Anti-Myeloperoxidase (MPO) associated Vasculitis in a Young Filipino Male with Bronchiectasis: A Case Report

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Abstract

Background: ANCA-associated vasculitis and its subtypes have been associated with pulmonary manifestations, with bronchiectasis being a unique clinical presentation.

Case Summary: We report the case of a 26-year-old Filipino male who presented with progressive dyspnea, neuropathic pain, and purpuric rash. Diagnostic evaluation revealed upper lobe bronchiectasis and lower lobe pneumonia, as well as hematuria and proteinuria. ANCA-associated vasculitis (AAV) and tuberculosis were considered. There was improvement of dyspnea, cough and rashes with antibiotics, glucocorticoids (GC), and anti-TB coverage. However, neuropathic pain progressed to the upper and lower extremities with development of weakness. Anti-myeloperoxidase (MPO) Anti-Neutrophil Cytoplasmic Antibody (ANCA) was positive, Electromyography-Nerve Conduction Velocity (EMG-NCV) revealed diffuse sensorimotor axonal polyradiculopathy of both upper and lower extremities. Cyclophosphamide was then given.

The patient gradually regained his motor strength while sensory deficits persisted. He was referred to rehabilitation medicine for physical therapy and eventually discharged. This case highlights vasculitis as an associated extrapulmonary manifestation of bronchiectasis, and the possible role of bronchiectasis in the immune-mediated pathogenesis of ANCA-associated vasculitides.

Keywords: *bronchiectasis, ANCA-associated vasculitis, anti-MPO*

Introduction

Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitides (AAV) are rare heterogenous autoimmune diseases with multisystemic manifestations.[1] Prominent of these is pulmonary involvement in 85% of granulomatosis with polyangiitis (GPA), 60% of eosinophilic granulomatosis with polyangiitis (EGPA), and up to 50% of microscopic polyangiitis (MPA).[2,3] The spectrum of involvement includes the sinonasal, subglottic region, endobronchial, parenchymal, and pleural tissue. Endobronchial involvement, in particular, occurs in up to 50% of granulomatosis with polyangiitis (GPA), 30% in microscopic polyangiitis (MPA) cases, and is rare in eosinophilic granulomatosis with polyangiitis (EGPA).[4] The association between certain ANCA subtypes and pulmonary manifestations have been described in literature. Chest CT scan abnormalities are reported in 4 out of 5 patients with ANCA-associated vasculitis. Findings consistent with granulomatous central bronchial disease occurred almost exclusively in anti-proteinase 3 (PR3) ANCA, while usual interstitial pneumonia and bronchiectasis were noted in anti-myeloperoxidase (MPO) ANCA.[1] Similarly, a French cohort revealed that bronchiectasis was noted to have a higher prevalence among anti-MPO ANCA (64%) compared to anti-PR3 (21%). This same group also had a certain unique phenotype with predominant peripheral neuropathy findings.[5] A similar association of anti-MPO ANCA and bronchiectasis was also noted in another retrospective multicenter study, where the timing of bronchiectasis diagnosis from the AAV also showed prognostic significance.[6]

We report a case of a 26 y/o male who presented with chronic cough, difficulty breathing, progressive neuropathic pain and weakness, and purpuric rash.

Case Presentation

A 26-year-old Filipino male, single, presented to our institution for difficulty of breathing, paresthesia, petechial rash, and hemoptysis of 3 weeks duration. Past medical history was pertinent for prior treatment of tuberculosis during his childhood, while family history was unremarkable. He is a known smoker but had no history of multiple sexual partners or illicit drug use.

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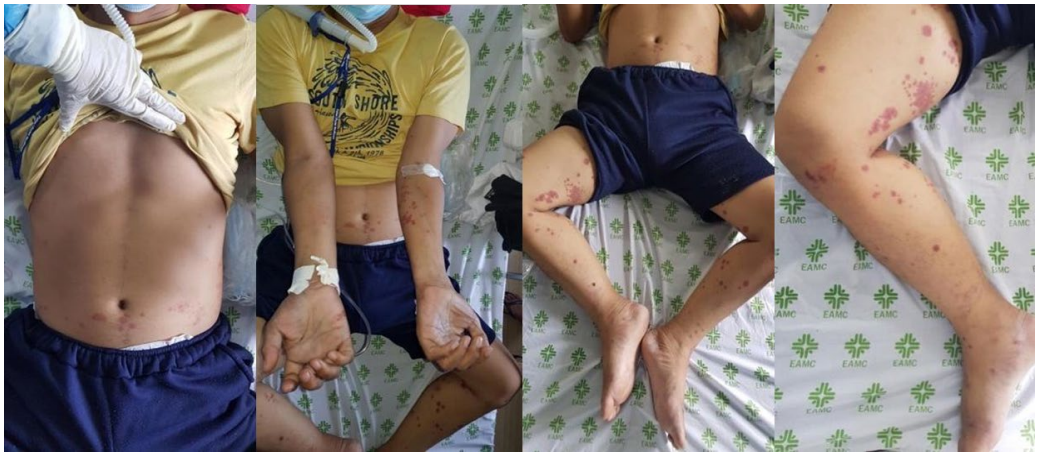

Figure 1. Multiple non-pruritic, non-blanching purpuric rashes on the abdominal area and both extremities

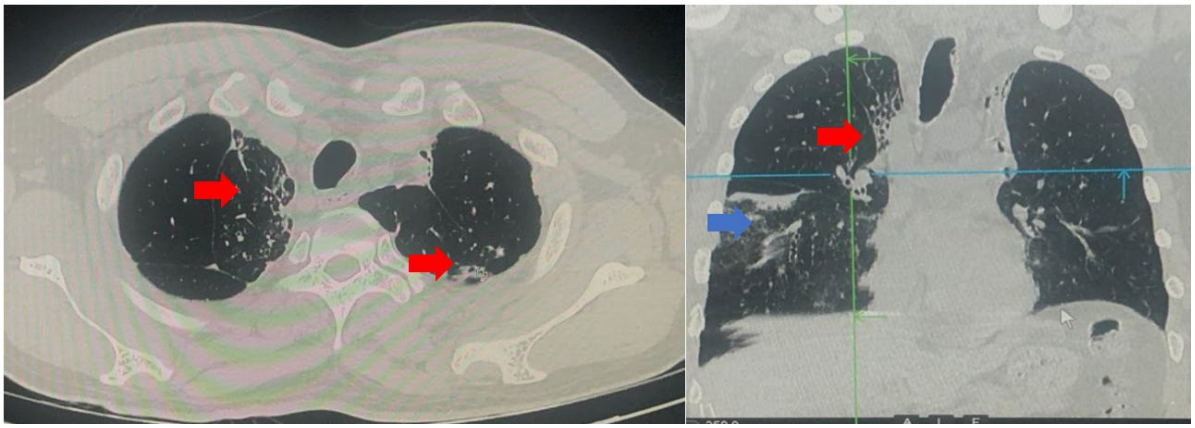

Figure 2. High-resolution Chest Computed Tomography Scan showing bronchiectatic changes on both upper lobes (red arrow), as well as a right lobe ground glass opacities (blue arrow) consistent with pneumonia

He had a one year history of daily productive cough not accompanied by any symptoms. until three weeks prior to admission, where he had hemoptysis, night sweats, anorexia, and undocumented weight loss. He was treated as a case of pneumonia and prescribed cefixime, but with minimal improvement of symptoms noted. He then developed bilateral lower extremity paresthesia over the next two weeks that was managed with potassium supplementation, but no relief was noted. Paresthesia later progressed to both upper extremities, now accompanied by bipedal edema, hematuria and bilateral flank pain. Over the next seven days prior to admission, cough and hemoptysis were accompanied by exertional dyspnea and the development of multiple palpable non-pruritic, non-tender rashes on the trunk and both upper and lower extremities. Progression of symptoms led to admission at our institution. Review of systems was negative for nasal congestion, anosmia, chest pain, changes in bowel movement, and joint pains.

Upon admission, he was awake but spoke in phrases, with initial vital signs showing the following – BP of 120/80 mmHg, heart rate of 99 bpm, respiratory rate of 30 cycles/minute, with Oxygen saturation of 98% at 8 liters per minute. He had pale conjunctivae and oral mucosa but no oral or nasal ulcers, cervical lymphadenopathy, or neck vein engorgement. Chest and examination showed right-sided mid to basal coarse crackles, but no wheezing. He was not tachycardic, and no murmurs were appreciated. Skin examination showed multiple non-tender, non-pruritic, non-blanching purpuric rashes on the anterior abdominal wall, and back. These rashes were also seen on both upper and lower extremities. A grade 2 bipedal edema was also noted, while musculoskeletal examination showed no joint tenderness, swelling or limitation of range of motion on examination. Neurologic examination during this time revealed paresthesia on both upper and lower extremities, but no focal weaknesses.

Pertinent laboratory results showed the following: Hemoglobin 104 g/L, Hematocrit 31%, with WBC of 18,400/mm^3 (with neutrophil predominance), and platelet count of 279,000/ul. Serum creatinine was elevated at 131 mmol/L (eGFR of 64 ml/min), BUN of 11.0 mmol/L, with electrolytes as follows– Sodium 129 meq/L,

Potassium 4.75 meq/L, elevated Phosphorus 1.97 mmol/L, elevated LDH 484 U/L. Urinalysis showed hematuria (Many RBCs) and pyuria (13-15 WBC/hpf), as well as proteinuria (+2). Urine Protein: Creatinine Ratio was elevated at 1.1 g/g. Chest roentgenogram revealed pneumonia on the right middle to lower lobe, while electrocardiogram showed sinus rhythm. Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) reverse transcriptase polymerase chain reaction (RT-PCR) nasopharyngeal swab was negative.

High-resolution chest CT scan was done, revealing multiple fibrotic densities and traction bronchiectasis on both upper lobes, as well as patchy ground glass opacities on the right lower lobe consistent with pneumonia. Piperacillin-tazobactam and hydrocortisone were both given. He was also treated with anti-TB agents, although sputum nucleic acid amplification test for *Mycobacterium tuberculosis* revealed negative results.

Upon admission, he was hooked to a high-flow nasal cannula device due to desaturations. Dyspnea, cough, and hemoptysis gradually resolved over the next 4 days. He was weaned from oxygen support until he was able to tolerate breathing in room air. His petechial rashes and bipedal edema were noted to gradually resolve as well. Antibiotics were completed then for a total of 14 days.

Paresthesia on his lower extremities, progressed to his upper extremities, associated with weakness and numbness. There was no fever, difficulty of breathing, changes in bowel movements or urination noted. Repeat electrolytes showed hypokalemia (potassium levels as low as 2.9 mEq/L and was corrected. Symptoms worsened over the next 3 days as the patient could not ambulate from the bed or grasp objects with his hand. He was awake and coherent without any changes in speech. Cranial nerves were intact, motor strength was at 2-3/5 on all extremities, with 60% sensory loss as well on the distal extremities. Deep tendon reflexes were also absent. No joint tenderness, swelling, or pain on active and passive motion were appreciated.

He was referred to neurology service, and started on gabapentin. ANCA results showed positivity for anti-MPO (>134 IU/ml), while C3 levels were normal. Cyclophosphamide at 1000 mg IV was then infused, while IV steroids were shifted to oral prednisone at 60mg/day. Anti-Koch's were then discontinued.

Over the next few days, his motor strength gradually recovered, but numbness and tingling sensation persisted. An EMG-NCV was conducted, revealing bilateral severe sensorimotor axonal polyradiculopathy involving both upper and lower extremities. He was referred to rehabilitation medicine for physical therapy.

He was subsequently discharged from our institution and advised follow-up.

Discussion

The etiology of ANCA-associated vasculitides remains unknown.[2] Its pathogenesis is known to lie on autoimmune reactions accompanying ANCA, which activate cytokine-primed neutrophils and monocytes possessing the MPO and PR3 antigens. These neutrophils and monocytes respond by adhering to cytokine-activated endothelial cells – which release proteolytic granules and result in multiple tissue destruction.[4]

The role of bronchiectasis in ANCA vasculitis is poorly understood. Literature has noted the influence of certain ANCA subtypes on the pulmonary manifestations. CT findings in a British study showed that anti-PR3 ANCA presented with nodular or central airway disease involvement, while anti-MPO ANCA manifested with usual interstitial pneumonia and bronchiectasis.[1] Although treatment protocols did not differ between the anti-PR3 and anti-MPO subjects, it was noted that the cumulative survival rate was inferior in the anti-MPO arm group (10-year survival rate of 60% in anti-MPO vs. 80.6% in anti-PR3).

In the French cohort by Neel et al, patients with anti-MPO ANCA vasculitis had a high prevalence (67.2%), with bronchiectasis and higher frequency of peripheral nerve involvement than those without bronchiectasis (54.5% vs. 17.6%). Patients in these cases tended to be older (i.e., 65-78 y/o) and more frequently female (77%).[5]

Another report notes that the peripheral nerve findings, particularly mononeuritis multiplex, occurred in only 38% of their subjects, but was specifically more prevalent among those with a history of bronchiectasis– with the median interval between bronchiectasis and AAV diagnosis at 16 years apart.[6] The case we report presented with progressive sensorimotor deficits of his extremities prior and during his admission. Furthermore, this case is a young male, a minority of those with bronchiectasis and AAV.

Although renal manifestations are common in association with anti-MPO ANCA, these are less prominent among those presenting with bronchiectasis than those without (40.9% vs. 82.3%). Proteinuria tends to be less severe, with a median level of 0.4 g/24 hour.[5,6] In the case we present, proteinuria was more than 1 gram/day and therefore can be regarded as a more severe renal involvement.

Bronchiectasis has been suggested to be a dynamic inflammatory process that may trigger vasculitis, even if small vessels are not present in bronchi. One theory could be neutrophil activation by ANCA within the bronchial lumen, thus triggering inflammation.[6] Another similar hypothesis says that the chronic suppurative bronchial inflammation contributes to the autoimmune reaction and development of vasculitis.[6] This is explained by how antigens from infectious agents stimulate the TH17 pathway, producing cytokines such as IL-17, TNF, and IL-1B that prime neutrophils. Simultaneously, these infectious antigens stimulate neutrophils to form neutrophil extracellular traps (NETs)– which can disrupt tolerance to specific self-antigens, including myeloperoxidase (MPO) and Proteinase-3 (PR3). These in turn are presented to CD4+ T-cells via dendritic cells, resulting in the production of ANCAs.[7]

Treatment with corticosteroids combined with immunosuppressants (cyclophosphamide, methotrexate, azathioprine) are shown to produce similar outcomes of progression-free survival, relapse-free survival and overall survival of patients with anti-MPO vasculitis with or without bronchiectasis.[5,6] Of note is the report that 30% of subjects with anti-MPO and bronchiectasis will have severe respiratory tract infection within 5 years observation.[6] These patients received cyclophosphamide with corticosteroids.

Prognosis is known to vary between those with a diagnosis of bronchiectasis preceding the vasculitis and those diagnosed after the vasculitis. Those diagnosed with bronchiectasis preceding the vasculitis have a more aggressive disease and poorer outcome.[6] This study noted that these subjects had fivefold increased risk of death, more frequent mononeuritis multiplex, and were more likely to present as microscopic polyangiitis. This may have prognostic significance for this patient, as symptoms suggestive of bronchiectasis (i.e., chronic productive cough) have been present for about a year prior to the development of the vasculitis manifestations.

Conclusion

We report a case of a young, male patient with ANCA-associated vasculitis and bronchiectasis presenting with chronic cough, dyspnea, neuropathic pain and weakness of extremities, and rash. Recognizing this disease entity is important because bronchiectasis may itself be a source of chronic inflammation and consequently, immune activation that can evolve to become systemic vasculitis. Prognosis is poor and management of these cases warrants astute evaluation, aggressive immunosuppression and consistent follow-up.

Conflict of Interest. The authors declare no conflicts of interest regarding the publication of this paper

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