

Sjögren's Syndrome with Polyserositis, Gastrointestinal Findings and Ascending Aortic Aneurysm

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Abstract

Sjögren's syndrome (SS) is an autoimmune disease with glandular and extraglandular manifestations. Pleural and pericardial effusions in association with SS are rare. Similarly, ascites is rare and it can occur in SS when combined with primary biliary cirrhosis (PBC). Inflammatory Abdominal Aortic Aneurysm together with SS has been described only in one case. We report herein the case of a 70-year-old man with SS presenting with polyserositis (pleural and pericardial effusion and ascites) and gastrointestinal manifestations (atrophic gastritis and candida esophagitis) and ascending aorta aneurysm. SS was diagnosed based on xerophthalmia, xerostomia, extraglandular manifestations, positive results for the Schirmer test, ocular surface staining score, histopathologic examination of labial buccal mucosa revealing focal lymphocytic sialadenitis and unstimulated salivary flow rate. The only positive autoantibody was against smooth muscle cells (ASMA). We thought that pleural, pericardial effusions, ascites, gastrointestinal findings and ascending aortic aneurysm may be related with autoimmuneological inflammation of SS. To evaluate the extent of aortic vasculitis, we performed a whole body 18-Fluorodeoxyglucose-positron emission tomography (FDG-PET) and showed increased uptake of FDG in aneurysmal section of the ascending aorta. Treatment with high dose corticosteroid was proved to be successful in both clinically and laboratory.

Keywords: Sjögren's syndrome; Pleural effusion; Pericardial effusion; Ascites; polyserositis; Ascending aortic aneurysm; Atrophic gastritis; *Candida esophagitis*

Introduction

Sjögren's syndrome (SS) is an autoimmune disorder and can cause many organic changes. Although disease pathogenesis has not yet been fully elucidated, substantial data has been demonstrated for diagnosis. Over the past 15 years, two sets of criteria have been published. New 2016 ACR/EULAR classification criteria for primary Sjögren's syndrome (SS) have been developed and endorsed by the ACR [1]. Pulmonary involvement in SS include xerotrachea, bronchial sicca, obstructive small airway disease, interstitial lung diseases, lymphoproliferative lung disease, pulmonary hypertension, pleurites, pleural effusion, and thickened pleura [2]. Cardiac involvement includes pericarditis, pericardial effusion, and atrioventricular conduction block [3]. Pleural and pericardial effusions in association with SS are rare. Similarly, ascites is rare and it can occur in SS when combined with primary biliary cirrhosis (PBC) [4]. Inflammatory abdominal aortic aneurysm (IAAA) together with Sjögren's syndrome was described only in one case in the literature [5]. Among the gastrointestinal manifestations of Sjögren's syndrome (SS), chronic atrophic gastritis (CAG) is the most common finding. In several previous investigations, the incidence of CAG in patients with SS was

more than 65% [6,7]. To our best knowledge, candida esophagitis has not been described before in the literature.

We herein describe the first case of SS in a patient with pleural and pericardial effusions and ascites and gastrointestinal involvement with candida esophagitis and ascending aortic aneurysm. The only positive autoantibody to smooth muscle cells may also support the autoimmune processes.

A 70-year-old male was admitted to our clinic due to fatigue, malaise, anorexia, weight loss (10 kg in 2 years), severe dyspnea, orthopnea, paroxysmal nocturnal dyspnea, dysphagia and epigastric pain. He also had a nearly ten-year clinical history of ocular and oral symptoms of xerophthalmia and xerostomia, respectively. He had recurrent severe pericardial effusion attacks for two years; had been performed a few times pericardial drainages (nearly 1000 cc pericardial effusion drainage at each time) and at last attack, pericardial window operation has been performed in another hospital nearly two months ago. He has described partial relief after pericardial window operation but severe clinical deterioration has started for one month. He was also on colchicum therapy for nearly one year.

Physical examination revealed weak chest sounds bilaterally. Neither skin rash nor swollen joints were evident. There were jugular venous distention and epigastric and right upper quadrant pain during abdominal palpation.

Chest roentgenogram showed consolidation in the middle and lower bilateral lung fields (Figure 1a). Pleural effusion disappeared totally during follow-up at first month and fourth month follow up (Figure 1b). Computed tomography (CT) without contrast taken one month ago demonstrated a fusiform ascending aortic aneurysm with a diameter of maximum 5.0 cm, 22 mm pericardial effusion, severe bilateral pleural effusion, with compression atelectasis, and no pericardial and pleural thickening and calcification (Figure 2). We also examined patient's enhanced CT taken two years ago in an another hospital and found that ascending aortic aneurysm diameter was 4.9 cm; 25 mm pericardial effusion and no pleural effusion and pathological lymph node enlargement and malignancy image. Laboratory findings were as follows: White blood cell count (WBC), 8.209/mL, aspartate aminotransferase 24 IU/L, alanine aminotransferase, 27 IU/L, blood urea nitrogen, 8 mg/dL, creatinine, 0.54 mg/dL; total protein 6.3 g/dL; albumin (Alb), 3.1 g/dL; albumin/globulin ratio: 0.39, C-reactive protein (CRP), 173, 13.8, 2 and 0.4 mg/dL and sedimentation rate 71, 64 and 24 mm/h consecutively during follow-up. Serological tests showed: rheumatoid factor, 7 IU/L (normal <15.0 IU/L); C3, 135 mg/dL; and C4, 38 mg/dL. Serum IgG4 level was normal (19 mg/dl). Hepatitis A surface antigen and anti-hepatitis C antibody were also negative. Anti-nuclear antibody (ANA), Anti ds DNA, Anti-SS-A antibody, anti-SS-B antibody, Anti-mitochondrial antibody (AMA), Anti Parietal Cell Antibody, Liver-kidney microsomal antibody (IFA), intrinsic factor antibody, anti-cardiolipin (CL) were also negative. The only positive antibody was against smooth muscle cell. Urine analysis revealed neither proteinuria nor hematuria. On ophthalmological examination, Schirmer test result was positive both eyes (right eye 4, and left eye 3 mm/5 min). Ocular surface staining was performed using fluorescein sodium and observed under cobalt blue illumination and yellow filter with slit lamp biomicroscopy. Corneal, temporal and nasal conjunctival staining was graded according to the Oxford grading scheme between 0 and 5 [8]. Punctate staining score was grade 4 in our patient.



Figure 1a: Chest x-Ray taken before the therapy shows severe bilateral pleural effusion and enlargement of aortic root.

We performed labial buccal mucosal biopsy two times because of the first specimen is superficial and not diagnostic. Second histopathologic examination revealed focal lymphocytic sialadenitis. We also measured unstimulated salivary flow rate and found as <0.1 ml/min. Pleural effusion was turbid and positive for the Rivalta test.

Total protein was 4.6 g/dL, albumin was 2.4 g/dL, LDH was 85 U/L, and glucose was 101 mg/dL, and of exudative nature. Aerobic and anaerobic cultures taken from pleural and pericardial effusion were negative. Smear tests and bacterial culture for *Mycobacterium tuberculosis* yielded negative results. Adenosine Deaminase level in pleural effusion was normal (10.8 U/L). No malignant cells were found in the pleural effusion except lymphocytes, histiocytes, lymphoplasmacytic cells and reactive mesothelial cells.



Figure 1b: Chest x-Ray just after the therapy shows minimal pleural effusion, with atelectasis in the lower right lung field.

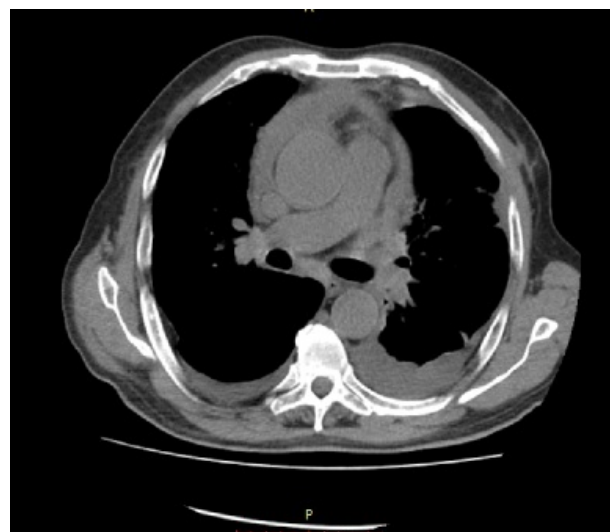


Figure 2: Chest computed tomography (CT) shows bilateral pleural effusions with atelectasis, pericardial effusion and ascending aortic aneurysm.



Figure 3: Pleural effusion containing dense fibrin deposits detected by echocardiography.

Colored Doppler Echocardiography revealed normal ejection fraction, aortic aneurysm with a diameter of maximum 5 cm, septal paradox motion, minimal pericardial effusion, massive pleural effusion containing fibrin deposits and no pericardial thickening (Figure 3). The echocardiograms taken one and four months later after prednisolone therapy demonstrated 2 mm decrease in maximum ascending aortic aneurysm diameters (Figure 4).

Abdominal CT examination revealed a small gallstone, a few small calcifications in the spleen, a few simple cystic formation in the kidneys, no malignant formation and pathologic lymph node, except minimal ascites. Portal venous system Doppler USG was also normal.

Due to patient's family history of colon carcinoma, epigastric pain and dysphagia, we performed gastrointestinal endoscopy. Upper GI endoscopy revealed biopsy proven candida esophagitis, loose lower esophageal sphincter tonus and atrophic gastritis (Figure 5). Because the patient had hypoxemia during the procedure we could not get biopsy samples from stomach. Colonoscopy findings were all normal except first degree internal hemorrhoids. Rectal biopsy for amyloidosis was negative. Esophageal biopsy revealed candida spores and hyphae and no metaplasia.

To exclude malignancy and detect possible inflammation of aortic aneurysm, we performed whole-body PET/CT imaging, following intravenous injection of 9.28 mCi F-18 labeled FDG (fluorodeoxyglucose). Blood glucose level was 93 mg/dL at the time of radioactivity injection and the patient was rested in a quiet, dark room for 60 minutes before imaging. We revealed that the diameter of ascending aorta was 51 mm and there was an increased FDG uptake on the left wall of ascending aorta (SUVmax: 3) which might indicate inflammation. There was also minimal pleural and pericardial thickening with no pathological FDG uptake and no hypermetabolic lesion was seen in other parts of the body (Figure 6). As a limitation of our case report, we performed PET/CT after prednisolone therapy and clinical improvement. In case of a PET scan a priori, the FDG uptake

could have been more systemic. Further this, corticosteroid therapy may also lead to prompt suppression of the systemic inflammation.

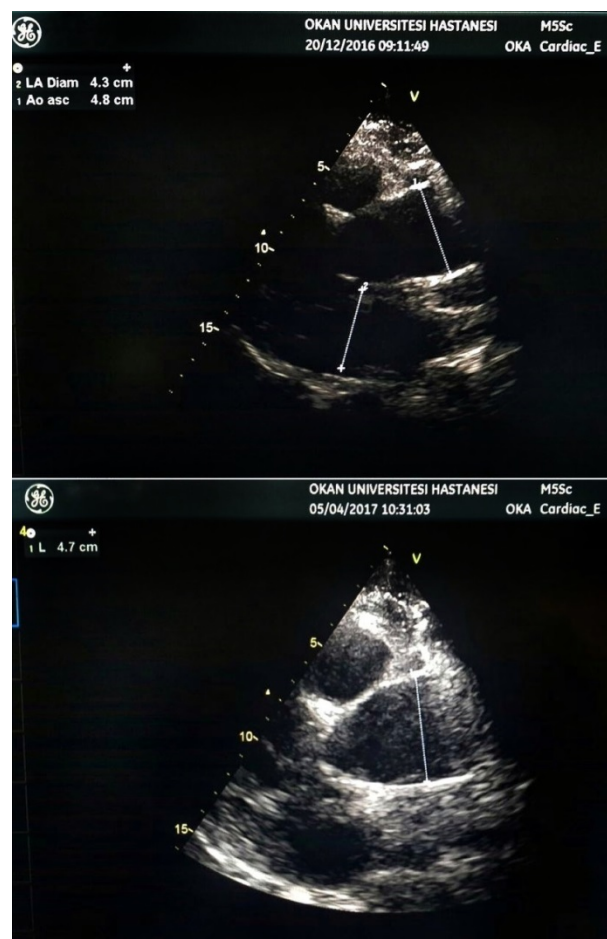


Figure 4: Echocardiograms showing progressive decrease in maximum ascending aortic diameters taken one and four months after prednisolone therapy.

We consequently diagnosed Sjögren's Syndrome (SS) with pleuritis, pericarditis, peritonitis, atrophic gastritis, candida esophagitis and ascending aortic aneurysm.

The patient was treated with prednisolone (PSL) at 30 mg/day, and pleural drainage was performed bilaterally. Due to patient's poor clinical status, we had to start prednisolone therapy just after strong clinical suspicion for SS. Esophageal candidiasis was treated with oral fluconazole therapy for two weeks.

In the fourth month's follow-up, the patient was totally asymptomatic, no dysphagia and epigastric pain after food intake were present, there was weight gain of nearly three kilograms, and pericardial and pleural effusion were not existent. There was two-mm decrease in maximum ascending aortic aneurysm diameter on follow-up echocardiograms and it was thought effective anti-inflammation on the aortic wall with prednisolone. Laboratory findings revealed normal sedimentation and CRP values.

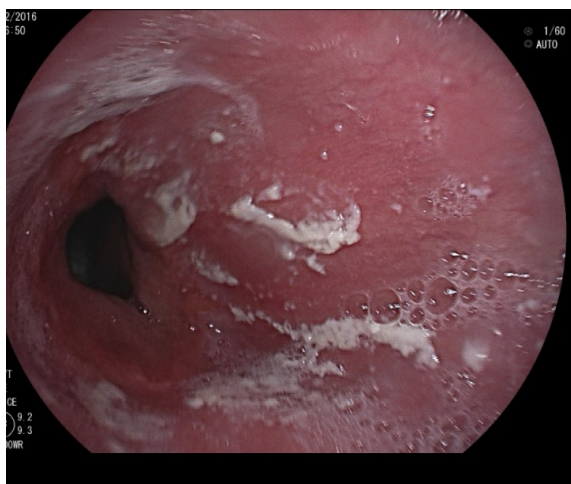


Figure 5: Endoscopic view of the esophagus revealing *Candida esophagitis*.



Figure 6: Positron emission tomography shows increased 18-Fluorodeoxyglucose uptake in the left lateral wall of the ascending aorta.

Discussion

Sjögren's syndrome (SS) has been defined as an autoimmune epithelitis characterized by lymphocytic infiltration of exocrine glands and epithelia in multiple sites. The involvement of lachrymal and salivary glands results in the typical features of dry eye and salivary dysfunction (xerostomia). However, one third of the patients present with systemic extra glandular manifestations. Finally, SS can be seen alone (primary SS) or in association with other autoimmune rheumatic disease (secondary SS). Thus, the diagnostic approach to SS is rather complicated because it must include two different goals: firstly, assessment of the ocular and salivary components, and secondly, differentiation between the primary and secondary variants of the syndrome [9]. Based on strong clinical symptoms and findings as

xerophthalmia, xerostomi, extraglandular symptoms and other tests as Schirmer, ocular surface staining score, histopathologic examination of labial buccal mucosa, unstimulated salivary flow rate and autoantibody to smooth muscle cells, we assumed that it can be primary variants of the syndrome with extra glandular involvement.

Because of the fact that there were no skin eruptions such as erythema, arthritis, renal dysfunction, neurological symptoms, and immunological abnormalities such as positive results for anti-DNA, anti-Sm and anti-CL antibodies, we could not diagnose SLE. Similarly, we also could not verify RA because of missing clinical signs of RA such as morning stiffness, arthralgia and articular swellings, additionally no laboratory findings of RA were present. We have been differentiated the case from Takayasu's Arteritis because pre-pulseless period of Takayasu's Arteritis may resemble to SS. Pre-pulseless period in Takayasu's Arteritis is characterized by non-specific systemic symptoms and manifestations as anemia, prolonged fever, pleurisy with or without effusion, haemoptysis, pericarditic pain, myalgia, arthralgia, migratory polyarthritits, erythema-nodosum-like lesions, ulceration of the legs, transient skin rashes, Raynaud's phenomenon, iritis, episleritis, cranio-cervical pain and splenomegaly [10]. However, we did not think Takayasu's Arteritis in our case because the ocular and oral symptoms as xerophthalmia and xerostomia are not specific to Takayasu's arteritis. In addition, male sex, older age, and no arterial narrowing or thrombus formation together with aneurysm of large arteries and main branches on angiograms are not specific to this syndrome. We ruled out Churg-Strauss syndrome because of the fact that there were no asthma and allergic rhinitis symptoms and signs on clinical examination in our patient. In addition, no hypereosinophilia on peripheral blood smear and no vascular involvement of small size arteries that is specific to this syndrome helped to us for differential diagnosis [11]. Immunoglobulin G4-related disease (IgG4-RD) is a condition characterized by truly multiorgan involvement occurring in a synchronous or metachronous fashion. The most frequent localizations include the pancreas and salivary glands. Other common manifestations are tubulointerstitial nephritis, dacryoadenitis, and periaortitis. We ruled out IgG4-related disease with clinically and laboratorally (normal IgG4 level) [12].

Gastrointestinal disease in SS may occur in one quarter of patients and includes dysphagia, gastritis, motility disorders, pancreatitis, pancreatic insufficiency, pernicious anemia, autoimmune hepatitis and symptoms consistent with irritable bowel syndrome (IBS), abdominal pain, diarrhea, constipation, bloating, flatulence, vomiting and nausea [13,14]. Among the gastrointestinal manifestations of SS, chronic atrophic gastritis (CAG) is the most common finding. In several previous investigations the incidence of CAG in patients with SS was more than 65%. [6,7].

Upper GI endoscopy revealed chronic atrophic gastritis and candida esophagitis in our patient. Candida esophagitis has also been verified with biopsy. Biopsy proven candida esophagitis in SS has not been described in the literature before. We thought that decreased acidity secondary to atrophic gastritis in the stomach may provide the basis for candida settling in the upper gastrointestinal tracts.

Due to the autoimmune basis of SS, we thought that ascending aortic aneurysm may be secondary to aortic inflammatory process. The diagnosis of inflammatory chronic aortitis was supported by FDG-PET in our patient. The clinical presentation of aortitis varies across a spectrum of symptoms and clinical signs, ranging from back or abdominal pain with fever to acute severe aortic insufficiency to an incidentally identified large aortic aneurysm. Acute aortic syndromes,

including aortic dissection and rupture, can also occur in persons with aortitis [15,16]. Chronic periaortitis has already been reported in association with various autoimmune disorders, such as Hashimoto's thyroiditis, systemic lupus erythematosus (SLE) and primary biliary cirrhosis [17-19]. We ruled out SLE, Hashimoto's thyroiditis and primary biliary cirrhosis on the basis of clinical and laboratory findings. Primary biliary cholangitis (PBC), is most frequently a disease of women and occurs between the fourth and sixth decades of life. The disease formerly known as primary biliary cirrhosis, is a chronic disease of the liver, presumably autoimmune in nature, that leads to progressive cholestasis and often end-stage liver disease. The name change reflects the fact that cirrhosis occurs only in the late stage and therefore does not correctly identify patients with early-stage disease. The hallmark of PBC is the presence of anti-mitochondrial antibodies (AMAs) in serum. AMAs can be found in 90-95% of patients with PBC, and they have a specificity of 98% for this disease [20]. Our patient's liver and bile ducts enzymes were in the normal range and Doppler ultrasonography imaging and CT scanning of the liver were also normal. AMAs were not found either. We thought that gallbladder stones could not be specific to PBC.

The only autoantibody was against smooth muscle cells in our patient. The smooth muscle cell autoantibodies can usually be associated with chronic liver disease. Anti-Smooth Muscle Antibodies (ASMA) are believed to be directed against either actin, tubulin or the intermediate filaments of the cell [21]. We did not find any studies showing the relationship between ASMA and aortic aneurysm. We only found an animal study showing that radioimmunosintigraphic visualization of aortic aneurysm dissection using 99 m Tc-anti-smooth muscle myosin monoclonal antibody (SM-MAb) [22]. In the aortic aneurysm or in the diseased aorta, mechanical tissue injury may result in a loss of cell membrane integrity, as evidenced by leakage of intracellular structural proteins such as myosin heavy chain, into the circulation. In the light of this animal study, we thought that autoantibodies to aortic wall tissue may cause to primary aortic disease or may be just a reaction to aortic wall injury.

In the literature, there is only one case study describing primary Sjögren's syndrome associated with inflammatory abdominal aortic aneurysm that had been secondary to chronic periaortitis (CP) [5]. To the best of our knowledge, ours is the first case reporting SS associated with ascending aortic aneurysm.

Recently, a case-control study, which compared inflammatory and non-inflammatory abdominal aortic aneurysms, showed an autoimmune disease in 19% of patients with IAAA, compared to control subjects [18]. Likewise, in a recent prospective study, Vaglio et al. found that in 7 (44%) out of 16 cases CP was associated with other autoimmune conditions, namely ANCA-positive renal disease and autoimmune thyroiditis [16]. The association with other autoimmune disorders suggests that CP is a manifestation of a systemic autoimmune process rather than an exaggerated local reaction to atherosclerosis [23].

In our case, the presence of constitutional symptoms, raised acute-phase reactants, complete clinical answer and deterioration of ascending aortic aneurysm diameter after prednisolone therapy and FDG-PET findings gave rise to the idea that ascending aortic aneurysm may be secondary to systemic inflammatory process.

In conclusion, physicians should take notice that SS may cause pleural, pericardial effusions and ascites and may be responsible for inflammatory processes in the aorta. GI involvement of SS, especially

atrophic gastritis related decreased PH in the stomach, may cause to settling of pathologic organisms like candida.

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