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(CASE REPORT)

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Coinfection of Nontuberculous mycobacteria with *Aspergillus fumigatus* and *Nocardia nova* in immunocompromised patient: A case report and literature review

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Abstract

Nontuberculous mycobacteria primarily affect individuals with chronic lung diseases and compromised immune status. Coinfections with other pathogens such as Mycobacterium tuberculosis, Aspergillus spp. and Histoplasma capsulatum are possible. These coinfections worsen prognosis and are associated with increased morbidity and mortality. Diagnosis and effective treatment are often challenging, raising many questions for clinicians regarding polypharmacy, drug interactions, and the management of the underlying disease. We present a clinical case of a patient with ANCA-negative vasculitis and coinfection with Mycobacterium avium, Aspergillus fumigatus and Nocardia nova.

Keywords: Nontuberculous mycobacteria; Coinfection; Diagnosis; Treatment

1. Introduction

Nontuberculous mycobacteria (NTM) are widely distributed in the environment and can be found in soil, water, and on various surfaces [1]. Many studies report an increasing incidence of infections with these pathogens in recent decades. They affect both immunocompetent and immunosuppressed individuals and are associated with four clinical syndromes: progressive lung disease, peripheral lymphadenitis, disseminated infection, and infections of the skin and soft tissues [2,3].

The lungs are the most commonly affected organ in NTM infections, especially in patients with underlying chronic lung disease [4,5]. Other conditions and therapies that increase the risk of these infections include primary immune deficiencies, HIV/AIDS, malignancies, hematological disorders, bone marrow and organ transplantation, systemic autoimmune diseases, and immunosuppressive medications [6,7]. Among immunocompromised individuals, the prevalence of pulmonary involvement varies from less than 5% in AIDS patients to 67% in those receiving biological therapy [6]. The most common causative agents are Mycobacterium avium complex (MAC), Mycobacterium abscessus subsp. abscessus and Mycobacterium kansasii [6].

In individuals with primary and certain secondary immune deficiencies, such as AIDS and hairy cell leukemia, disseminated infections are significantly more frequent [6]. They are mainly caused by MAC and, less commonly, by rapidly growing mycobacteria (M. abscessus, M. fortuitum and Mycobacterium chelonae) [6,8,9].

Coinfections with other pathogenic microorganisms, including Mycobacterium tuberculosis, bacteria, fungi (Aspergillus spp., H. capsulatum) and Nocardia are possible [10]. These coinfection presenting additional challenges to clinicians in terms of diagnostic algorithms and therapeutic strategies. Additionally, it is not always clear whether the isolated pathogen represents a true infection or mere colonization.

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2. Clinical Case

We present the case of a 34-year-old female patient diagnosed with bronchial asthma in 2010. She was prescribed therapy with ICS/LABA (Fluticasone furoate/vilanterol 184/22 mcg) and a leukotriene receptor antagonist (Montelukast 10 mg). Her medical history includes nasal mucosa atrophy with frequent epistaxis, hearing impairment since childhood, and chronic pyelonephritis.

In 2013, she was hospitalised in the pulmonology department with dyspnea, cough, and hemoptysis.

Laboratory findings at that time showed Hb – 112 g/L (120-160g/L), eosinophils – 3% (0,7-7%), creatinine – 208 μmol/L (58-100 μmol/L), erythrocyturia (12-15 RBCs per field), and proteinuria (0.45 g/24h). Immunological screening revealed negative anti-MPO and anti-PR3 antibodies. A thoracic computed tomography (CT) scan showed consolidation in the left upper lung lobe (segments 1+2), adjacent ground-glass opacities, and solitary nodular lesions. Sinus and temporal bone CT revealed maxillary and frontal sinusitis, mastoiditis, and otitis media. Fibrobronchoscopy showed edematous and granulomatous tracheal mucosa, similar changes bilaterally in the bronchial tree leading to deformities and stenosis, as well as signs of bleeding. Histological examination of biopsy samples confirmed vasculitic involvement of small blood vessels, granulomatous inflammation with eosinophilic infiltration, ulcero-necrotic, and hemorrhagic inflammatory lesions. The diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was established. The patient underwent eight pulse therapies with Methylprednisolone and Cyclophosphamide (July, August, September, December 2013; January, February, March 2014), followed by maintenance therapy with Prednisolone (maintenance dose of 10-15 mg). Azathioprine (100 mg/day) was introduced in 2014 and continued for five years. Clinical and endoscopic improvements were observed following treatment.

In 2022, she was hospitalised due to left lumbar pain, and an abdominal ultrasound revealed nephrolithiasis. A chest X-ray showed infiltrative changes in the left lung, accompanied by complaints of cough with yellowish sputum. Chest CT revealed an irregular consolidation zone in the left lower lobe (segment 8) and multiple small nodules of varying density, most with cavitary changes in the right upper lobe (figure 1).

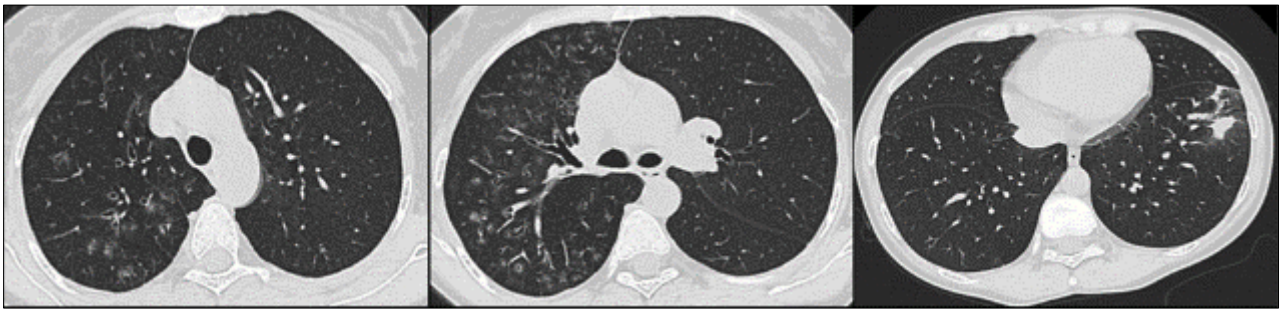

Figure 1 Computed tomography pulmonary changes

Fibrobronchoscopy showed inflammatory changes in the tracheal and bronchial mucosa, with necrotic areas (figure 2). Bronchoalveolar lavage (BAL) cultures isolated Staphylococcus aureus, Nocardia nova, Aspergillus fumigatus, and a positive PCR test for Mycoplasma pneumoniae.

Acid-fast bacilli microscopy was negative. Histological examination of biopsy specimens showed no evidence of vasculitis. The patient was initially treated with Levofloxacin, followed by Trimethoprim/Sulfamethoxazole (TMP/SMX) and concurrent therapy with Itraconazole. Oral corticosteroids were discontinued following a rheumatology consultation.

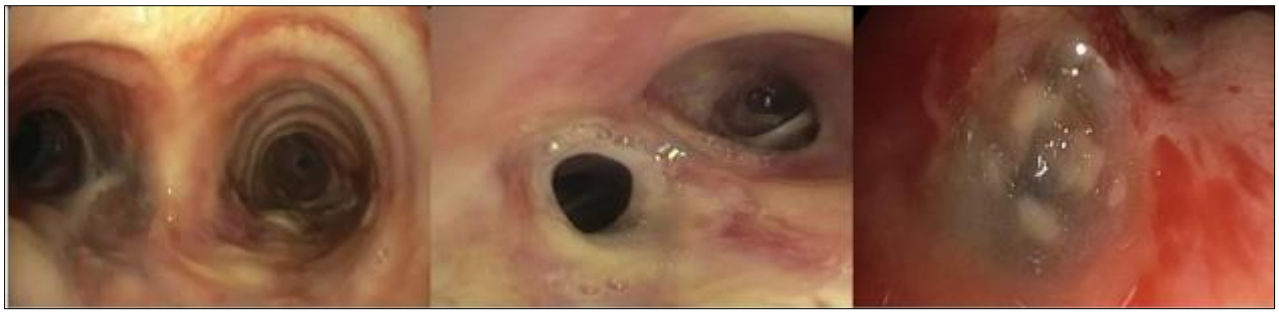

Figure 2 Bronchosopic findings

Approximately six weeks later, BAL cultures on solid media isolated Mycobacterium avium, sensitive to macrolides and aminoglycosides. Treatment was initiated with Rifampicin 600 mg daily, Ethambutol 15mg/kg/day, and Clarithromycin 500 mg daily. Therapy with Itraconazole and TMP/SMX was discontinued due to the absence of fungal and nocardial growth in follow-up BAL cultures and minimal clinical improvement. In addition, no Aspergillus-specific IgG-antibodies were detected. Clinical and radiological improvement was observed after one year of antimycobacterial therapy (figure 3).

Figure 3 Follow-up imaging study conducted after one year antimyobacterial therapy

3. Discussion

Conditions and medications that suppress cell-mediated immunity are associated with an increased risk of nontuberculous mycobacterial disease [11,12].

Patients with immune deficiency due to primary or acquired immunodeficiency syndromes (such as HIV/AIDS or hairy cell leukemia) typically develop disseminated infections [6].

Identified risk factors for NTM infection in HIV/AIDS patients include: CD4+ cell count below 50/microL, HIV RNA levels >1000 copies/mL, persistent viral replication despite antiretroviral therapy, previous or concurrent opportunistic infections [13].

In organ transplant recipients, clinical manifestations of NTM infection vary [14]. Pulmonary involvement, including pleural infections, is common, with the highest risk observed in lung transplant recipients [14,15]. These patients are often colonized before transplantation due to pre-existing structural lung damage [16]. Therapeutic approaches range from no treatment to prophylactic therapy before and/or after transplantation [17,18]. A systematic review and meta-analysis identified key risk factors for posttransplant NTM disease, including prior colonization, cystic fibrosis, and bronchiectasis of other etiologies as an indication for transplantation [19].

For patients on immunosuppressive therapy, pulmonary involvement is more frequent, but disseminated infection can also occur [6]. Anti-TNF-alpha agents are widely used in the treatment of autoimmune inflammatory diseases [20]. TNF-alpha is a pro-inflammatory cytokine essential for host defense against granulomatous infections caused by mycobacteria and fungi [21]. A study in the United States reported a 5- to 10-fold increase in the incidence of NTM infections among patients receiving anti-TNF therapy compared to those not on therapy and the general population [22].

Corticosteroids modulate immune function, which is essential for host defense against various pathogens. A study conducted in Oregon and Washington reported that oral corticosteroid use was 8 times higher among cases with NTM infections compared to controls [23]. Inhaled corticosteroids (ICS), particularly at moderate and high doses, have also been linked to an increased risk of NTM infections, as demonstrated in studies on patients with COPD (Chronic obstructive pulmonary disease) and bronchial asthma [24,25]. A statistically significant association has been reported for Fluticasone but not for Budesonide [26]. The risk of infection correlates with the duration of use and cumulative dose [26,27]. Discontinuation of ICS for more than 120 days has been shown to reduce this risk to an insignificant level [28].

In our reported case, prolonged use of oral corticosteroids in combination with other immunosuppressants was observed in a patient diagnosed with ANCA-negative vasculitis. Due to airflow obstruction the patient was also receiving ICS/LABA therapy.

In the differential diagnosis of a newly emerging pulmonary infiltrate on chest radiography in the context of immunosuppression, both infectious causes, including opportunistic pathogens, and non-infectious causes, such as pulmonary involvement of the underlying disease, were considered.

Early diagnosis of opportunistic infections is crucial for effective treatment. In many cases, invasive procedures are required to obtain secretions and tissue samples for microbiological and histopathological testing [29]

Atypical mycobacterial disease is diagnosed based on positive microbiological findings combined with clinical presentation and imaging abnormalities [30]. Microbiological criteria include: 1) Two positive culture results from at least two separate sputum samples 2) One positive culture result from bronchoalveolar lavage 3) Mycobacterial histological features in biopsy samples along with a positive culture for NTM [30].

Coinfections with other pathogens affecting individuals with structural lung disease and immunocompromised status are possible. Reported coinfections include Mycobacterium tuberculosis, fungi (Aspergillus, Histoplasma capsulatum), Nocardia, and others [31-34]. Clinical symptoms are often nonspecific and overlapping. A high level of suspicion is needed, considering the difficulty in culturing some microorganisms (such as Nocardia), which require special nutrient medium and prolonged incubation times [35].

Conditions associated with an increased risk of NTM and Aspergillus spp. coinfection include fibrocavitary lesions, bronchiectasis, COPD with emphysema, bronchial asthma, corticosteroid use, and prior tuberculosis infection [36-38]. Various forms of aspergillosis have been reported in these cases of coinfection such as chronic pulmonary aspergillosis [37,39], allergic broncho-pulmonary aspergillosis [40], chronic necrotising pulmonary aspergillosis [41]. The most frequently isolated species is Aspergillus fumigatus, followed by Aspergillus niger according to a systematic review of case reports [36].

Given the widespread environmental presence of these pathogens, distinguishing colonization from active infection can be challenging [42, 43]. A multidisciplinary approach is essential, requiring collaboration between various specialists to ensure early and accurate diagnosis, maximise therapeutic outcomes, and minimise complications. Treatment is typically prolonged, involving multiple medications with significant adverse effects and potential drug interactions. A major challenge is the interaction between azoles and rifampin, which can lead to subtherapeutic drug levels of the antifungal medications [36,44]. A systematic review of 507 articles, comprising 1538 cases, found that both infections were treated simultaneously in 47.3% of cases, while 23.4% of patients received only antimycobacterial therapy and 1.6% received only antifungal therapy. No treatment was provided in 27.7% of individuals suspected of colonization. Initial clinical improvement was more closely associated with antifungal treatment, because of which some authors recommend starting with antifungal therapy and after its discontinuation to complete the NTM treatment [36].

In our case, microbiologically confirmed diagnosis was initially established for Aspergillus fumigatus, leading to the initiation of antifungal treatment with Itraconazole. Simultaneously, therapy with TMP/SMX was introduced due to the isolation of Nocardia nova. After a culture result confirmed the presence of Mycobacterium avium, the antifungal therapy was reassesed. Due to minimal clinical improvement, lack of Aspergillus-specific IgG-antibodies, negative mycological tests from a follow-up bronchoscopy after six weeks, antifungal treatment was discontinued. Instead, therapy with Rifampin, Ethambutol, and Clarithromycin was initiated.

Nocardiosis is another opportunistic infection primarily affecting individuals with impaired cell-mediated immunity, although it can also occur in immunocompetent individuals without underlying disease [45]. Disease manifestation depends on the site of entry—either pulmonary or cutaneous infection. Dissemination to other organs can occur via the

bloodstream or direct tissue invasion [46]. Risk factors (except in cutaneous infections) include HIV infection, organ transplantation, corticosteroid or immunosuppressive therapy, and diabetes mellitus. Underlying pulmonary diseases such as COPD and bronchiectasis also contribute to increased risk [35,46]. Coinfections have been reported in 20% to 60% of affected individuals in some case series, most commonly with M. tuberculosis, NTM, and fungal infections [47,48].

4. Conclusion

Underlying lung disease and immune dysfunction predispose individuals to infections with opportunistic pathogens such as fungi and nontuberculous mycobacteria. Coinfections worsen prognosis, increase morbidity and mortality, and pose challenges in diagnosis, polypharmacy, and drug interactions, while also requiring concurrent management of the primary disease.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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