprising bortezomib (1.3 mg/m^2/week) plus dexamethasone (20 mg/week) was applied but discontinued 6 months later due to an unexpected lumbar vertebra fracture. The patient's ascites and arthritis improved during BD regimen but quickly relapsed with drug cessation. Despite the restart of BD regimen, her symptoms were not satisfactorily

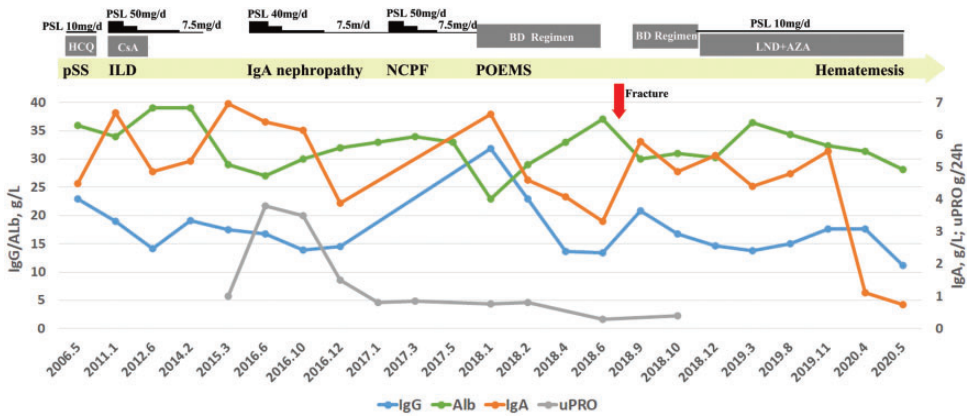

Figure 2. Clinical features, treatments, and laboratory values over time. Alb: albumin; AZA: azathioprine; BD: bortezomib and dexamethasone; CsA: cyclosporine A; HCQ: hydroxychloroquine; ILD: interstitial lung disease; LND: lenalidomide; NCPF: non-cirrhotic portal fibrosis; pSS: primary Sjögren's syndrome; PSL: prednisolone; uPRO: urine protein.

relieved. Lenalidomide and azathioprine were used to replace BD regimen, which partially alleviated her symptoms. In 2020, she had several episodes of hematemesis despite endoscopic variceal ligation. The patient died of intractable variceal bleeding 3 months later.

Institutional review board approval was waived because of the retrospective and observational nature of case report. Written informed consent was obtained from the patient's husband for the publication of this case report. The reporting of this study conforms to the CARE guidelines.[5]

Discussion

Although autoimmune disorders may frequently overlap and coincide in the same patient, the combination of SS with IgA nephropathy, NCPF, and POEMS syndrome in one individual is extremely rare. Data in the literature are remarkably sparse. It should be argued that systemic complications occurred in SS might be ascribable to the development of systemic lupus erythematosus (SLE). As was documented previously, SS antedating SLE by many years was not uncommon.[6,7] In fact, it is hard to differentiate between SS overlaps and SLE as they share common characteristics, including genetic, as well as clinical and serological characteristics.[8] Nevertheless, the absence of typical anti-dsDNA and anti-Sm antibodies in the long-term follow-up of this patient argued against the diagnosis of SLE. Furthermore, a variety of manifestations in this patient, such as salivary gland with lymphocytic infiltration, endocrinopathy and portal hypertension may indicate different underlying themes, which could not be directly explained by SLE. Recent studies suggested that SS and SLE may share immunologic features that span diagnostic boundaries.[9,10] It is reasonable that treatment in the future should focus on pathogenic communalities across diseases, rather than specific diagnostic labels.

Systemic complications of SS may indicate common underlying immunopathogenesis in different organs. The patient notably presented with lymphoproliferative features, as reflected by lymphadenopathy and hyperglobulinemia. She received multiple regimens comprising steroids and

immunosuppressants, which were effective for interstitial lung disease and IgA nephropathy. However, these measures did not hinder the progression of portal fibrosis, which led to variceal bleeding, a medical emergency with a high mortality. Hepatic involvement besides primary biliary cholangitis was rare in patients with SS. NCPF is a rare disorder that leads to portal hypertension in the absence of liver cirrhosis.[11] NCPF in this patient was diagnosed based on the following findings: (a) evidence of portal hypertension indicated by splenomegaly, esophageal varices, and ascites with increased SAAG; (b) absence of liver cirrhosis; and (c) a confirming liver biopsy. The pathophysiology of NCPF remains largely unknown but is considered to be associated with chronic infection, immunologic disorders, and prothrombotic states.[11,12] The incidence of NCPF was underestimated because of the difficulty in performing liver biopsy in case of symptom onset, including ascites. We fortunately obtained valuable pathological information when the patient's ascites was reduced on prednisolone therapy. This opportunity for liver biopsy can be easily missed in many circumstances. The typical pathological features of NCPF include luminal narrowing, sclerosis, or disappearance of the portal vein branch, as well as portal lymphocytic infiltrates and portal fibrosis.[12]

Ascites in POEMS syndrome was considered to originate from increased immune activation and vascular permeability.[4] In patients with POEMS syndrome who underwent abdominal paracentesis, the ascitic fluids had low SAAG, suggesting non-portal hypertension.[13] Obviously, ascites in our patient was related to non-cirrhotic portal hypertension. Meanwhile, the patient showed markedly increased levels of VEGF and IL-6, and her ascites responded well to sustained prednisolone treatment, making it at least partially attributable to increased immune activation and inflammatory status related to POEMS syndrome. Overproduction of IL-6 and VEGF were considered pivotal in the pathogenesis of POEMS syndrome, which leads to microvascular permeability and extravascular overload.[14,15] The efficacy of prednisolone in POEMS syndrome-associated ascites primarily involves its anti-inflammatory potency in suppressing IL-6 and VEGF production. Moreover, it is susceptible that early-stage portal hypertension in NCPF might be reversible, provided that causative factors such as excessive lymphoproliferation could be rapidly eliminated. In our unpublished data, we observed similar resolution of ascites in a patient with new-onset autoimmune hepatitis after treatment with prednisolone and immunosuppressive drugs. Thus, anti-inflammatory effects of prednisolone and ameliorated portal hypertension may together contribute to reduced ascites in this case. In fact, lymphoproliferative disorders and NCPF might be closely related. Increasing cases of NCPF in combination with POEMS syndrome were reported recently, suggesting an overlapping pathogenesis.[16,17] Since the incidence of NCPF was much underestimated previously, it is important to raise awareness upon this entity.

The diagnosis of classic POEMS syndrome requires the presence of peripheral neuropathy and a plasma cell clone. In contrast, Castleman disease variant of POEMS syndrome has no peripheral neuropathy but usually presents with polyclonal hyperglobulinemia and several of the minor diagnostic criteria for POEMS syndrome, such as skin changes, ascites and endocrinopathy. The patient showed typical features of polyclonal hyperglobulinemia and had increased levels of IgG and IgA in the long-term follow-up, which responded to prednisolone and immunosuppressive drugs. A sudden decline in IgA and IgG levels after hematemesis (Figure 2) might result from a rapid

blood loss and subsequent fluid resuscitation.

The mesangial deposition of IgA may reflect an overabundance of circulating IgA immune complexes in chronic liver disease.[18] In cirrhosis-associated IgA nephropathy, impaired hepatic clearance of polymeric IgA1 (e.g., portosystemic shunting due to portal hypertension) leads to systemic accumulation of galactose-deficient IgA1, which deposits in the mesangium.[19,20] In contrast, SS may drive IgA deposition via chronic lymphoproliferation or systemic autoimmunity, potentially involving IgA immune complexes with autoantigens. Another distinctive feature of renal involvement in SS is interstitial and tubular lesions characterized by lymphocytic infiltrates, reflecting SS-driven autoimmunity.[3,20] This is consistent with the renal biopsy findings in our patient with multiple lymphocytic interstitial infiltrates (Figure 1(d)). On the contrary, interstitial and tubular lesions in cirrhosis-associated IgA nephropathy is generally mild unless compounded by comorbidities (e.g., hemodynamic instability related to decompensated cirrhosis).[21] In summary, while both variants involve mesangial IgA deposition, SS-associated IgA nephropathy reflects systemic autoimmunity with prominent interstitial/tubular involvement, whereas cirrhosis-associated IgA nephropathy stems from hepatic dysfunction and is less likely to exhibit severe tubulointerstitial pathology without comorbidities. The present case encompassed rare combinations of SS and portal hypertension. Thus, it is possible that a number of factors including impaired hepatic clearance of IgA immune complexes, and polyclonal B cell activation with enhanced IgA secretion, together contribute to the development of secondary IgA nephropathy. In our patient, her proteinuria and peripheral edema dramatically reduced after prednisolone therapy. However, ascites related to NCPF did not significantly improve until prolonged steroid usage, which indicated that different regimens may be needed to achieve remission of disease in these rare cases. Treatment should be tailored to the type and severity of organ involvement, ideally based on multidisciplinary cooperation.

In summary, we herein reported a rare combination of IgA nephropathy, NCPF, and POEMS syndrome in the long-term follow-up of a patient initially diagnosed with SS. Valuable pathological information of multi-organ involvement as well as detailed clinical course were provided to facilitate further understanding of this rare entity. Excessive lymphoproliferation might play an important role in the development of systemic complications in SS, which requires prolonged immunosuppression and organ-specific treatment.

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Author contributions

Lina Zhang conceived the idea for this study. Xiuhong Wang and Lina Zhang interpreted all data and drafted the manuscript. Tong Zhang and Bozhi Lin collected the data and supported in writing the manuscript. Jing Xu, Meixiang Zhang, and Zhicheng Liu contributed to reviewing and editing the manuscript. All authors have reviewed and approved the final manuscript. All authors declare final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent statement

Consent was obtained from the patient's husband.

Data availability statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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