CASE REPORT

Pulmonary consolidation with fever is not always pneumonia: A case of microscopic polyangiitis and review of the literature

Katerina M. Antonioua, Foteini Economidoua, Argiro Voloudaki b, Charalambos Protopapadakis a, Ioanna Mitrouska a, Nikolaos M. Siafakasa, *

aDepartment of Thoracic Medicine, Interstitial Lung Disease Unit, Medical School, University of Crete, Heraklion, Crete 71110, Greece
bDepartment of Radiology, Medical School, University of Crete, Heraklion, Greece

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Summary
Microscopic polyangiitis is a non-granulomatous, systematic and small-vessel vasculitis in which necrotizing glomerulonephritis is very common and pulmonary capillaritis often occurs. We report a patient with fever, fatigue and dry cough who initially had been diagnosed as having pneumonia. A thoracic CT was performed showing widespread multiple nodular lesions, some with a central air-bronchogram and thickened bronchovascular bundles and some connected to nodules. No cavitation or ground glass opacities were observed. Fibreoptic bronchoscopy was normal and the cultures from the BAL were negative. Additionally, during his stay in the hospital his hematocrit was gradually falling, while the erythrocyte sedimentation rate increased. Urinanalysis revealed proteinuria and active urinary sediment. p-ANCA was positive and renal biopsy revealed focal pauci-immune necrotic glomerulonephritis. Pulmonary–renal syndrome was suspected and renal biopsy was performed. The diagnosis of microscopic polyangiitis was established and the patient began treatment with pulse intravenous methylprednisolone and cyclophosphamide. After induction of remission, the patient received maintenance therapy. Finally, an extensive review of the literature on microscopic polyangiitis is presented.

Introduction
Microscopic polyangiitis (MPA) is defined as systemic necrotizing vasculitis with few or no immune deposits, affecting small vessels (capillaries, arterioles or venules) in
which necrotizing glomerulonephritis is very common and pulmonary capillaritis often occurs. Although MPA can involve any organ, renal and pulmonary involvement predominate.\textsuperscript{1–4} Pulmonary involvement can present from fleeting focal infiltrates to massive lung hemorrhage and hemorrhage secondary to alveolar capillaritis.\textsuperscript{5}

Case history

This is a case of a 39-year-old male who was admitted to hospital due to fever of unknown origin. He was an ex-smoker (stopped 3 years ago) and his medical history is unremarkable. Ten days back he was examined by his doctor due to fever, fatigue and dry cough. He was diagnosed as having pneumonia. He received cefuroxime axetil 500 mg bid for 7 days plus azithromycin once daily for 3 days with no resolution of his symptomatology and he was referred to the hospital. On examination, the patient was in no apparent distress. He had normal breath sounds with normal blood gases and his temperature was 38°C. His laboratory studies revealed white cell count: 13,900 (N:79, L:11.5, M:8.5, E:0.6) hemoglobin 13.7 g/dl. The erythrocyte sedimentation rate was elevated (72 mm/h). Renal, liver function and urinalysis were normal. An arterial blood gas measurement while the patient was breathing room air demonstrated a \(P_{aO_2}\) of 88 mmHg, a \(P_{aCO_2}\) 41 mmHg and \(pH = 7.39\). Chest radiograph revealed a consolidation in the right upper lobe (Figure 1).

The patient was admitted in our department and began treatment with moxifloxacin 400 mg once daily. Samples such as sputum and blood cultures, were obtained and serology tests were conducted to rule out bacterial or viral infection. A new radiograph showed an increase of the consolidation (Figure 2). Due to nonresolving of the shadowing on the X-ray, the treatment was switched to ticarcillin/clavulanate potassium (5.2 mg three times daily) plus teicoplanine (400 mg once daily).

Chest spiral computed tomography showed a few enlarged lymph nodes in the paratracheal and carinal regions, up to 1.5 cm in the short axis. Apart from the consolidation in the right upper lobe, CT revealed multiple nodular lesions, some with a central air-bronchogram, scattered in all lobes, more prevalent in the upper and middle lung fields. Thickened bronchovascular bundles were seen, some connected to nodules (Figures 3A, 4A, 5A). No cavitation or ground glass opacities were observed. Taking into account the febrile patient and nonresolving “pneumonia”, the differential diagnosis was broadened widespread infections, tuberculosis, whereas thickened bronchovascular bundles connected with nodules and lymphadenopathy indicated Wegener granulomatosis and lymphoma.

Fibreoptic bronchoscopy was normal and the cultures from the BAL were negative. In addition, his hematocrit was gradually falling (from 41% to 32%) while the erythrocyte sedimentation rate was increasing (from 72 to 90 mm/h). A new urine analysis revealed proteinuria and active urinary sediment. Pulmonary–renal syndrome was suspected and tests for the detection of anti-GBM and antineutrophil cytoplasmic antibody (ANCA) antibodies were performed. Renal biopsy and a new sequential high-resolution computed tomography of the thorax were performed.

HRCT showed extensive patchy areas of ground-glass attenuation near the pre-existing lesions as well as in previously normal areas, throughout both lungs. Resolution of some nodules was observed. A halo of ground-glass surrounding nodules was also seen, a CT sign known as the halo sign, strongly indicative of hemorrhagic infiltration (Figures 3B, 4B, 5B). The rapidity of nodules resolution coupled with the appearance of ground-glass and halo-sign, and in the absence of cavitary lesions that would include Wegener’s granulomatosis, indicated intrapulmonary hemorrhage and capillaritis compatible with MPA, in the proper clinical settings.

Figure 1

Chest radiograph on admission shows a consolidation in the right upper lobe.

Figure 2

Repeat chest radiograph a few days later shows worsening of consolidation.
p-ANCA were positive and renal biopsy revealed focal pauci-immune necrotic glomerulonephritis. Thus, the diagnosis of MPA was established and the patient began the treatment with pulse intravenous 1000 mg methylprednisolone for 3 days, followed by pulse intravenous cyclophosphamide 0.75 mg/m². The dose of the steroids was gradually tapered to 10 mg/day of prednisolone and the patient had in total received six cycles of intravenous cyclophosphamide. Remission was achieved and during his last reevaluation, p-ANCA were negative and HRCT of the thorax had no signs of activity.

After induction of remission, the patient received maintenance therapy with 10 mg/day plus azathioprine 150 mg/day (Table 2).

Discussion

The primary systemic vasculitides are heterogeneous, multi-system disorders characterized by inflammation and necrosis of small and medium blood vessels. These disorders are also known as the ANCA-associated vasculitides and include Wegener’s granulomatosis (WG), Churg-Strauss syndrome (CSS) and microscopic pulmonary angiitis (MPA). In these conditions, lung involvement predominates in 50–95% of affected patients. Their etiology is unknown.

Serum ANCA are involved in the pathogenesis of these conditions and has been recognized as a useful marker for diagnosing small vessels vasculitis.1,6,7 ANCA include three categories of antibodies based on their pattern of indirect immunofluorescence on ethanol-fixed neutrophils: a diffuse cytoplasmic granular pattern, a perinuclear pattern, and an atypical pattern.8 Two staining patterns are known, perinuclear (p-ANCA) and cytoplasmic (c-ANCA). The major target antigen of p-ANCA associated with vasculitis is myeloperoxidase (MPO), while that of c-ANCA is proteinase 3 (PR3). MPO-ANCA is related to MPA, where it has been reported in 15–45% of the patients9–11 and PR3-ANCA is the marker antibody in WG.

The most common presenting clinical symptoms of MPA are fever, weight loss, malaise, followed by myalgias and arthralgias. Many patients describe a “flu-like” syndrome early in the course of their disease. Other involvement include hemoptysis, hematuria, proteinuria, abdominal
pain, gastrointestinal bleeding secondary to mucosal vasculitis, peripheral neuropathy, arthritis, myositis and sinusitis.1,11,12

MPA can cause a variety of pulmonary abnormalities. Diffuse alveolar hemorrhage (DAH) with or without pulmonary capillaritis is the main pulmonary manifestation.9,13,14 A small-vessel vasculitis causing DAH is reported in 10–30% of patients with MPA.9 Pulmonary interstitial fibrosis can also be an initial manifestation of MPA and seems to be associated with a poorer prognosis.15 Other pulmonary presentations of MPA are nonspecific interstitial pneumonia, pulmonary aneurysm and alveolar hemorrhage, pleural effusion, pulmonary edema and diffuse panbronchiolitis.16–18

Chest radiographic abnormalities consist of patchy, bilateral airspace opacities ranging in intensity from vague ground-glass opacity to extensive intense consolidation caused by hemorrhagic filling of the airspaces. The most commonly referred CT findings are ground-glass attenuation followed by consolidation, thickening of bronchovascular bundles, interlobular septal thickening and nodules ranging from centrilobular micronodules sized a few mm to over 1 cm. Rarer manifestations are honeycombing and bronchiectasis.13–15,19–21

CT–pathologic correlation20 has shown that the extent of ground-glass attenuation corresponds to that of alveolar hemorrhage, interstitial chronic inflammation in the alveolar septa and vasculitis in the small-sized arteries, the consolidation corresponds mostly to diffuse alveolar hemorrhage and the thickening of bronchovascular bundles corresponds to the infiltration of lymphocytes and mild fibrosis along the bronchovascular bundles.

The zonal predominance is not characteristic and a random distribution is almost equal to an upper or lower zones predominance.13,14,20 Although spiral and high-resolution CT have a higher sensitivity than chest radiography for demonstrating the extent and nature of parenchymal lesions, often the CT features are not specific, as was the case in the onset CT of our patient. However, during the evolution of the disease, new CT findings evolved, strongly suggestive of intraparenchymal hemorrhage and possible capillaritis. The rapidity of clearing of small nodules, consolidations representing absorption of intra-alveolar blood and the appearance of ground-glass attenuation areas often surrounding nodules creating the known halo sign are all features of pulmonary hemorrhage.13,19,20 Nevertheless, a high confident level diagnosis can be reached only in the proper clinical context.

Routine laboratory tests are not specific. Urinanalysis reveals dysmorphic red cells of glomerular origin, red-cell casts and other cellular and granular casts. Proteinuria is always present, but rarely in the range of nephritic syndrome.22

In contrast to WG, most ANCA-positive MPA patients have MPO-ANCA, with a minority having PR3-ANCA. We must underline the fact that according to the International Consensus Statement on Testing and Reporting of antineutrophil cytoplasmic antibodies, combining indirect immunofluorescence assays and enzyme immunoassays (ELISAs) is more accurate than either assay alone.23 Not everybody with PR3-c-ANCA or MPO-p-ANCA has active vasculitis. Alternatively, not every ANCA vasculitis patient relapses when the ANCAs recur or persist. This suggests that, pathogenetically, a sufficient number of ANCAs need to persist long enough, before an exposure of the patient to cofactors that, via subsequent neutrophil and monocyte priming, leads to interaction between ANCAs and their target antigen on the effector cell surface. This interaction, in turn, triggers the cascade, leading to endothelial cell damage.

Bronchoscopy should be performed to rule out infection and to evaluate the presence of the DAH. Bronchoalveolar lavage fluid in MPA patients with alveolar hemorrhage is

Figure 5 (A) Initial spiral CT at the level of basal segments of the lower lobes shows a rather smooth nodule in the right lower lobe. (B) Follow-up HRCT shows a halo of ground-glass surrounding the nodule and neighboring peripheral bronchovascular bundle thickening (arrow).
 typically grossly hemorrhagic and contains numerous erythrocytes and hemosiderin-laden macrophages.24

The gold standard for the diagnosis of ANCA-associated vasculitides is now well defined, but must be adjusted for each patient according to the type of vasculitis, its precise form (e.g., limited versus systemic Wegener's granulomatosis) and severity, and patients' characteristics such as age and renal function. The therapeutic decision must also take into account the risk of adverse events inherent to each treatment. Immunosuppression is the cornerstone of treatment in MPA.

The induction therapy in generalized MPA-severe form (multi-organ involvement, a renal–pulmonary type and rapidly progressive glomerulonephritis (RPGN)) consists of oral prednisolone (0.6–1 mg/kg/day) plus oral cyclophosphamide (0.5–2 mg/kg/day). Intravenous methylprednisolone (0.5–1.0 g/day for 3 days) can be considered. As the life threatening features subside, the dose can then be reduced to 1 mg/kg prednisolone (or equivalent) daily for the first month, tapered over the next 3–4 months. Instead of oral administration, intravenous cyclophosphamide (0.5–0.75 g/m², monthly) can also be considered.23,27 For the RPGN type, anti-coagulation therapy (heparin at 10,000 units/day or low-molecular heparin at 5000 units/day) and anti-platelet therapy (dipyridamole at 300 mg/day) are also employed.28–30 In patients with impaired renal function (serum creatinine level >1.8 mg/dl) or those more than 60 years old, the dose of cyclophosphamide should be reduced to 75–50%. Severe disease defined by major renal impairment (serum creatinine >5.7 mg/dl) was recently suggested to be treated with corticosteroids and cyclophosphamide coupled with plasma exchange at least for the first week to increase the likelihood for renal function restoration.31,32 There are reports suggesting that extracorporeal membrane oxygenation and activated human factor VII may be beneficial in some critically ill patients with DAH33–35 (Table 2).

With this treatment remission is evaluated by approximately 85% and in general can be achieved within 6 months.36,37 Patients who have attained remission receive maintenance therapy for additional 1 year.38 The maintenance therapy includes prednisolone (5–10 mg/day) and in most cases oral cyclophosphamide or azathioprine (25–75 mg/day). Relapse will occur in 11–57% of patients in remission. Female, black race, severe kidney disease, upper airway disease and anti-PR3 serum antibodies are shown to be risk factors for resistance to initial treatment.38

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<th>Table 1</th>
<th>Diagnostic criteria for microscopic polyangiitis.</th>
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<td>1. Symptoms</td>
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<td>(1) Rapidly progressive glomerulonephritis</td>
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<td>(2) Pulmonary hemorrhage</td>
<td></td>
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<td>(3) Other organ symptoms:</td>
<td></td>
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<td>Purpura, subcutaneous hemorrhage, gastrointestinal bleeding and mononeuritis multiplex</td>
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<td>2. Histological findings</td>
<td></td>
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<tr>
<td>(1) Necrotizing vasculitis of arterioles, capillaries, and venules, and perivascular infiltration of inflammatory cells</td>
<td></td>
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<td>3. Laboratory findings</td>
<td></td>
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<tr>
<td>(1) Positive MPO-ANCA</td>
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<td>(2) Positive CRP</td>
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<td>(3) Proteinuria, hematuria, elevation of BUN and serum creatinine</td>
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**Diagnosis**

1. **Definite MPA**
   - (1) Positive for two or more of the symptoms, and positive histological findings
   - (2) Positive for two or more of the symptoms including the symptoms (1) and (2), and positive MPO-ANCA

2. **Probable MPA**
   - (1) Positive for three of the symptoms
   - (2) Positive for one of the symptoms, and positive MPO-ANCA

From the Research Group of Intractable Vasculitis, MHLW of Japan (2002).2

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<th>Table 2</th>
<th>Pulmonary function tests of patient at presentation, after pulse therapy and under maintenance therapy.</th>
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<td>At presentation</td>
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<tr>
<td>FVC (%pred)</td>
<td>108</td>
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<tr>
<td>FEV₁ (%pred)</td>
<td>105</td>
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<tr>
<td>FEV₁/FVC</td>
<td>80.5</td>
</tr>
<tr>
<td>TLCO (%pred)</td>
<td>83.6</td>
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<tr>
<td>TLCO/VA (%)</td>
<td>94.8</td>
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Recent studies have focused on TNF-α inhibitors, B-cell depletion agents, mycophenolate mofetil, leflunomide and antithymocyte globulin. Most of these agents are associated with strong adverse effects. So in the absence of further data, these experimental treatments should not be used.

In conclusion, the diagnosis of vasculitis is often delayed because the clinical manifestation can be mimicked by a number of other disorders. Establishing the diagnosis of microscopic polyangiitis is a particularly difficult task, especially in patients presenting with pulmonary infiltrates and fever, having no prior disease label and without hemoptysis—a clinical scenario resembling “pneumonia”. Renal and pulmonary symptoms are characteristic in microscopic polyangiitis (MPA), and intestinal pneumonitis and pulmonary hemorrhage are common. The treating physician should always bear in mind that pulmonary–renal syndrome at first presentation may not only mimic pneumonia, but in certain cases could be triggered by pneumonia.

References


