Microscopic polyangiitis in a case of silica exposure: a rare presentation

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Abstract

A 28-year-old male was admitted for breathlessness, haemoptysis, fever and fatigue. The patient had occupational exposure to silica dust. Arterial blood gas test ABG revealed hypoxemic respiratory failure. Chest CT demonstrated ground glass opacities with interlobular septal thickening and small centrilobular nodules with patchy areas of consolidation in bilateral lungs. He was mechanically ventilated for refractory hypoxemia. The treatment with cyclophosphamide and methylprednisolone lead to recovery and extubation. The final diagnosis was diffuse alveolar haemorrhage due to perinuclear antineutrophil cytoplasmic antibody (ANCA)-associated microscopic polyangiitis (p-ANCA-associated MPA). In a tuberculosis endemic country, for patients presenting with diffuse alveolar haemorrhage (DAH), with history of silica exposure, differential diagnosis of ANCA associated vasculitis must be considered.

Case Report

A 28-year-old male, non-smoker, presented to our emergency with sudden onset breathlessness (mMRC grade 2) and haemoptysis (3 episodes; each with 20-30 ml) for 2 days. He had no wheeze, chest pain and no history of bleeding from any other site. There were no complaints indicative of a connective tissue disorder. There was no past history of similar complaints, history of tuberculosis or contact with a case of tuberculosis. There was no family history of similar complaints. He worked at a stone crushing mill for past ten years. On general physical examination, his respiratory rate was 38/min and temperature of 37.78°C. The oxygen saturation at room air was 84%. There was no pallor, clubbing or cyanosis. On auscultation, vesicular breath sounds of equal intensity were audible bilaterally along with fine end-inspiratory crackles in bisablar areas. Arterial blood gas analysis showed respiratory alkalosis with hypoxemia and wide alveolar-arterial gradient (FiO₂: 21%, pH: 7.51; pCO₂: 29 mmHg; pO₂: 46 mmHg; HCO₃: 22 mmol/L). Patient was admitted in critical care unit and initiated on high flow oxygen therapy and subsequently intubated and mechanically ventilated due to refractory hypoxemia.

Chest X-ray (Figure 1a), showed coalescent parenchymal alveolar opacities having ill-defined margins and air-bronchogram bilaterally. The haemoglobin, total leucocyte counts and liver function tests were normal. The serology for HIV was negative. The renal function tests showed urea value of 78 mg/dL and creatinine value of 1.9 mg/dL. The urine analysis showed 20-25 red blood cells (RBCs), 2-4 pus cells, no RBC casts or crystals. Urine protein was 2+, with spot protein/creatinine ratio of 2.48, suggestive of moderate proteinuria. Ultrasonography of abdomen was normal. The contrast enhanced/ high resolution computed tomography of the thorax demonstrated ground glass opacities with interlobular septal thickening and small centrilobular nodules with patchy areas of consolidation in bilateral lungs (Figure 1b). The differentials on radiology were acute silico-proteinosis, acute alveolar proteinosis and diffuse alveolar haemorrhage (DAH). Fibreoptic bronchoscopy revealed normal tracheal and bronchial mucosa; the serial aliquots of broncho-alveolar lavage (BAL) fluid did not reveal increasing bloody aspirate or milky effluent. Examination of BAL fluid was negative for acid-fast bacilli (AFB) and the cartridge-based nucleic acid amplification test (CB-NAAT) was negative for tuberculosis (Xpert MTB/RIF). The BAL fluid revealed presence of haemosiderin-laden macrophages. The histopathology of trans-bronchial lung biopsy specimen demonstrated alveolar spaces filled with pigment laden macrophages and RBCs with surrounding fibrosis suggestive of diffuse alveolar haemorrhage (Figure 2a). Thus, renal failure in association with respiratory failure and DAH lead us to provisional diagnosis of pulmonary-renal syndrome. Serum anti-nuclear antibodies (ANA) was negative. The ELISA based peri nuclear-anti-neutrophil cytoplasmic antibody (pANCA) for myeloperoxidase (MPO-ANCA) value was positive 91.92 (normal <20), cytoplasmic-anti-neutrophil...
Cytoplasmic antibody (cANCA) directed against proteinase 3 (PR3-ANCA) was negative. The patient underwent renal biopsy and treatment with a combination of pulse glucocorticoids and i.v. cyclophosphamide as per EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis (AAV) [1]. The renal biopsy report demonstrated focal necrotising glomerulonephritis with crescents and fibrinoid tufts, absence of granulomas (Figure 2b).

The history of respiratory symptoms, laboratory urine analysis and positive MPO-ANCA antibody along with the renal biopsy report were consistent with the diagnosis of microscopic polyangiitis (MPA) in accordance with the 2012 Chapel Hill Consensus Conference definitions for ANCA-associated vasculitis diagnostic criteria [2]. The patient subsequently recovered from respiratory failure in next 3 days and from renal failure within 7 days of 1st dose of pulse cyclophosphamide and corticosteroids. The chest radiograph done after 2 weeks of therapy showed resolution of the alveolar opacities (Figure 3).

Discussion

Microscopic polyangiitis (MPA) in a person with silica exposure is an uncommon presentation, only eight of such cases have been documented in the literature [1-7] (Table 1). Of these, four had presentation as acute hypoxemic respiratory failure, with diffuse alveolar haemorrhage (DAH) in two such cases. The present case had 10 years exposure to silica, presenting with haemoptysis and acute hypoxaemic respiratory failure, positive serology for p-ANCA and diagnostic renal biopsy, leading to diagnosis of MPA.

Exposure to crystalline silica has been associated with the development of a spectrum of respiratory ailments, including silicosis, progressive pulmonary fibrosis, chronic obstructive pulmonary disease and lung cancer [8]. It has also been related to the development of several other autoimmune diseases, including rheumatoid arthritis (RA), systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). The overall significant summary effect estimate of silica “ever exposure” with development of MPA is OR 3.95, 95% CI 1.89-8.24 [8].

The pathogenesis of increased risk of AAV in subjects with silica exposure is intriguing. Silica is one of the strongest environmental substances causing overall autoimmunity by two different proposed pathways. Firstly, silica has been shown to cause cell death by necrosis and apoptosis [9]. Secondly, individuals exposed to crystalline silica may have silica particles trapped in their alveoli permanently [10]. Silica is known as a strong T cell adjuvant and there is activation of both responder and regulatory T-cells leading to autoimmune dysregulation [1]. It is also plausible that free-oxygen radicals produced from silica-stimulated-polymorphonuclear lymphocytes (PMN) could trigger a pathway leading to endothelial damage. The interaction with silica and the cell membrane induces the expression of myeloperoxidase on the cell membrane of PMN’s and monocytes; its subsequent release could induce an autoimmune reaction characterized by the development of ANCA [2]. Thus, dysregulated immune response triggered in genetically predisposed individuals could induce an uncontrolled systemic inflammatory response, leading to AAV.

Thus, patients with suspected or diagnosed silicosis in a tuberculosis endemic country, presenting with haemoptysis and acute hypoxemic respiratory failure, apart from tuberculosis an aetiology, AAV needs to be considered as a differential. The present case adds to the growing literature on the probable association between MPA and prolonged exposure to silica.
### Table 1. Microscopic polyangiitis with silica exposure: the case reports in literature.

| Age, sex, reference | Occupation and duration | Silicosis previously diagnosed | Symptoms | Pulmonary complication | Renal complication | Treatment | Clinical outcome |
|---------------------|-------------------------|-------------------------------|----------|------------------------|--------------------|-----------|------------------|
| 74 yrs, male [3]    | Shipyard worker, 43 yrs  | Yes                           | Dry cough, fever, fatigue pain, haematuria | Acute hypoxemic respiratory failure | Acute renal failure (RPGN) | Corticosteroids and cyclophosphamide | Remission |
| 56 yrs, male [4]    | Precious metal processing, 30 yrs | Yes                           | Dyspnoea | No                     | Acute renal failure (RPGN) | Corticosteroids and cyclophosphamide | Remission |
| 76 yrs, male [5]    | Not stated               | Yes                           | Dyspnoea | Pneumothorax           | No                  | Corticosteroids and cyclophosphamide | Remission |
| 45 yrs, male [6]    | Mines, 3 yrs             | No                            | Initially fever, chills and myalgia. Later dyspnoea and haemoptysis | Acute hypoxemic respiratory failure | Acute renal failure (RPGN) | Corticosteroids and cyclophosphamide | Remission, haemodialysis continued |
| 52 yrs, female [6]  | Not stated               | No                            | Fever, chills, dyspnoea and haemoptysis | Not stated failure (RPGN) | Acute renal failure (RPGN) | Corticosteroids, Cyclophosphamide and haemodialysis | Remission, haemodialysis continued |
| 34 yrs, male [7]    | Marble installer, 6 yrs  | No                            | Malaise, fever and haemoptysis | Acute hypoxemic respiratory failure and DAH | Acute renal failure (RPGN) | Corticosteroids, cyclophosphamide and plasmapheresis | Died |
| 68 yrs, male [11]   | Processing quartz-containing stones, 50 yrs | Yes                           | Fever | Pleural effusion | No | Corticosteroids, cyclophosphamide and plasmapheresis | Remission |
| 68 yrs, male [12]   | Sand-blasting, 10 yrs    | No                            | Dyspnoea, cough and haemoptysis | Acute hypoxemic respiratory failure and DAH | Acute renal failure (RPGN) | Corticosteroids and cyclophosphamide | Remission |
| 28 yrs, male, current case | Stone crusher for 10 years | No                            | Dyspnoea and haemoptysis | Acute hypoxemic respiratory failure and DAH | Acute renal failure (RPGN) | Corticosteroids and cyclophosphamide | Remission |

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