

A Case of Sjögren's Syndrome with Wegener's Granulomatosis-like Pulmonary Involvement

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ABSTRACT

Background: We report a case of Sjögren's syndrome with pulmonary involvement resembling that seen in Wegener's granulomatosis. The patient was a 69-year-old woman who presented with a three-week history of persistent cough and fever. The chest radiograph and CT scans revealed multiple consolidations in the middle and lower lung fields bilaterally.

Methods & Results: Lung biopsy specimens obtained by video-assisted thoracoscopy showed infiltration of the alveoli by lymphocytes with scattered neutrophils, and microscopic vasculitis of the small arteries. The patient tested positive for antineutrophil- cytoplasmic antibodies (ANCA) against myeloperoxidase (MPO-ANCA) and for anti SS-A & SS-B antibodies ; however, the test for ANCA against proteinase 3 (PR3-ANCA) was negative.

Conclusions: Based on the presence of the clinical features of the sicca syndrome and positive findings on Schirmer's test and sialoscintigraphy, the patient was given a diagnosis of Sjögren's syndrome with Wegener's granulomatosis-like involvement of the lungs. Neither upper airway nor renal involvement was detected.

KEY WORDS

MPO-ANCA, PR3-ANCA, Sjögren's syndrome, vasculitis, Wegener's granulomatosis

INTRODUCTION

Wegener's granulomatosis (WG) is a relatively uncommon condition that involves mainly the upper and lower airways, and the kidney.¹ It is pathologically characterized by necrotizing granulomatous vasculitis of the medium and/or small arteries and veins. On the other hand, Sjögren's syndrome (SS) is a more commonly encountered autoimmune disorder in which various types of pulmonary involvement, but rarely pulmonary angiitis, have been reported. We encountered a case of primary SS with pulmonary nodules showing the characteristic features of WG.

CLINICAL SUMMARY

A 69-year-old woman was admitted to our hospital with a three-week history of cough and fever. Body temperature on admission was 37.1 degrees C, and

her blood pressure and pulse were normal. The laboratory findings at admission were as follows : hemoglobin, 9.5 g/dl; normal total and differential white cell count ; ESR, 135 mm in the first hour ; CRP, 2.90 mg/dl; serum total protein 8.4 g/dl (IgG, 3129 mg/dl ; IgA, 438 mg/dl). The patient tested positive for rheumatoid factor, antinuclear antibody ($\times 86.8$), anti-SS-A antibody ($\times 256$), and anti-SS-B antibody ($\times 32$). The serum level of myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA) was 19 EU, while the test for proteinase-3 ANCA (PR3-ANCA) was negative. The urinalysis and renal values were normal. The chest X-ray revealed multiple nodules in the middle and lower lung fields bilaterally (Fig. 1). Chest CT revealed the presence of large and small nodules without cavitation bilaterally (Fig. 2). The patient had a six-month history of symptoms suggestive of the sicca syndrome, such as dry eyes and dry

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Fig. 1 Chest radiograph on admission showing multiple nodules in the middle and lower lung fields bilaterally .

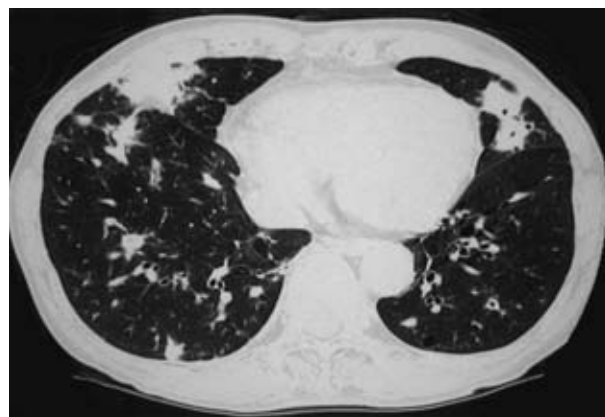


Fig. 2 CT scan showing multiple consolidations in the lower lobe bilaterally .

mouth, but there was no evidence of involvement of the ears, nose or upper airway. Schirmer's test result was 2 mm bilaterally, and the Rose Bengal test was (+ +). Sialoscintigraphy was strongly positive, with poor visualization of the parotid glands and submandibular glands bilaterally and poor response to stimulation. Sialography and lip biopsy were not performed because the patient refused to give consent for these procedures.

PATHOLOGICAL FINDINGS

Video associated thoracoscopic surgery was performed to obtain biopsy specimens for characterization of the lung involvement. Histopathological examination of the lung biopsy specimens revealed infiltration of the alveoli by lymphocytes with scattered neutrophils, and microscopic vasculitis of the small arteries. Granulomas with multinucleate giant cells were detected in the lung (Figs. 3(a), (b)). These findings were pathologically consistent with the diagnosis of WG, associated with limited involvement of the lung (Table 1).

DISCUSSION

Considering the presence of sicca symptoms, positive findings on the Schirmer's test and sialoscintigraphy, and positivity for anti SS-A and SS-B antibodies in the absence of any associated collagen vascular disease, this patient had a definitive diagnosis of SS.² On the other hand, considering the negative test for PR3-ANCA and the localized distribution of necrotizing granulomatous vasculitis in the lung, the diagnosis of atypical WG was also considered. Thus, there were three possible diagnostic interpretations of the findings in this case : SS associated with WG-like pulmo-

nary disease involvement, WG associated with the sicca syndrome due to vasculitis in the salivary glands and eyes, and coincidental existence of both conditions.

SS may be classified as either primary SS or secondary SS. In the primary form, dry eyes and dry mouth usually occur alone, without other associated connective tissue disease. On the other hand, in secondary SS, dryness often occurs in association with other connective tissue diseases, most commonly rheumatoid arthritis. Patients with SS are reported to have an ever-increasing list of systemic manifestations, including involvement of the lung, kidney and nervous system. Although many types of pulmonary involvement have been described previously,³⁻⁵ the prevalence of pulmonary involvement in this condition has not been definitively established, with a wide range of reports varying from 19 to 75%. Xerotrachea, bronchitis, bronchiolitis and interstitial pneumonia are relatively common. Amyloidosis and lymphoproliferative disorders, such as LIP, pseudolymphoma, and malignant lymphoma have also been reported in SS.⁶⁻¹³ Granulomatous or other types of angiitis has also been reported as a type of pulmonary involvement in SS.^{13,14} However, only three cases of SS with WG-like pulmonary involvement have been reported previously in the literature.¹⁵⁻¹⁷

Indeed, our patient did not present with the classical triad of WG, although the diagnosis of a limited form of WG could be considered. There are several reports of patients with WG presenting with isolated lesions of the submandibular glands,^{15,18-20} salivary glands^{15,18-22} and sclera.^{18,19} A review of the reported cases in the literature suggests that salivary gland involvement may be associated with the limited form of WG. In most cases, the chief complaints are salivary gland enlargement, jaw pain and difficulty in opening the mouth, but symptoms of dry mouth are rarely reported. The gold standard for the diagnosis of WG re-

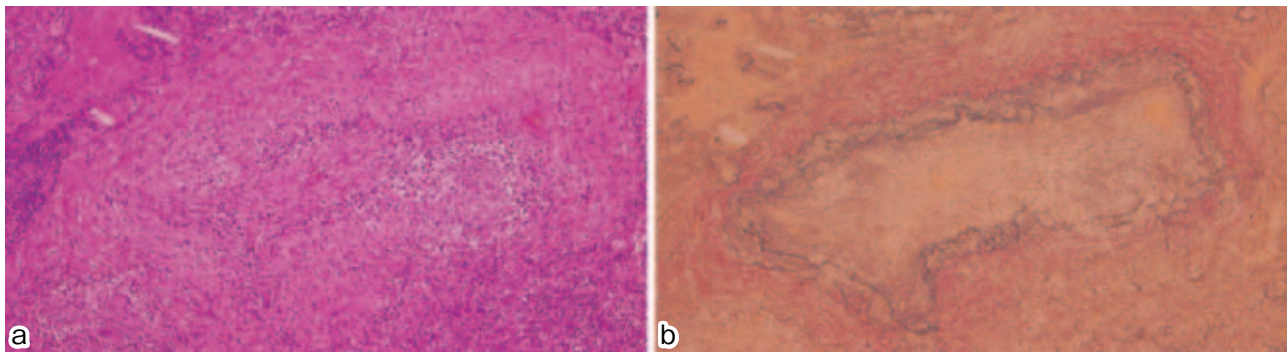


Fig. 3 Biopsy specimens showing irregular infiltration of the alveoli by lymphocytes with scattered neutrophils, and necrotizing vasculitis of the small blood vessels. (a) H.E. ×400 (b) EVG ×400

Table 1

Reporter/year	Age/Sex	Immunological Measures	Organs involved	Drug Regimen	Final Clinical Status
C Young 2000	65/F	SS-A · B (+) PR3-ANCA (+)	L	PSL AZA	Full remission
Karargyris G 2000	61/F	PR3-ANCA (+) ANA (+), RF (+)	L	PSL	Full remission
Böttinger EP 1992	63/F	PR3-ANCA (-) MPO-ANCA (+)	E, K Salivary gland	CPA mPSL pulse	Full remission
The present case 2002	69/F	RF (+), SS-A · B (+) PR3-ANCA (-), ANA (+) MPO-ANCA (+)	L, K	PSL	Full remission

E: upper respiratory tract, L: lung, K: kidney
ANA: antinuclear antibodies, PSL: prednisolone, CPA: cyclophosphamide
AZA: azathioprine

A table showing the differences in the characteristics among 3 cases and the present case.

mains the PR3-ANCA assay. However, in our case, the test for PR3-ANCA proved negative, while that for MPO-ANCA was positive. On the other hand, 15–33% of cases of WG may be negative for PR3-ANCA, therefore PR3-ANCA assay alone is not sufficient to make the diagnosis of WG, and histopathological study is required for a definitive diagnosis.²⁰

A study to evaluate the prevalence of ANCA in patients with primary SS reported that the presence of ANCA correlated positively with the presence of extraglandular and immunological manifestations in SS.²³ Furthermore, ANCA positivity may be found in 11% of patients with primary SS (8.6% had MPO-ANCA and 2.4% had an atypical staining pattern), and its detection is associated with the presence of clinical manifestations attributable to vascular involvement (cutaneous vasculitis, peripheral neuropathy, and Raynaud's phenomenon).

There have been few reports of SS associated with a specific diagnosis of WG. The relationship between the two conditions remains unclear. It is possible that Wegener's granulomatosis observed in association with Sjögren's syndrome is an atypical presenta-

tion as compared with that of classical WG in terms of severity, sites of involvement and immunoserology.

REFERENCES

1. Wegener F. Über eine einartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und der Nieren. *Beitr. Pathol.* 1939;**38**:102.
2. Yoshida S. Sjögren's syndrome. *Nippon Rinsyo* 1999;**57**:110-113.
3. Vitali C, Tavoni A, Viegi G *et al.* Lung involvement in Sjögren's syndrome: a comparison between patients with primary and with secondary syndrome. *Ann. Rheum. Dis.* 1985;**44**:455-461.
4. Papatheanasiou MP, Constantopoulos SH, Tsampoulas C *et al.* Reappraisal of respiratory abnormalities in primary and secondary Sjögren's syndrome: a controlled study. *Chest* 1986;**90**:370-374.
5. Deheinzeln D, Capelozzi VL, Kairalla RA *et al.* Interstitial lung disease in primary Sjögren's syndrome. *Am. J. Respir. Crit. Care Med.* 1996;**154**:794-799.
6. Strimlan VC, Rosenow EC, Havvison EG Jr *et al.* Pulmonary manifestations of Sjögren's syndrome. *Chest* 1976;**70**:354-361.
7. Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM. Respiratory manifestations in primary Sjögren's syn-

- drome. *Chest* 1985;**88**:226-229.
8. Lahdensuo A, Korpela M. Pulmonary findings in patients with primary Sjögren's syndrome. *Chest* 1995;**108**:316-319.
 9. Papisir SA, Maniati M, Constantopoulos SH *et al.* Lung involvement in primary Sjögren's syndrome is mainly related to the small airway disease. *Ann. Rheum. Dis.* 1999;**58**:61-64.
 10. Matteson EL, Ike RW. Bronchiolitis obliterans organizing pneumonia and Sjögren's syndrome. *J. Rheumatol.* 1990;**17**:676-679.
 11. Usui Y, Kimura Y, Miura H *et al.* A case of Bronchiolitis obliterans organizing pneumonia associated with primary Sjögren's syndrome who died of superimposed diffuse alveolar damage. *Respiration* 1992;**59**:122-124.
 12. Kobayashi H, Matsuoka R, Kitamura S *et al.* Sjögren's syndrome with multiple bullae and pulmonary nodular amyloidosis. *Chest* 1988;**94**:438-440.
 13. Whitehouse AG, Buckley CE III, Nagaya H *et al.* Macroglobulinemia and vasculitis in Sjögren's syndrome. *Am. J. Med.* 1967;**43**:609-919.
 14. Hunninghake GW, Fauci AS. State of the art : Pulmonary involvement in the collagen vascular diseases. *Am. Rev. Respir. Dis.* 1979;**119**:471-503.
 15. Böttinger EP, Niles JL, Collins AB *et al.* Antineutrophil cytoplasmic autoantibody-associated vasculitis presenting as Sjögren's syndrome. *Arthritis Rheum.* 1992;**35**:1373-1376.
 16. Young C, Hunt S, Watkinson S *et al.* Sjögren's syndrome, cavitating lung disease and high sustained levels of antibodies to serine proteinase 3. *J. Rheumatol.* 2000;**22**:267-269.
 17. Karagyris G, Stamatopoulos K, Kittas C *et al.* Sjögren's syndrome co-existing with limited Wegener's granulomatosis. *Rheumatology* 2000;**39**:805-806.
 18. Murty GE, Mains BT, Bennett MK. Salivary gland involvement in Wegener's granulomatosis. *J. Laryngol. Otol.* 1990;**104**:259-261.
 19. Specks UM, Colby TV, Olsen KD *et al.* Salivary gland involvement in Wegener's granulomatosis. *Arch. Otolaryngol. Head Neck Surg.* 1991;**117**:218-223.
 20. Ah-See KW, McLaren K, Maran AG. Wegener's granulomatosis presenting as major Salivary gland enlargement. *J. Laryngol. Otol.* 1996;**110**:691-693.
 21. Mitchell RB, Tolley N, Croft CB *et al.* Wegener's granuloma-presenting as a Unilateral parotid swelling. *J. Laryngol. Otol.* 1994;**108**:431-432.
 22. Kavanaugh AF, Huston DP. Wegener's granulomatosis presenting with unilateral parotid enlargement. *Am. J. Med.* 1988;**85**:741-742.
 23. Font J, Ramos-Casals M, Cervera R *et al.* Antineutrophil cytoplasmic antibodies in primary Sjögren's syndrome : prevalence and clinical significance. *Br. J. Rheumatol.* 1998;**37**:1287-1291.