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CASE REPORT

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Silicosis, then microscopic polyangiitis—antineutrophil cytoplasmic antibodies-associated vasculitis may be work-related disease in patients with silicosis

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Abstract

A 74-year-old man with silicosis was admitted to the hospital because of prolonged fever. After referral to internal medicine for persistent fever and renal dysfunction, workup revealed antineutrophil cytoplasmic antibodies (ANCA) positivity. He was diagnosed with microscopic polyangiitis (MPA). After treatment with immunosuppressive therapy, his condition improved. Herein, we discuss silica exposure and the risk of ANCA-associated vasculitis (AAV), particularly in terms of work-related diseases. Silica exposure is a notorious risk factor for developing AAV, which is potentially lethal when not identified. When we see a silicosis patient with new-onset prolonged fever and generalized fatigue, AAV should be taken into consideration. This case report provides beneficial information to reliably assess patients at high risk of developing AAV in primary care settings.

KEYWORDS

antineutrophil cytoplasmic antibodies, microscopic polyangiitis, silicosis, work-related disease

1 | INTRODUCTION

Microscopic polyangiitis (MPA) is a primary systemic vasculitis commonly known as antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), characterized by inflammation of small-sized blood vessels and serum positivity of ANCA.[1] Patients with MPA typically present with pulmonary, kidney, and neurologic manifestations.[2] Although the definitive pathophysiology of MPA is still not fully understood, certain factors such as drugs, bacteria, and dust exposure are known to trigger the development of this disorder.[1,3–5] Herein, we describe a case of MPA in a patient with longstanding occupational dust exposure.

2 | CASE REPORT

A 74-year-old Japanese man with silicosis was admitted to our hospital because of generalized fatigue and fever, which began 2 weeks before presentation. He also complained of a dry cough, but he had no chills, night sweats, or unintentional weight loss. He had a history of type 2 diabetes mellitus and right pneumothorax managed with thoracoscopic pleurodesis one-and-a-half years prior to this admission. He had been diagnosed with silicosis based on his history of dust exposure and bilateral lower lung dominant micronodular infiltrates on imaging many years prior to this presentation. He had worked as a shipyard worker for 43 years until he was 65 years old. He denied

visiting any shipyards after his retirement. His medications included linagliptin 5 mg a day for diabetes mellitus. He had never smoked or drunk alcohol. On physical examination, his vital signs were significant for low-grade fever and mild tachypnea with a body temperature of 37.8°C, blood pressure 128/62 mm Hg, heart rate 80 beats/min with regular rhythm, respiratory rate 20 breaths/min, and oxygen saturation 97% with 2L oxygen on nasal cannula. Bilateral fine crackles were noted on lung auscultation. There was no purpura, costovertebral tenderness, or neurologic abnormalities. A blood test and urinalysis on the day of admission revealed increased inflammatory response and hematuria. Other test results are shown in Table 1. Chest computed tomography (CT) without contrast media after admission revealed ground-glass opacity (GGO) mainly in the right lung (Figure 1A). He was initially diagnosed with pneumonia and was administered oral levofloxacin 500 mg a day for7 days, which did not improve his condition. Because of persistent fever and acute renal dysfunction, he was referred to an inpatient internal medicine team 24 days after admission to further investigate the cause of his symptoms. Additional workup revealed positive myeloperoxidase (MPO) -ANCA (<300 U/mL; reference range <3.5 U/mL) and bilateral pulmonary GGO on chest CT (Figure 1B). Consequently, he was subsequently diagnosed with MPA with rapidly progressive glomerulonephritis (RPGN), based on the diagnostic criteria for MPA published in 1998 by the Ministry of Health and Welfare, with interstitial pneumonia, and positive MPO-ANCA. Because he was in distress, we could not perform a renal biopsy for him. Prednisone 30 mg a day was begun on day 36 after admission. An intravenous cyclophosphamide pulse was also administered on day 49. Because his renal dysfunction persisted, aggressive immunosuppression therapy including a 500 mg methyl prednisone pulse for 3 days was commenced on day 69. After the prednisone pulse therapy, his general condition began to improve with prednisone 20 mg a day and oral cyclophosphamide 50 mg a day. He was discharged approximately 4 months after admission following improvement of his symptoms.

TABLE 1 Laboratory data

Variable	Reference range	On admission (Day 1)	On referral (Day 24)
Blood			
Hematocrit (%)	39.0-52.0	30.9	25.9
Hemoglobin (%)	13.6-17.0	10.6	9.0
White-cell count (/mm^3)	3,500-8,500	9,920	11,400
Platelet (/mm^3)	130-300x10^3	249x10^3	271x10^3
Sodium (mEq/L)	135-147	136	139
Potassium (mEq/L)	3.6-5.0	3.6	3.4
Chloride (mEq/L)	96-110	105	101
BUN (mg/dL)	9.0-20.0	21.5	37.9
Creatinine (mg/dL)	0.40-1.10	1.12	2.26
CRP (mg/dL)	0.00-0.40	13.27	11.73
IgG (mg/dL)	870-1,700		1,781
IgA (mg/dL)	110-410		362
IgM (mg/dL)	35-220		204
C3 (mg/dL)	65-135		102
C4 (mg/dL)	16-45		26.6
KL-6 (U/mL)	–499		282
Antinuclear antibody (dilution)	<1:40		<1:40
PR3-ANCA (U/mL)	<2.0		<1.0
MPO-ANCA (U/mL)	<3.5		300>
Anti-GBM antibody (U/mL)	<3.0		<2.0
Urine			
Protein	–	2+	
Blood	–	3+	
Red-cell count (/hpf)	–	100 >	
White-cell count (/hpf)	–	40-49	
Hyaline cast	–	3+	
Granular cast	–	2+	

3 | DISCUSSION

Microscopic polyangiitis is the most frequent AAV in Japan.[6] Several factors are known to trigger the occurrence of AAV.[1,3,4] As a report of rheumatoid arthritis associated with pneumoconiosis, referred to as Caplan's syndrome, silica exposure has been related to the development of several autoimmune disorders including systemic lupus erythematosus, systemic sclerosis, and AVV.[7] Previous reports indicate an increased prevalence of diffuse alveolar hemorrhage and AAV after major earthquakes, and this implicates the causal relationship of environmental dust exposure and the development of AAV.[8,9] Likewise, according to Bartunkova et al., [10] among 86 patients with silica exposure, 18 patients were positive for MPO-ANCA. Moreover, Gregorini et al.[11] reported approximately 30%-40% of patients with ANCA-associated renal disorder had MPO-ANCA positivity. A meta-analysis conducted by Gomez-Puerta et al.[12] also points to an association between silica exposure and an increased risk of developing AAV. It is speculated that particles in environmental silica induce systemic autoimmunity, inducing T responder cells and Treg cells.[7,13] However, silica exposure alone would be insufficient to cause new-onset AAV because there are substantial latency periods between the development of AAV and the exposure in previous cases.[12] It is assumed that additional factors such as drugs, infections, and surgical procedures are necessary for onset of the disease. Diagnosing AAV in patients with silicosis is essential because the Japanese government has chosen "epidemiologic consideration to complications of AAV in silicosis patients" as the main theme of national work-related disease research.[14] All primary physicians caring for those patients should recognize the potential association between silica exposure and the development of AAV for early diagnosis. Welders, shipyard workers, mine workers, and even construction workers are at high risk as they have environmental dust exposure. Patients with silicosis typically present with

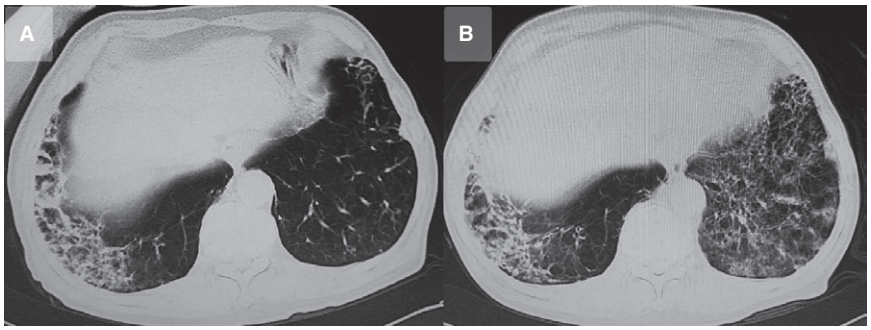

FIGURE 1 Chest computed tomography without contrast on admission. Chest computed tomography (CT) without contrast on admission revealed ground-glass opacity (GGO) in right lung (A). Bilateral pulmonary GGO suggestive of interstitial pneumonia was noted on chest CT on referral (B)

diffuse lower lung dominant nodular infiltrates. New onset reticular infiltrates or renal dysfunction can be hallmarks of the development of AAV, which we should carefully review for early recognition.

In our present case, the patient developed MPA following 43 years of occupational silica exposure. Hematuria and persistent fever were the symptoms that led us to add AAV to the differential diagnosis. Even though the definitive relationship between the exposure and the disease is difficult to prove, thoracoscopic pleurodesis performed one-and-a-half year prior to this admission may have been a possible additional trigger of the abrupt onset of MPA. Because it is typically difficult to check auto-antibodies in primary care settings, we, primary care physicians should have the relationship in our minds and thoroughly take histories especially in patients with silicosis.

In conclusion, with respect to work-related disease and potential compensation, it is essential to recognize silica exposure as a risk factor for developing AAV such as MPA. Our case emphasizes the importance of primary physicians identifying this relationship in addition to taking a thorough occupational history.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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