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CLINICAL VIGNETTE

Sjögren's Syndrome-associated Neuropathy and Cirrhosis

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Case Report

A 56-year-old female with history of hypothyroidism presented to neurology clinic for evaluation of progressive left-sided hemiparesis and right foot numbness. She was in her usual state of health until approximately one year ago when she began to have left upper and lower extremity "clumsiness," manifested by frequent dropping of items, progressive gait instability, and recurrent falls. Her symptoms continued to progress, and she began to have persistent left-sided and right foot numbness, causing significant disability. Her only medication was levothyroxine. She had no history of tobacco, alcohol, or recreational drug use. Family history was unremarkable. She was then admitted to the hospital for further evaluation of an underlying systemic illness.

On examination, the patient was a well-developed and well-nourished woman who appeared her stated age. Vital signs were normal. Physical exam was largely unremarkable except for the neurologic exam. She demonstrated 4/5 strength in the distal lower extremities and 3/5 strength in the proximal lower extremities. She had 4/5 strength in the left upper extremity and 5/5 strength in the right upper extremity. Sensation was absent on the left side, and affected extremities also were areflexic.

Initial laboratory work showed leukopenia, anemia, thrombocytopenia, elevated alkaline phosphatase, hypoalbuminemia, mildly elevated INR, and mildly elevated TSH with a normal T4. Routine serum electrolytes, transaminases, total bilirubin, ESR, CRP, and rheumatoid factor (RF) were normal or negative.

On hospital day 1, an MRI of the head, neck, and spine demonstrated multiple parotid cysts and a questionable T2-weighted hyperintensity in the mid-lower cervical spinal cord, consistent with inflammation versus artifact. Abdominal ultrasound revealed evidence of liver cirrhosis. On hospital day 2, she suddenly developed massive hematemesis. An EGD showed large bleeding esophageal varices which were banded (Figure 1).

Subsequent whole body PET-CT scan was negative for malignancy but did show morphologic features of liver cirrhosis with sequelae of portal hypertension. Liver biopsy ultimately revealed macrovesicular steatosis as well as periportal and bridging fibrosis, consistent with hepatic lupus (Figure 2). Her autoimmune serologies were positive for ANA (> 1:1280 antibody titer) and anti-SSA, and negative for anti-SSB. She also had low complement levels. Other autoimmune serologic markers were negative, including anti-ds DNA, anti-smooth muscle antibody (SMA), anti-mitochondrial antibody (AMA), RNP, c-ANCA, and p-ANCA.

Primary Sjögren's syndrome (SS) was suspected, given the high suspicion for a systemic disease process and findings of multiple parotid cysts on MRI, as well as the positive ANA and anti-SSA. Upon further questioning, the patient did acknowledge mild sicca symptoms that were not bothersome to the patient. A parotid gland biopsy was non-diagnostic. A sural nerve biopsy showed axonal degeneration and myelinated fiber loss with perineural angiitis and dense perivascular lymphocytic infiltration (Figure 3). Schirmer's test was positive for wetting of <5 mm in five minutes of lacrimal production indicative of Sjögren's syndrome.

The patient was diagnosed with primary SS with associated neuropathy and cirrhosis. She received high dose intravenous methylprednisolone on hospital days 22-25, with noticeable improvement in her strength. She was eventually transitioned to an oral prednisone taper and mycophenalate. Upon follow-up after several weeks, the patient continued to report improvement in her overall strength and sensation.

Discussion

Primary Sjögren's syndrome (SS) is an autoimmune inflammatory disease that classically presents with sicca symptoms, such as parotid gland enlargement, dry mouth (xerostomia), and dry eyes (xerophthalmia), due to the involvement of the salivary and lacrimal glands. The prevalence of the disease has been estimated to range from 0.1 to 4.8%, making SS the second most common rheumatologic disorder in the United States. SS affects mostly middle-aged women, with a female to male ratio of 9:1.[1,2]

While the diagnosis for primary SS characteristically includes an objective assessment of ocular symptoms (eg, Schirmer's Test, Rose Bengal Score) and histopathologic assessment of the salivary glands to evaluate for lymphocytic infiltration, no

single test can readily diagnose SS.[3] Often, a mixture of laboratory abnormalities is observed including elevation in serum inflammatory markers, leukopenia, normocytic anemia, polyclonal hypergammaglobulinemia, and the presence of autoantibodies.[1] Autoantibodies frequently found to co-exist with a diagnosis of primary SS include ANA, RF, and characteristically, anti-SSA/Ro and anti-SSB/La.[4,5] Anti-SSA/Ro and anti-SSB/La autoantibodies are found in 30-60% of patients with primary SS but can also be found in other rheumatologic conditions including systemic lupus erythematosis (SLE), rheumatoid arthritis (RA), and in idiopathic inflammatory myopathies.[4]

In 2012, the Sjögren's International Collaborative Clinical Alliance (SICCA) suggested a new classification criteria for the diagnosis of primary SS based on expert consensus.[6] The 2012 SICCA proposed criteria requires confirmation of at least 2 of the 3 of the following:

a) Positive anti-SSA/Ro and/or anti-SSB/La antibody testing, or a positive ANA (>1:320) and RF;
b) Ocular staining score ≥ 3; or
c) Presence of focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2 in labial salivary gland biopsy samples.

However, criticism over the lack of use of clinical symptoms in the criteria has limited universal acceptance.[6] The mainstay of treatment for primary SS is largely supportive with use of both non-pharmacologic and pharmacologic agents to combat symptoms associated with ocular and salivary dysfunction. The use of systemic therapies including steroids, disease-modifying agents, and immunosuppressives for sicca symptoms associated with primary SS is uncommon with unclear benefit.[1]

Extraglandular complications resulting from SS occur in approximately one-third of patients, involving the musculoskeletal, pulmonary, gastrointestinal, and neurologic systems.[3] The prevalence of neurologic complications in SS varies and can range between 2% to 60%.[7] A variety of distinct neuropathic clinical manifestations have been observed including both the central nervous system (CNS) and peripheral nervous system (PNS). When the CNS involvement occurs, it is frequently focal and can involve the optic nerve, resulting in optic neuritis, although manifestations such as vasculitis and transverse myelitis have been reported.[8,9] CNS symptoms may imitate multiple sclerosis (MS) as a result of potential multifocal involvement with a relapsing-remitting course.[10] Moreover, a retrospective study of 82 consecutive patients at a single university hospital found that 40% of their patients had white matter changes appreciable on MRI that were compatible with an imaging diagnosis of MS.[11] In differentiating these diagnoses, patients with SS-related CNS involvement were more likely to be older, female, and less likely to have oligoclonal bands.[11]

PNS involvement is varied and can present as painful, ataxic, trigeminal or autonomic sensory neuropathy, or as a motor neuropathy, including multiple mononeuropathy and multiple cranial neuropathy.[12] Interestingly, clinical manifestations of neuropathy often precede the development of sicca symptoms or laboratory findings of SS, regardless of the form of neuropathy, suggesting that neural tissues may be primary targets in SS.[12,13] While not yet clearly elucidated, the literature exploring the pathophysiologic basis of neuropathic disease suggests that sensory and autonomic neuropathy may be secondary to T cell lymphocytic infiltration of ganglion cells, whereas vasculitis and resultant axonopathy may be the etiology of the neuropathies of primarily motor origin.[12,14] Although double-blinded, placebo-controlled studies do not exist with regard to treatment of SS-associated neuropathy, there is evidence to suggest that corticosteroids, IVIG and cyclophosphamide can variably improve disability.[12,15,16] Given the heterogeneity of neurologic manifestations and limited data, it is difficult to suggest a particular pharmacologic treatment for a specific type of neuropathy.

Involvement of the liver in patients with primary SS is not atypical. A single-institution retrospective review of 73 patients with primary SS that fulfilled diagnostic criteria who also had liver function testing at the time of diagnosis demonstrated 49.1% to have abnormal liver function tests, with 60% of these patients having no explanation for their hepatic disease other than primary SS.[5] Liver diseases that have frequently been associated with primary SS include autoimmune and viral hepatidities, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).[17-20] Those with abnormal hepatic biochemistries have also been found to have a greater frequency of systemic findings, including neuropathy, hematologic abnormalities, lung disease, renal involvement, vasculitis, autoimmune hypothyroidism, and the presence of positive antibodies, including ANA and AMA.[5,21]

Asymptomatic primary SS patients with positive AMA or SMA have been found to more frequently develop symptomatic PBC and autoimmune hepatitis respectively upon 5-year follow-up.[22] An aberrant interaction between lymphocytes and epithelial tissues has been suggested as a mechanism for the damage identified in different organs in primary SS patients.[23] Particular treatment regimens for patients with liver involvement in primary SS has not been extensively studied and is otherwise aimed at the pathologic entity that has been identified (eg, immunosuppressives for autoimmune hepatitis).

Patients with primary SS may not present with typical sicca symptoms. Our patient initially presented with nonspecific neurologic findings and later was found to have hepatic cirrhosis. Early recognition of CNS involvement in primary SS is essential in minimizing long term disability in these patients as the presence of neuropathy may precede classic sicca symptoms. In addition, patients diagnosed with primary

SS should have a full evaluation for liver disease. Although some liver conditions may be irreversible, treatments are available and may be beneficial for PBC, viral and autoimmune hepatidities. Recognition of atypical features of primary SS is important in making the diagnosis in a timely manner and setting up the appropriate treatment course for these patients.

Figures

Figure 1: Bleeding esophageal varices.

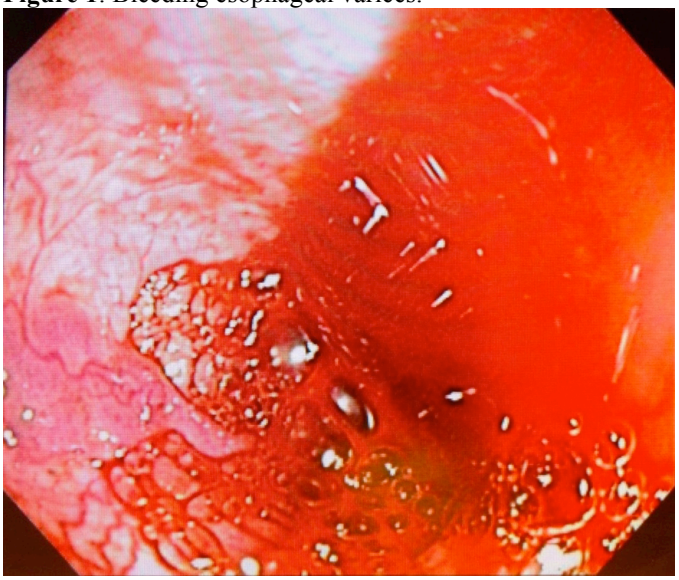
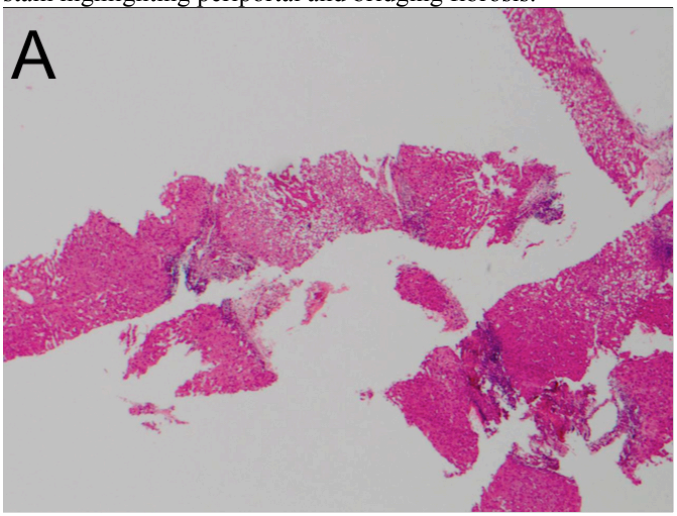


Figure 2: Liver biopsy. (A) H&E stain showing liver parenchyma with macrovesicular steatosis. (B) Trichrome stain highlighting periportal and bridging fibrosis.



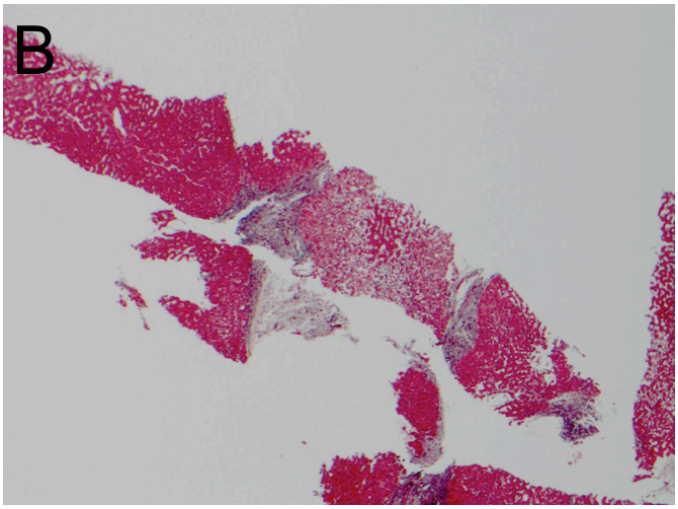
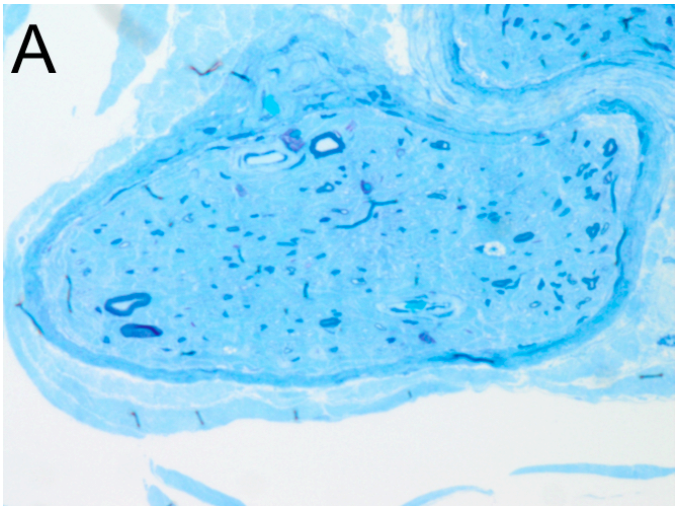
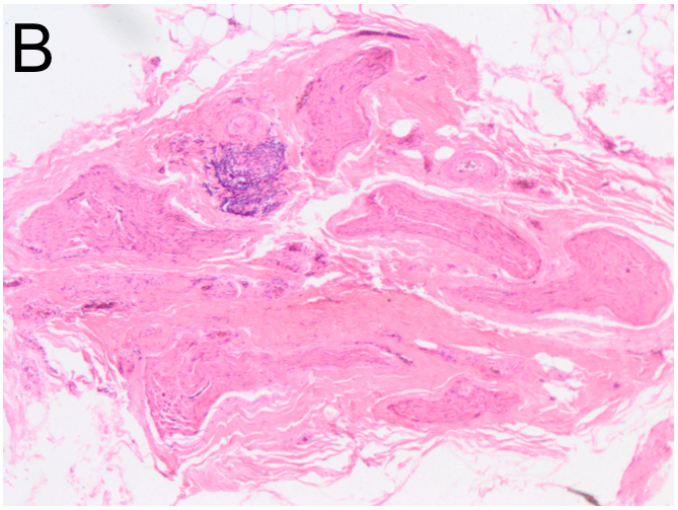


Figure 3: Sural nerve biopsy. (A) Pan-fascicular diffuse large and small myelinated fiber loss with scattered degenerating axons. (B) Small perineural vessels with dense perivascular lymphocytic inflammation. No vessel wall necrosis or thrombosis noted.





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