Microscopic polyangiitis associated with myelodysplastic syndrome mimicking infectious pneumonia, with complications including complete atrioventricular block and fatal intra-alveolar hemorrhage.

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Case Report

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Abstract

The association between ANCA-associated vasculitis and hematologic malignancy has been previously described and remains a rare phenomenon, albeit potentially underdiagnosed. We report the case of an 81-year-old patient with myelodysplastic syndrome who was managed for an infectious-appearing pneumonia, which subsequently complicated into complete heart block and severe acute respiratory distress syndrome with a fatal outcome. The final diagnosis is severe hemorrhagic alveolitis associated with ANCA-associated vasculitis meeting the criteria for microscopic polyangiitis. This article provides an opportunity to discuss the association between ANCA-associated vasculitis and hematologic malignancies and the adverse prognosis associated with it.

1. Introduction

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are characterized by inflammation of small-caliber blood vessels (arterioles, capillaries, and venules) [1]. This entity comprises three different diseases: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA). Two specific types of ANCA antibodies have been described: anti myeloperoxidase (MPO) antibodies, more often associated with MPA and EGPA, and antiproteinase 3 (PR-3) antibodies, which are more specific to GPA. In a recent systematic review: annual incidence in Europe was 8.5 (7.2–9.9, 95% CI) /1,000,000 individuals per year for GPA, 4.7 (3.1–6.6, 95% CI) /1,000,000 individuals per year for MPA, and 1.7 (1.0–2.7, 95% CI) /1,000,000 individuals per year for EGPA [2]. We describe a case of MPA that stands out due to its association with myelodysplastic syndrome (MDS) and the development of complete atrioventricular block (AVB).

2. Case presentation

An 81-year-old woman with a history of hypothyroidism, osteoporosis, and lower extremity deep vein thrombosis treated with rivaroxaban for 4 months, was admitted to our intensive care unit (ICU) for acute respiratory distress syndrome. She had no history of arthralgia or sinusitis. Her renal function had been normal with a baseline creatinine of 61 µmol/l one year ago. Four months earlier, the patient had consulted a hematologist for pancytopenia, presenting with a hemoglobin level of 11 g/dL, a platelet count of 54 × 10^9/L, and a total leukocyte count of 2.3 × 10^9/L, with a neutrophil count of 1.14 × 10^9/L and lymphocytes of 0.84 × 10^9/L. Bone marrow aspiration smears revealed normal overall cellularity with discrete qualitative anomalies and a 5% blast count. The karyotype was normal. In the following months, she experienced a general deterioration without fever.

Ten days before her admission to the ICU, she presented to the emergency department. She had been treated with levofloxacin for 5 days for right laterobasale pneumonia, which was revealed by chest X-ray, but her health condition worsened. She complained of nausea, vomiting, difficulty eating, and thirst. A physical examination revealed a temperature of 37.2°C, blood pressure of 125/108 mmHg, a pulse rate of 63 beats/min, peripheral blood oxygen saturation (SpO2) of 95% on room air and a respiratory rate of 28
breaths/min. Wet crackles could be heard on auscultation of the right pulmonary base. Arterial blood gases on room air indicated a pH of 7.48, a partial pressure of oxygen (PaO2) of 66.1 mmHg, and a partial pressure of carbon dioxide (PaCO2) of 27.2 mmHg. Inflammatory markers were elevated, with a C-reactive protein (CRP) level of 227 mg/L and procalcitonin (PCT) of 1.59 ng/L. The total leukocyte count was 14.7 × 10^9/L, consisting of 12.8 × 10^9/L neutrophils, 0.5 × 10^9/L lymphocytes, and 1.4 × 10^9/L monocytes. There was no eosinophilia. She had renal failure with a creatinine level of 163 µmol/L. A thoraco-abdominal-pelvic scan revealed a right middle lobe consolidation and several pseudo-nodular consolidations, along with moderate hepatomegaly (hepatic arrow = 14 cm) (Figure 1). Tests for legionella and pneumococcal antigenuria, as well as polymerase chain reaction (PCR) testing for influenza A, influenza B, and COVID-19, all returned negative. Urine culture on the second stream was sterile, but cytology revealed leukocyturia (71 white blood cells /mL) and hematuria (65 red blood cells/mL). A combination therapy with ceftriaxone and spiramycin was initiated, and the patient was admitted to the hospital.

On the following day, the patient developed a well-tolerated complete AVB, and a cardiac pacemaker was implanted (Figure 2). On hospital day 4, she became oxygen-dependent at a rate of four liters per minute, and the inflammatory syndrome persisted. Treatment with piperacillin/tazobactam was initiated. By day 7, the patient exhibited subconjunctival and oral bleeding, without significant hemoptysis. Additionally, there was a notable decrease in hemoglobin levels to 7 g/dl, a substantial increase in leukocyte count to 65 × 10^9/L, and thrombocytopenia with a count of 28 × 10^9/L. The patient received platelet and red blood cell transfusions. A repeat CT scan was performed, revealing the progression of lung lesions (Figure 3). On day 9, she experienced a sudden deterioration in her respiratory condition, requiring high-flow oxygen therapy and necessitating her transfer to our unit. On admission, the vital signs were as follows: a temperature of 37.2°C, blood pressure of 128/68 mmHg, a pulse rate of 62 beats/min, SpO2 of 84% with a high-concentration mask, a respiratory rate of 56 breaths/min, and a Glasgow Coma Scale score of 12/15. Acute pulmonary edema was ruled out based on intermediate left ventricular filling pressures with a thin and compliant inferior vena cava. She was rapidly intubated, arterial blood gases with a fraction of inspired oxygen of 100%, showed a pH of 7.16, a PaO2 of 78.2 mmHg, a PaCO2 of 81.2 mmHg, a lactate level of 7.4 mmol/L. Laboratory findings showed anemia at 5.5 g/dL, necessitating the transfusion of 2 units of red blood cells. There was important leukocytosis with 78 × 10^9/L of neutrophils and 7.0 × 10^9/L of monocytes, lymphopenia at 0.8 × 10^9/L, and myeloid cell abnormalities (6% metamyelocytes, 5% myelocytes, 1% promyelocytes, 0% blasts). Protected distal aspiration revealed only a few red blood cells. 12 hours later, leukocytosis continued to rise to 110 × 10^9/L. Hemodynamic instability developed with lactic acidosis, requiring increasing doses of norepinephrine up to 2 µg/kg/min. Prone positioning had no effect. The situation was further complicated by KDIGO stage 3 anuric acute kidney injury and shock liver, ultimately leading to her death in less than 24 hours. Respiratory and blood cultures all remained sterile.

In hindsight, anti-MPO antibodies were strongly positive (titer > 134 IU/ml), and anti-PR3, anti-glomerular basement membrane, and antinuclear antibodies were negative. Aspergillus antigenemia was negative. Post-mortem lung biopsies revealed severe lesions of hemorrhagic alveolitis with minimal leukocyte
infiltration indicating a diagnosis of IAH. A repeat bone marrow examination found supporting evidence for a myelodysplastic syndrome among with toxic granulations: dyserythropoiesis (megablastic appearance, occasional basophilic punctuations in erythroblasts) and dysgranulopoiesis (subtle granulated myeloid clone with chromatin condensation abnormalities). The medullary karyotype was normal. Testing for BCR-ABL rearrangement by FISH and PCR was negative. Molecular analysis of the bone marrow (90-genes panel) contributed with findings of 3 mutated genes: CBL (double mutation, exon 8, 1211 VAF 57%, and 1150 VAF 2%), TET2 (double mutation, exon 3, VAF 46%, and exon 11, VAF 48%), and PHF6 (exon 8, VAF 9%).

3. Discussion

AAV typically presents with renal involvement, ranging from urinary abnormalities to rapid glomerulonephritis, often accompanied by respiratory symptoms. Our case was diagnosed as microscopic polyangiitis (MPA) based on the ACR/EULAR 2022 criteria, which include high levels of perinuclear ANCA of the MPO type, the presence of IAH, and the absence of facial sinus abnormalities [3]. While anti-MPO antibodies are found in around 90% of MPA cases, they are also present in about 15% of granulomatous polyangiitis (GPA) cases [4]. Regrettably, our patient's severe renal involvement, indicated by suggestive hematuria and renal insufficiency, was initially underdiagnosed.

Pulmonary symptoms, less common in MPA, affect 30-50% of patients, with varying patterns from focal infiltrates to diffuse IAH [5]. Approximately 25% of cases lack hemoptysis but exhibit a sudden drop in hemoglobin level and respiratory distress, strongly suggesting IAH [6]. Diagnosis is confirmed through analysis of bronchoalveolar lavage fluid, which shows a hemorrhagic appearance or hemosiderin-laden macrophages. Initial imaging in our case indicated infectious pneumonia, and MPA typically displays diffuse, bilateral ground-glass opacities, reflecting hemorrhagic alveolitis. However, the progressive and insidious nature of the disease can cause areas of IAH to appear consolidative when alveoli are completely filled with blood [7]. The use of oral anticoagulants and thrombocytopenia in our case likely contributed to this consolidative appearance in IAH areas.

A recent retrospective multicenter study, involving 368 patients with MPA from the French Vasculitis Study Group Registry, revealed a 20.6% incidence of cardiovascular involvement, primarily manifesting as heart failure and pericarditis [8]. Furthermore, cardiac rhythm abnormalities, notably atrial fibrillation, and occasionally conduction issues, ranging from asymptomatic bundle branch block to complete AVB, were observed. Autopsy findings in some cases showed infarctions of the atroventricular node or bundle of His and arteritis of the supplying arteries, along with one instance of granulomas in the interventricular septum [9, 10]. Complete AVB cases are uncommon in MPA, with only one reported case occurring in an elderly patient with multiple cardiovascular comorbidities, diagnosed eight months after MPA diagnosis [11]. In the presented case, AVB onset coincided with the MPA diagnosis during the active inflammatory phase of the disease. A retrospective analysis of 2371 patients with AAV demonstrated a higher prevalence of cardiovascular events in the year leading up to the AAV diagnosis, peaking one month before diagnosis, and persisting during the first three months post-diagnosis, particularly in cases
of atrial fibrillation and congestive heart failure [12]. This suggests a strong likelihood of a significant association between MPA and the observed AVB case.

Autoimmune diseases occur in 10-20% of MDS cases, mostly systemic medium and large vessel vasculitis (such as polyarteritis nodosa), connective tissue diseases, and neutrophilic dermatosis [13]. ANCA positivity is also more common in MDS patients, although it is not often associated with vasculitis symptoms and therefore systematic ANCA testing isn't recommended [14]. Symptomatic small vessel vasculitis in MDS patients is rarer. In a large retrospective multicenter study involving 2244 patients, ANCA-associated vasculitis estimated to occur in 0.37% to 1.6% of hematologic malignancy patients, often preceding or following the vasculitis diagnosis by approximately 6 months. Sixteen cases of patients with AAV and hematologic malignancy could be identified of whom 38.5% had MDS. In this series, MPA was the primary type of vasculitis. This combination had a poor prognosis, with a median survival of 3 years, much lower than AAV without hematologic issues (where the mortality is estimated to be 25% at 5 years) [15]. Regarding our patient: cytopenias and cytologic abnormalities along with hepatomegaly, significant leukocytosis with monocytosis, circulating myeloid precursors, and negative BCR-ABL transcript suggest the presence of a myelodysplastic/myeloproliferative syndrome. CBL mutation is common in these syndromes, more so than in pure myelodysplastic syndromes [16]. TET2 mutation is also very frequent and characteristic, though not exclusive to this disease, and not sufficient for diagnosis [17]. However, not all criteria were met to establish this diagnosis (relative monocytosis was below 10%, which is not compatible with a diagnosis of chronic myelomonocytic leukemia, and there were no characteristic cytological abnormalities of atypical chronic myeloid leukemia). Additionally, the onset of leukocytosis was too rapid [18]. Hence, the diagnosis is considered as myelodysplastic syndrome (with features overlapping with myeloproliferative disorder). To this date and our knowledge there isn’t any reported case of myelodysplastic/myeloproliferative syndrome associated with AAV.

4. Conclusion

This case highlights the rare co-occurrence of MDS and MPA, with the unexpected complication of AVB. The delay in identifying pneumo-renal syndrome is regrettable. It underscores the importance of systematically assessing urinary sediment abnormalities and proteinuria in patients with radiological pneumopathy and acute renal insufficiency. In such cases, considering AAV is essential. Our patient’s specific hematological condition might have contributed to a presentation that more closely mimicked an infectious pneumonia. Early intervention with corticosteroids and immunosuppressants could have altered the course of this fatal IAH episode, although the overall prognosis would have remained challenging due to extensiveness of the disease, infection risks, advanced age, and underlying hematological issues.

Declarations

Data Availability
The clinical and laboratory data used to support the findings of this study are available from the corresponding author upon request.

**Conflicts of Interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

**Consent**

The patient's relatives did not object to the writing of this case report.

**References**


Figures
Figure 1

Unenhanced chest CT: consolidation of the middle lower lobe with air bronchogram and presence of several pseudonodular condensation areas.

Figure 2

Complete atrioventricular block with sinus rhythm at 108 beats/mn and junctional escape rhythm with narrow QRS complexes at 59 beats/mn, suggestive of intranodal block.
Figure 3

A) Chest X-ray: bilateral alveolar opacities predominantly at the right base. B) Unenhanced chest CT scan: bilateral consolidations with air bronchogram and indistinct borders.