Pulmonary Interstitial Fibrosis as a Presenting Manifestation in Perinuclear Antineutrophilic Cytoplasmic Antibody Microscopic Polyangiitis*

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Microscopic polyangiitis (MPA) is one of the vasculitides that is included in the pulmonary renal syndromes. Pathologically, MPA has been defined as necrotizing vasculitis with few or no immune deposits, primarily affecting small vessels including arterioles, venules, or capillaries. Pulmonary interstitial fibrosis (PIF) as an accompanying manifestation in MPA has not been widely appreciated. In the present study, we report six cases of MPA at our institution with radiographic evidence of PIF that was apparent before any treatment was administered. All had biopsy evidence of renal disease that was consistent with MPA as well as positive serum perinuclear antineutrophilic cytoplasmic antibody titers. Hemoptysis was observed in approximately one half of the patients. As determined by CT of the chest, PIF was detected in all of the patients and was often present years before a diagnosis of MPA was made. We conclude that PIF may occur as a pulmonary manifestation of MPA. Further appreciation of this finding may lead to more data with respect to the incidence of PIF in MPA, and to a better understanding of the mechanisms that are involved in the development of this finding.

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Key words: microscopic polyangiitis; perinuclear antineutrophilic cytoplasmic antibodies; pulmonary interstitial fibrosis

Abbreviations: ANA = antinuclear antibodies; ANCA = antineutrophilic cytoplasmic antibodies; DLco = diffusing capacity of the lung for carbon monoxide; MPA = microscopic polyangiitis; p-ANCA = perinuclear antineutrophilic cytoplasmic antibodies; PIF = pulmonary interstitial fibrosis

Microscopic polyangiitis (MPA) is one of the vasculitides that is included in the pulmonary renal syndromes. MPA is rare disease, with an estimated prevalence of three cases per million. The etiology of this condition is unknown. The patient typically presents with renal failure due to glomerulonephritis and alveolar hemorrhage secondary to pulmonary capillaritis. Pathologically, MPA has been defined as necrotizing vasculitis with few or no immune deposits, primarily affecting small vessels including arterioles, venules, or capillaries. The three key histopathologic features are a segmental distribution of vascular injury, infiltration with neutrophils, and fibrinoid necrosis. Circulating antineutrophilic cytoplasmic antibodies (ANCA) are present in 74.5% of patients with MPA. Patients may have perinuclear ANCA (p-ANCA) with specificity for myeloperoxidase or, more rarely, cytoplasmic ANCA with specificity to proteinase-3.

Depending on the extent and nature of renal, pulmonary, and systemic vascular involvement, clinical findings can be quite variable. Renal findings reflect a pauci-immune necrotizing glomerulonephritis. Cutaneous findings may include purpura and splinter hemorrhages; musculoskeletal symptoms may encompass myalgias, arthralgias, and arthritis; GI symptoms may include abdominal pain and bleeding; and neurologic findings may reflect a peripheral neuropathy. In terms of pulmonary findings, the predominant symptom is hemoptysis that reflects the alveolar hemorrhage caused by capillaritis. Cough, chest pain, and shortness of breath may also be present. Chest radiographic features consist of patchy, bilateral airspace opacities caused by alveolar hemorrhage.

Pulmonary interstitial fibrosis (PIF) as an accompanying manifestation in MPA has not been commonly appreciated. In the present study, we report on six cases of MPA at our institution with radiographic evidence of PIF that was apparent before any treatment was administered. We believe this to be the largest published series of this phenomenon.

CASE REPORTS

The cases reported were encountered by the Respiratory Service at St. Boniface General Hospital over an approximate 3-year period. St. Boniface General Hospital is one of the university-affiliated hospitals that provides tertiary care for renal patients in the Province of Manitoba.

Case 1

A 67-year-old woman with a history of idiopathic pulmonary fibrosis (usual interstitial pneumonitis) of 4 years in duration presented because of acute renal failure. Although there was no prior lung biopsy, her history and present thoracic radiographic findings were consistent with a diagnosis of idiopathic pulmonary fibrosis. Over this 4-year interval, the patient described shortness of breath on exertion that was progressive, but there was no history of hemoptysis. On hospital admission, physical examination was remarkable only for bibasilar crackles. There was no evidence of congestive heart failure, cor pulmonale, or clubbing. Findings on plain chest radiography revealed diffuse pulmonary fibrosis with pronounced bibasilar fibrosis located predominantly at the lung periphery. CT of the chest revealed extensive honeycombing in a peripheral distribution (Fig 1). There was marked traction bronchiectasis as well as evidence of dilation of the pulmonary arteries consistent with pulmonary hypertension. Pulmonary function tests revealed a restrictive defect with an FEV1 of 1.05 L (57% of predicted), a FVC of 1.9 L (46% of predicted), and an FEV1/FVC of 88%. Diffusing capacity of the lung for carbon monoxide (DLco) was severely reduced at 28% of predicted. Total lung capacity could not be obtained because of the patient’s inability to cooperate with the procedure.

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Examination of the urine showed an active sediment with 50 to 100 RBCs per high-power field with some dysmorphia. The serum creatinine level on hospital admission was 2.19 mg/dL (192 mmol/L), and creatinine clearance corrected for weight was 12 mL/min. p-ANCA (antimyeloperoxidase) was positive at a titer of 1:16,384. There were no antiglomerular basement membrane antibodies in the serum. Antinuclear antibodies (ANA) as well as extractable nuclear antigen antibodies were negative, and complement levels were within normal limits. Renal biopsy revealed a total of 26 glomeruli. Six glomeruli were obsolescent, while 10 had evidence of epithelial crescents. The remaining glomeruli showed focal segmental necrosis of the tufts with an occasional afferent arteriole showing necrotizing vasculitis. Immunofluorescence revealed granular fluorescence of fibrin along the basement membrane in relation to the necrotic areas with C3 staining along the capillary walls and mesangium. Other Igs and complement were not present. These results were thought to be in keeping with MPA.

Because of her glomerulonephritis, the patient was started on IV cyclophosphamide, 750 mg IV monthly, and prednisone, 50 mg/d orally. She was discharged from the hospital but was readmitted 1 month later with hypoxemic respiratory failure. It was thought that this was due to an accelerated form of pulmonary fibrosis, since bronchoscopy and BAL findings were negative for pathogens. She died because of respiratory failure after a protracted course of mechanical ventilation.

Case 2

A 63-year-old white man presented initially with microscopic hematuria, renal insufficiency (creatinine level, 6.47 mg/dL [572 mmol/L]), and hemoptysis in 1997 at another institution. Serum test results for ANA, extractable nuclear antigens, and antiglomerular basement membrane antibodies were negative. A renal biopsy demonstrated crescentic glomerulonephritis with mild interstitial inflammation. On admission to St. Boniface Hospital, a CT scan of the chest revealed bibasilar fibrosis with a peripheral distribution (Fig 2). Further investigation revealed a p-ANCA titer (confirmed to be an antimyeloperoxidase antibody) of 1:512. Immunologic staining revealed a moderate amount of C3 in the peripheral capillary loop with some in the arterioles. A repeat of the serologic investigations revealed a p-ANCA titer of 1:512. The dosage of prednisone was increased to 30 mg/d, and the patient was administered oral cyclophosphamide, 250 mg/d, after which his disease stabilized. In 1998, he was again seen because of dyspnea on exertion. Physical examination was remarkable for bibasilar inspiratory crackles but no clubbing. A repeat high-resolution CT scan of the chest revealed again bilateral, lower-zone peripheral fibrotic changes, as well as a thrombus in the right lower lobe pulmonary artery. Pulmonary function test results were essentially unchanged since 1997. Therapy was begun with IV heparin and oral anticoagulation with warfarin. He has remained clinically well at the time of this writing.

Case 3

A 68-year-old woman with hypertension and longstanding type II diabetes presented in 1991 with severe dyspnea. She was found to be in advanced renal failure with gross volume overload. Renal biopsy showed glomeruli to be obsolescent with extensive vascular and interstitial damage. Immunofluorescence demonstrated IgM and complement positivity in some glomeruli. Although a definitive diagnosis of the cause of her renal failure could not be
made, it was thought to be most in keeping with focal glomerular sclerosis. After volume removal with hemodialysis, plain chest radiographs revealed bilateral, lower-lobe honeycombing. Later in 1991, she had an episode of hemoptysis. In the workup it was found that antihemase membrane antibodies were negative as were ANA and extractable nuclear antigens. Complement levels were normal. p-ANCA titer was positive at 1:1024. Bronchoscopy revealed bleeding from all segments, which became progressively bloodier as the BAL proceeded. Approximately 1 year later, she again had an episode of severe hypoxemia and hemoptysis. Her hemoglobin decreased from approximately 90 to 56 g/L, and a plain chest radiograph revealed new bilateral airspace disease consistent with both alveolar hemorrhage and fluid overload. Her symptoms improved with aggressive volume removal, although she was not treated with immunosuppressive agents. A CT scan of the chest showed resolution of the airspace disease, but revealed mild, bilateral, peripheral lower-lobe honeycombing.

Over the next 6 years, progressive pulmonary fibrosis developed. In 1998, a p-ANCA (antimyeloperoxidase titer) was demonstrated at 1:512. Simple spirometry performed in 1998 revealed an FEV1 of 0.88 L (41% predicted) and an FVC of 0.9 L. Pulmonary function testing in 1999 revealed an FEV1 of 0.76 L (31% predicted) and an FVC of 0.97 L in keeping with a restrictive ventilatory pattern. Complement levels were normal. p-ANCA titer was positive at 1:1024. Bronchoscopy and BAL revealed bleeding from all segments, which became progressively bloodier as the BAL proceeded. Approximately 1 year later, she again had an episode of severe hypoxemia and hemoptysis. Her hemoglobin decreased from approximately 80 to 56 g/L, and a plain chest radiograph revealed new bilateral airspace disease consistent with both alveolar hemorrhage and fluid overload. Her symptoms improved with aggressive volume removal, although she was not treated with immunosuppressive agents. A CT scan of the chest showed resolution of the airspace disease, but revealed mild, bilateral, peripheral lower-lobe honeycombing.

Case 4

A 64-year-old white man with a previous diagnosis of usual interstitial pneumonitis of approximately 3 to 4 years in duration was admitted to St. Boniface Hospital because of newly diagnosed renal failure. Although there was no prior lung biopsy, the patient’s chest radiographs confirmed the presence of extensive bilateral honeycombing. His serum creatinine level was 4.5 mg/dL (399 μmol/L), and urine sediment was active with > 20 RBCs per high-power field. Further investigations revealed no evidence of antiglomerular basement membrane antibodies in the serum, as well as negative test results for ANA and extractable nuclear antigens. Serologic investigations revealed a p-ANCA titer of 1:128 that was confirmed to be an antimyeloperoxidase antibody. Renal biopsy revealed a nonimmune crescentic necrotizing glomerulonephritis with an artery showing fibrinoid necrosis. There were no normal pulmonary function test results available from our laboratory, but desaturation was documented to decrease from 96 to 80% on a 6-min walk while breathing room air. Since the kidney biopsy was thought to be in keeping with a diagnosis of MPA, treatment was commenced with prednisone and cyclophosphamide. The patient was readmitted to St. Boniface Hospital 5 months later with hypoxemic respiratory failure that required mechanical ventilation. A repeat CT scan of the chest showed progression of honeycombing and ground-glass opacities. No infectious etiology was obtained by BAL. Slow recovery was made by administration of supportive care, empiric broad-spectrum antibiotics, and high-dose steroids. He recovered enough to be discharged home with pulmonary rehabilitation as an outpatient. Unfortunately, he was again admitted to the hospital with acute respiratory failure a few months later. Chest radiographs demonstrated dramatic progression of his pulmonary fibrosis. The patient did not desire further workup of his respiratory decompensation and died of progressive respiratory failure.

Case 6

A 78-year-old woman with a history of ischemic heart disease, chronic atrial fibrillation, and remote radiotherapy to the right parotid gland for a tumor presented because of a 10-month history of cough and a 12-kg weight loss. Progressive generalized weakness, dyspnea, and night sweats developed that were unresponsive to several courses of antibiotics. On examination, she was cachectic, the lungs revealed bilateral crackles, and she displayed no clubbing. There was no cutaneous evidence of a vasculitis or stigmata of collagen vascular disease observed. A chest radiograph demonstrated extensive honeycombing and some traction bronchiectasis. In addition, there was an ill-defined infiltrate observed in the right upper lobe. Spirometry revealed an FEV1 of 0.89 L and an FVC of 1.1 L. The initial workup included bronchoscopy that revealed purulent secretions coming from the right upper and left lower lobes. BAL of the right upper lobe revealed acid-fast bacilli that later grew Mycobacterium avium-intracellulare, for which the patient was started on clarithromycin, ethambutol, and pyrazinamide. Neither virus nor P carinii were detected in the BAL fluid. Because of progressive hypoxemic respiratory failure that was unresponsive to the antibiotics, an open-lung biopsy was performed in which samples were obtained from the upper lobes. The biopsy revealed alveolar hemorrhage and a nonspecific interstitial pneumonitis composed of lymphocytes and polynuclear cells. There was no evidence of an active vasculitis. Since all microbiological stains on the lung specimen were negative, and with fever, weight loss, epigastric discomfort, exertional dyspnea, and a new onset of a normocytic, normochromic anemia in which hemoglobin fell from 152 to 109 g/L over several weeks. There was no history of hemoptysis. At presentation, physical examination was remarkable only for the presence of bilateral inspiratory crackles. Clubbing was not present. Erythrocyte sedimentation rate was elevated at 109 mm/min. There was mild renal impairment with a serum creatinine level of 2.04 mg/dL (180 μmol/L) with associated hematuria in which > 100 RBCs per high-power field were found, of which many were dysmorphic. CT scan of the thorax revealed bilateral honeycombing with traction bronchiectasis with lesser but similar changes in the upper lobes. Pulmonary function testing demonstrated a mild restrictive ventilatory pattern with a mildly reduced DLCO. Vital capacity was 2.7 L (74% predicted), while FEV1 was 2.2 L (93% of predicted).

Serum tests for ANA and extractable nuclear antigens were negative. Complement levels were within normal limits. A renal biopsy was performed that showed an artery with fibrinoid necrosis. Immunofluorescence studies on the renal biopsy showed no immune deposits. Serum p-ANCA titer was positive at 1:126 and was confirmed to be antineutrophil cytoplasmic positive. A diagnosis of MPA was suspected, and the patient was begun on therapy with corticosteroids and monthly IV injections of cyclophosphamide.

The patient was re-admitted to St. Boniface Hospital 5 months later with hypoxemic respiratory failure that required mechanical ventilation. A repeat CT scan of the chest showed progression of honeycombing and ground-glass opacities. No infectious etiology was obtained by BAL. Slow recovery was made by administration of supportive care, empiric broad-spectrum antibiotics, and high-dose steroids. He recovered enough to be discharged home with pulmonary rehabilitation as an outpatient. Unfortunately, he was again admitted to the hospital with acute respiratory failure a few months later. Chest radiographs demonstrated dramatic progression of his pulmonary fibrosis. The patient did not desire further workup of his respiratory decompensation and died of progressive respiratory failure.

Case 5

A 79-year-old man with a mechanical aortic valve prosthesis placed 20 years previously presented to St. Boniface Hospital with fever, weight loss, epigastric discomfort, exertional dyspnea, and a new onset of a normocytic, normochromic anemia in which hemoglobin fell from 152 to 109 g/L over several weeks. There was no history of hemoptysis. At presentation, physical examination was remarkable only for the presence of bilateral inspiratory crackles. Clubbing was not present. Erythrocyte sedimentation rate was elevated at 109 mm/min. There was mild renal impairment with a serum creatinine level of 2.04 mg/dL (180 μmol/L) with associated hematuria in which > 100 RBCs per high-power field were found, of which many were dysmorphic. CT scan of the thorax revealed bilateral honeycombing with traction bronchiectasis with lesser but similar changes in the upper lobes. Pulmonary function testing demonstrated a mild restrictive ventilatory pattern with a mildly reduced DLCO. Vital capacity was 2.7 L (74% predicted), while FEV1 was 2.2 L (93% of predicted).

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granulomas were not observed, it was concluded that *M avium-intracellulare* was only a contaminant and therapy for this organism was discontinued.

A renal biopsy was performed. The results showed chronic crescentic glomerulonephritis that was consistent with a diagnosis of MPA. No immunofluorescent staining was observed on the biopsy. Since the clinical picture included renal failure due to a rapidly progressive glomerulonephritis, alveolar hemorrhage, honeycombing, and a positive serum p-ANCA, a diagnosis of MPA was made. The patient was begun on immunosuppression with methylprednisolone, 1 g/d IV for 3 days, and IV cyclophosphamide. Oral steroids were then continued after the IV boluses. However, the patient became progressively weaker over the hospital course, did not tolerate renal dialysis, and died after a prolonged hospitalization.

**Discussion**

The classification of pulmonary vasculitides into specific categories is often difficult because of the lack of precise criteria. Because of this difficulty, consensus guidelines have been developed in order to gather data and to develop treatment strategies. At the Chapel Hill Consensus Conference, MPA was defined as necrotizing vasculitis of small vessels (ie, capillaries, venules, or arterioles), with few or no immune deposits, while a necrotizing arteritis that involves medium-sized arteries may also be observed. In MPA, necrotizing glomerulonephritis is a very common clinical presentation, while pulmonary capillaritis, involving alveolar hemorrhage occurs frequently. MPA is generally associated with ANCA. Patients may have p-ANCA with antineutrophilic cytoplasmic specificity or, more rarely, c-ANCA with antiproteinase-3 specificity. Cutaneous, musculoskeletal, GI, neurologic, and ear, nose, and throat organ system involvement may also be found, but occur less frequently than renal involvement, the latter of which is reported in 90% of cases.

Based on consensus guidelines, we believe that all the patients described in this series would fit into the category of MPA. All patients had renal disease consistent with MPA, and all had serum evidence of p-ANCA positivity. There was no evidence of immunofluorescence on renal biopsy to suggest Henoch-Schönlein purpura, collagen vascular disease, or Goodpasture syndrome, and no evidence of granulomatous vasculitis to suggest Wegener granulomatosis or Churg-Strauss syndrome. In approximately one half of the patients in the present series, hemoptysis developed over the course of their disease, consistent with the finding of pulmonary capillaritis, a common manifestation of this disease. Finally, all patients had the constitutional symptoms of fatigue and weight loss that would also go along with MPA.

We believe that the above-mentioned cases greatly strengthen the association between PIF and the presence of p-ANCA in the serum. Although previous reports have described this association, to the best of our knowledge this is the largest series that reports PIF as an initial manifestation of MPA. Furthermore, our series underscores the fact that PIF may predate the onset of vasculitis by some years, and that it is associated with a relatively poor prognosis. We recognize however that in our study, the diagnosis of PIF was made clinically and not by lung biopsy. Nevertheless, a diagnosis of interstitial fibrosis by CT scan is an accepted manner by which this diagnosis can be made. Thus, the findings of peripheral honeycombing and traction bronchiectasis that are discerned by a radiologist correlate well with lung biopsy specimens. Other entities, such as nonspecific interstitial pneumonitis and acute interstitial pneumonitis would not be expected to show honeycombing on CT scan at an early stage. Moreover, all patients were screened for other factors that could cause interstitial fibrosis, such as occupational risks, drugs, collagen vascular diseases, hypersensitivity exposures, and family history. Although the entities of idiopathic interstitial fibrosis and MPA could have occurred concomitantly by chance, each in itself is a rare disease. The possibility of both entities occurring in the same patient seems remote.

In this series, PIF could also not be explained by previous exposure to immunosuppressive agents. Agents such as cyclophosphamide could result in interstitial lung disease, and none of patients was treated with this immunosuppressive agent prior to diagnosis. Another possibility to consider in these patients is that repeated episodes of hemoptysis, either symptomatic or occult, may have also occurred over a period of time resulting in interstitial pneumonitis, in turn leading to honeycombing and traction bronchiectasis. In one patient (case 6), lung biopsy was performed over the course of the disease. The results showed that in the upper lobe, within the area of alveolar hemorrhage, a nonspecific interstitial pneumonitis was found without the presence of fibrosis or honeycombing, while in the lower lobes, honeycombing was seen on the chest radiograph. Thus, it is conceivable that repeated episodes of alveolar hemorrhage could be the forerunner of interstitial fibrosis in MPA. More information would be required to make this assessment.

Many of the patients observed in our series acquired severe hypoxic respiratory failure over the course of their disease that was not associated with alveolar hemorrhage and that often led to death. CT of the chest often revealed new ground-glass opacities, a progression of the honeycombing, and an increase in traction bronchiectasis. BAL was often negative for bacterial and viral pathogens as well as for *P carinii* pneumonia. A fulminating form of idiopathic interstitial pneumonia has been described in which findings of acute interstitial pneumonitis may develop in a patient with already established idiopathic pulmonary fibrosis. On biopsy, the histologic findings reveal evidence of diffuse alveolar damage in addition to evidence of idiopathic pulmonary fibrosis. In many of the patients in this series, we believe that this was the cause of the worsening hypoxemia that often led to the patient’s death.

In summary, we report an underappreciated aspect of MPA, in that PIF may be an early manifestation of this disease. The presence of pulmonary fibrosis many antedate the clinical suspicion of vasculitis by several years and appears to be associated with a poor prognosis. Further appreciation of this finding may lead to more data with respect to the incidence of pulmonary fibrosis in MPA, and to a better understanding of the mechanisms that are involved in the development of this finding. Whether or not obtaining an ANCA profile on all patients presenting with PIF is a worthwhile endeavor requires further investigation.
Granulomatous Pneumonitis Following Exposure to the World Trade Center Collapse*

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We describe a 37-year-old male engineer who presented with cough and dyspnea 3 weeks after exposure to dust resulting from the collapse of the World Trade Center (WTC). Radiographs of the chest and high-resolution CT demonstrated diffuse pulmonary nodularity. Lung biopsy specimens confirmed the presence of diffuse, noncaseating granulomatous nodules. Scanning electron microscopy and energy-dispersive radiograph analysis revealed large quantities of silicates. Cellular immunologic studies showed normal response to beryllium, and results of Kveim testing were negative.

We suspect that exposure to one or more materials resulting from the WTC catastrophe may be implicated in the development of granulomatous pulmonary disease. (CHEST 2003; 123:301–304)

Key words: dust inhalation; granulomatous pneumonitis; World Trade Center

Abbreviations: OSHA = Occupational Safety and Health Administration; WTC = World Trade Center

On September 11, 2001, the two towers of the World Trade Center (WTC) collapsed and sent > 1 million tons of steel, glass, cement, and other debris to earth in clouds of smoke. The result of an intentional attack by suicide hijackers who crashed two commercial jetliners with almost 100,000 L of jet fuel into the towers, the resulting explosions set fires at > 952.2°C, burning a vast number of materials, such as concrete, asbestos, plastic, computers, furniture, and carpeting, which created a cloud of dust and smoke that continued to smolder for weeks.

We describe a patient who presented with mild, nonspecific respiratory complaints with radiographic and light microscopic findings initially suggestive of sarcoidosis. Lung biopsy specimens submitted to scanning electron microscopy and energy-dispersive radiograph analysis revealed large quantities of silicates and the presence of multiple, well-defined pulmonary granuloma. Cellular immunologic studies showed a normal response to beryllium, and results of Kveim testing were negative.

Granulomatous disease of the lung may occur in response to a variety of infectious agents and to the inhalation of both organic and inorganic substances.1 When a specific agent cannot be identified, sarcoidosis may be suspected, often on clinical, radiographic, and immunologic grounds. In most instances, a search for a causative agent that results in the granulomatous tissue reaction is unrewarding. We suspect that exposure to one or more materials resulting from the WTC catastrophe may be implicated in the development of granulomatous pulmonary disease.

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