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THE BALANCE BETWEEN AUTOIMMUNITY AND INFECTION: A CASE REPORT OF CONCOMITANT PATHOLOGY OF PULMONARY NOCARDIA AND GRANULOMATOSIS WITH POLYANGIITIS AT INITIAL PRESENTATION

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ABSTRACT

Concurrent presentation of pulmonary nocardiosis and granulomatosis with polyangiitis (GPA) is exceptionally rare and diagnostically challenging, given the overlapping clinical and radiological features. We report a 54-year-old female with fever, cough, weight loss, and arthralgia. Chest imaging showed multiple pulmonary nodules; serology revealed positive anti-neutrophil cytoplasmic antibodies -proteinase 3, and lung biopsy demonstrated necrotizing granulomatous inflammation with Nocardia species. This led to a dual diagnosis of pulmonary nocardiosis and limited form GPA. The patient improved with co-trimoxazole however methotrexate is set to be initiated concomitantly with close monitoring as the manifestations of limited form GPA were still present. This case highlights the importance of considering infectious mimics during initial evaluation of suspected vasculitis, the possibility of dual pathology of both entities, and the emphasis of the staged approach of treating such cases in the background of controlling infection followed by initiating immunosuppressive therapy.

KEYWORDS

Granulomatosis with polyangiitis, pulmonary nocardia, immunosuppressive therapy, dual pathology, trimethoprim/sulfamethoxazole

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LEARNING POINTS

- Pulmonary nocardiosis may clinically and radiologically mimic granulomatosis with polyangiitis, and both conditions can rarely present simultaneously.
- Histopathological examination is crucial to distinguish infectious mimics from vasculitis in anti-neutrophil cytoplasmic antibodies-positive patients.
- A stepwise treatment strategy in which controlling infection before initiating immunosuppression can reduce the risk of complications in dual pathology.

INTRODUCTION/BACKGROUND

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is an autoimmune phenotype belongs to anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV). AAV are characterized by necrotizing inflammation affecting small blood vessels predominantly as a result of self-antigen recognition of proteinase 3 (PR3). Several organs are commonly affected by GPA including ear, nose, throat, and pulmonary system, leading to systematic clinical manifestations like constitutional symptoms, hearing loss, epistaxis, skin rash, and arthralgia[1]. The antineutrophil cytoplasmic antibodies-proteinase 3 (ANCA-PR3) biomarker has been playing a role in the diagnosis of GPA however some studies investigated the effects of infectious organisms on ANCA titer as some infections are thought to trigger ANCA positivity and thus mimicking GPA[1,2]. Immunosuppression is the cornerstone in the treatment of GPA however It carries high risk of opportunistic infections such as nocardiosis[1,3]. Nocardiosis is an opportunistic infection caused by *Nocardia* specie, a Gram-positive bacterium which have been described as filamentous, weakly positive acid-fast, branching rods and commonly infects the pulmonary system[4]. As both GPA and pulmonary nocardiosis share similar symptoms, we report this case of an adult female who was newly diagnosed with limited form GPA with concomitant pulmonary nocardia isolated from tissue biopsy at the initial presentation in a rare event.

CASE DESCRIPTION

A 54-year-old lady with a past medical history of diabetes mellitus and hypothyroidism, presented with a productive cough with blood streaks and shortness of breath. The patient also reported night sweat, weight loss, hearing loss, and arthralgia in the last 2 months. Her family history was unremarkable for malignancy or autoimmune diseases. The vital signs were stable, and no pertinent physical findings were found during the assessment of chest, cardiovascular, dermal, lymph nodes, joints, and abdomen. Basic laboratory tests were unremarkable whereas inflammatory markers including erythrocyte sedimentation rate (115 mm/hr) and C reactive protein, (181 mg/l) were significantly elevated. Additionally, the autoimmune serologies revealed a strongly positive ANCA (PR3) titre 119 Units (reference range < 20 Unit), while other autoimmune tests including antinuclear antibodies, rheumatoid factor, and ANCA-myeloperoxidase (MPO) were negative *(Table 1)*.

Bilateral pulmonary nodules were identified on computed tomography (CT) scan of the chest along with mucosal thickening of maxillary sinus in CT sinus. Laboratory investigations to evaluate variable infections were uneventful including respiratory culture, acid-fast bacillus (AFB) smears, and mycobacterial cultures. The histopathological exam from the lung biopsy, which was conducted to rule out possible malignancies, surprisingly described necrotizing granulomatous inflammation with giant cells *(Fig. 1)* alongside AFB-stained thin and filamentous small rods suggesting *Nocardia (Fig. 2)*.

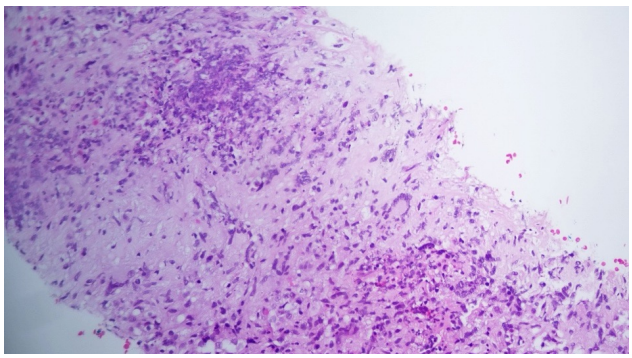


Figure 1. Photomicrograph of the biopsy showing necrotizing granulomatous inflammation with aggregates of histiocytes and multinucleated giant cells. A mixed inflammatory infiltrate is present, including eosinophils and neutrophils (haematoxylin and eosin stain, magnification ×200).

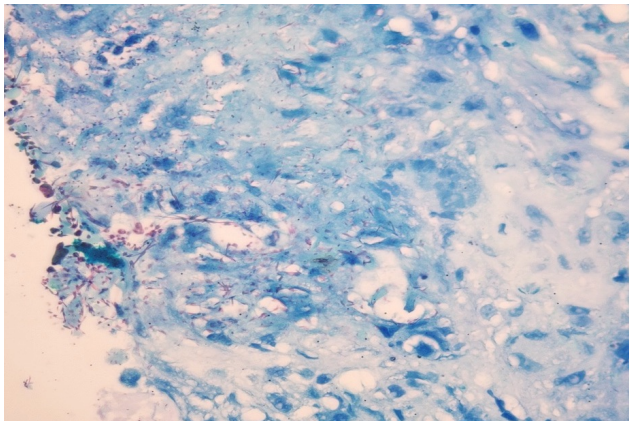


Figure 2. Acid-fast bacillus stain showing thin, filamentous acid-fast bacilli within the necrotic zone, morphologically consistent with Nocardia (Ziehl–Neelsen stain, magnification ×400).

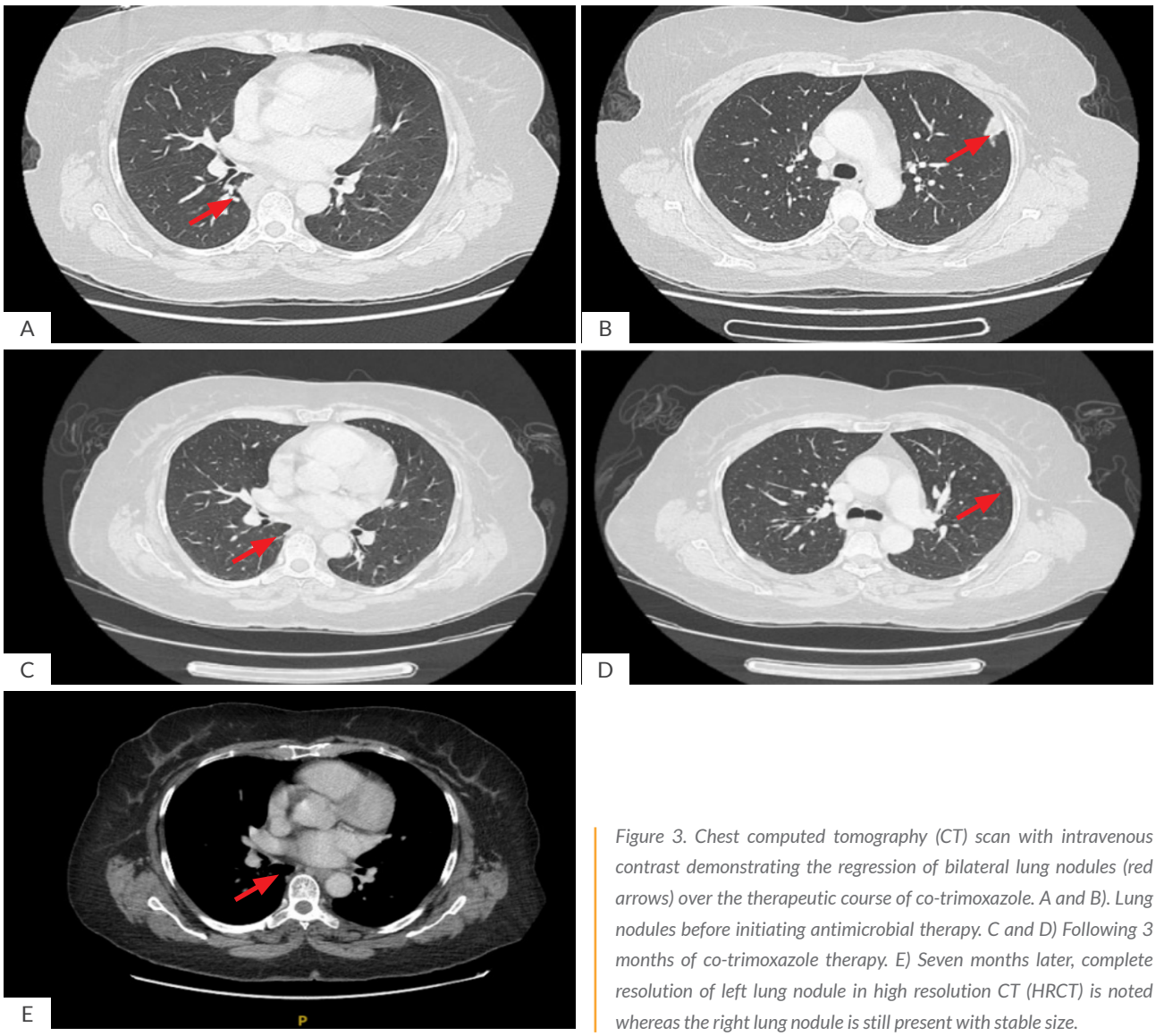


Figure 3. Chest computed tomography (CT) scan with intravenous contrast demonstrating the regression of bilateral lung nodules (red arrows) over the therapeutic course of co-trimoxazole. A and B). Lung nodules before initiating antimicrobial therapy. C and D) Following 3 months of co-trimoxazole therapy. E) Seven months later, complete resolution of left lung nodule in high resolution CT (HRCT) is noted whereas the right lung nodule is still present with stable size.

With the combination of clinical presentation, biochemical, and radiographic findings in addition to histopathological exam, rheumatology expertise couldn't exclude the diagnosis of granulomatosis with polyangiitis (GPA). However, the presence of nocardia species in histopathology was also suppurative of pulmonary nocardiosis given the clinical picture despite the lack of molecular tests such as 16S ribosomal ribonucleic acid (rRNA) sequencing in the facility. As a result, the comprehensive evaluation by rheumatology and infectious diseases specialists concluded the diagnosis to be concurrent pulmonary nocardiosis and limited form GPA. Since there was no focal lesion or acute pathology in CT head suggestive of cerebral nocardiosis, advanced imaging was not further pursued. Bronchoalveolar lavage (BAL) was planned for further identification of *Nocardia* specie by advanced microbiological tests in other hospitals, however the patient rejected the procedure. Consequently, a multidisciplinary decision was made by rheumatology and infectious disease specialists to start oral sulfamethoxazole-trimethoprim (known as co-trimoxazole) double strength 800/160 mg three times daily for 9 months before initiating immunosuppressive therapy in order to control the risk of disseminated nocardiosis. Following up after 3 months of co-trimoxazole therapy, resolution of constitutional and respiratory symptoms was observed in addition to remarkable improvement of lung nodules on CT chest along with achieving negative ANCA titer. Despite the favourable response to antimicrobial therapy, the patient was still complaining of arthralgia, bilateral hearing loss (concluded to be conductive in nature by audiologists), and the development of eye redness (diagnosed to have conjunctivitis by ophthalmologist) with morning stiffness following 7 months of an ongoing antibiotic course. On the other hand, complete resolution of lung nodules *(Fig. 3)* was documented in high resolution CT while others were still present along with re-elevation of the PR3-ANCA titer up to 139.6 *(Table 2)* indicating the need to control limited form GPA.

Therefore, a multidisciplinary approach was set by rheumatology and infectious disease specialists to start oral methotrexate and folic acid on a weekly basis in combination with completing the therapeutic course of 12 months of co-trimoxazole to ensure the resolution of *Nocardia* infection. Besides methotrexate, daily co-trimoxazole double strength

Laboratory test	Results	Reference Range
WBC (×10³/µl)	9.39	3.9-11
Haemoglobin (g/dl)	12	Female: 11-116
Platelets (×10³/µl)	330	150–450
Creatinine (µmol/l)	38	40–90
Sodium (mmol/l)	136	135–145
Potassium (mmol/l)	4.1	3.5–5.1
ALT (U/l)	10	7–55
AST (U/l)	34	5–34
Alkaline phosphatase (U/l)	111	40–150
Total bilirubin (µmol/l)	7	3–30
Albumin (g/l)	35.1	35-55
CRP (mg/l)	181.8	<5
ESR (mm/Hr)	115	<20
ANA (IFA TITER) (Index)	0.7	<1
Rheumatoid factor (IU/ml)	12.5	<30
ANCA (MPO) (Units)	0.98	<20
ANCA (PR3) (Units)	119.76 (moderate to strongly positive)	<20

Abbreviations: WBC, white blood cells; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate, IFA, indirect immunofluorescence assay; ANCA, antineutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3.

Table 1. Laboratory results at the initial presentation.

ANCA (PR3) level at initial presentation	3 months following Co-trimoxazole therapy	7 months following Co-trimoxazole therapy
119.76 units (strongly positive)	13 units (negative)	139.6 units (strongly positive)

Table 2. The trend of antineutrophil cytoplasmic antibodies (ANCA) proteinase 3 (PR3) level: ANCA (PR3) declined after initiating co-trimoxazole treatment. Despite antimicrobial therapy, ANCA (PR3) picked up which indicts unmasked granulomatosis with polyangiitis activity.

is also set to be used as a prophylaxis to other opportunistic infections and prevent nocardiosis relapse.

DISCUSSION

Differentiating GPA from vasculitis mimics is diagnostically challenging due to overlapping clinical presentations and imaging findings. In our case, the combination of PR3-ANCA positivity, pulmonary nodules, ear nose throat (ENT) symptoms (including conductive hearing loss), and arthralgia raised a strong suspicion for GPA. According to the 2022 American College of Rheumatology/European League Against Rheumatism classification criteria, our patient met the diagnostic threshold with a cumulative score of 10 points, comprising: positive ANCA PR3 (+5), conductive hearing loss (+2), pulmonary nodules on imaging (+2), and necrotizing granulomatous inflammation (+1), supporting the diagnosis of GPA[5]. However, this case was complicated by histopathological identification of thin, filamentous, acid-fast organisms morphologically consistent with *Nocardia*. The presence of *Nocardia* within necrotizing granulomas introduced a diagnostic dilemma whether this was a true GPA, a vasculitis mimic, or a coexisting pathology. Although the biopsy did not demonstrate classic vasculitis features such as fibrinoid necrosis or leukocytoclastic vasculitis, which often support a definitive GPA diagnosis, the patient's constellation of symptoms, systemic signs, and PR3-ANCA titer positivity was difficult to explain by nocardiosis alone. This case also underscores a practical limitation in real-world settings— the advanced microbiological confirmation (e.g., matrix-assisted laser desorption/ionization time-of-flight MALDI-TOF, or 16S rRNA sequencing) which is not available in every centre and

the rejection of BAL by the patient, which might have aided speciation. Consequently, the diagnosis and management had to rely on histology, clinical response, and expert consensus. While nocardiosis is a well-known opportunistic infection in immunocompromised patients, especially those on immunosuppressive therapy, simultaneous presentation of nocardiosis with new-onset GPA is extremely rare. Gibb and Williams reported a case where nocardiosis mimicked Wegener's granulomatosis, leading to misdiagnosis and inappropriate immunosuppressive treatment, which worsened the patient's condition[6]. This increased the diagnostic complexity of the current case. Previous case reports, such as those by Hirayama et al. and Kavandi et al., describe the development of nocardiosis after immunosuppressive treatment for GPA[7,8]. Additionally, other case reports described a dual pathology consisting of *Mycobacterium tuberculosis* and granulomatous inflammation with clinical features suggestive of GPA leading to a complex diagnostic and therapeutic process[9]. In contrast, our case highlights a potential dual pathology of *Nocardia* and granulomatous inflammation at the initial presentation, a complex scenario that, to our knowledge, has not been previously documented. The initial favourable response to co-trimoxazole, including resolution of pulmonary nodules and normalization of ANCA PR3 titres, was consistent with nocardial infection. However, persistent ENT symptoms, the re-elevation of PR3-ANCA, and new-onset conjunctivitis after 7 months of antibiotics suggested unmasked GPA activity. Notably, Co-trimoxazole has been proposed to exert immunomodulatory effects that may transiently suppress ANCA activity, which complicates the clinical interpretation of the biomarker[10]. Indeed, the joint decision of initiating antimicrobial agents while delaying the immunosuppressive therapy minimizes the risk of disseminated nocardiosis while still addressing vasculitis progression. In uncertain cases like this, a multidisciplinary team and serial re-evaluation are key to safely navigating dual pathology and avoid serious complications.

Additionally, more research is required to address such dilemmas and develop safe therapeutic interventions to avoid serious complications. This case highlights the utmost necessity of considering vasculitis mimics, the important role of histopathology examination, and the staged treatment strategy, beginning with infection control before initiating immunosuppressive therapy.

CONCLUSION

This report demonstrates the challenging process of diagnosing vasculitis, the importance of considering other differential diagnosis including infectious diseases, and the valuable rule of histopathological examination in such cases. It also sheds light on the possibility of the coexistence of both entities. Moreover, it emphasizes the challenges in the management of infections in the setting of autoimmune diseases and the need for a balanced approach between infection control and immunosuppressive therapy.

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