

Co-Infection with *Nocardia* Terpene and *Pneumocystis jirovecii* in a Patient with Anti-Synthetase Syndrome: A Case Report

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Background: Pulmonary infection is a common clinical complication associated with glucocorticoid. There have been no reported cases of mixed infections involving *Nocardia* and *Pneumocystis jirovecii* combined with anti-synthetase syndrome (ASS) activity.

Methods: This study conducted a retrospective analysis of the clinical data from a patient with active ASS, treated for a pulmonary coinfection.

Results: The patient exhibited fever, asthma, and cough as initial symptoms. Chest CT scan revealed multiple infiltration shadows, consolidation shadows, nodules, mass shadows, and internal cavities in both lungs. BALF mNGS detected *Nocardia* terpene and *Pneumocystis jirovecii*. Treatment with sulfamethoxazole/trimethoprim and corticosteroids led to an improvement. However, the patient experienced recurrent fever and a new rash with the reduction of the glucocorticoid dosage. Further investigation identified positive anti-Jo-1 and anti-Ro-52 antibodies and myogenic lesions on electromyography, which confirmed the diagnosis of ASS. Following treatment with immunoglobulin, methylprednisolone, and cyclosporine, the patient's condition significantly improved.

Conclusion: Immunodeficiency patients are susceptible to opportunistic infections. mNGS is valuable for diagnosis and treatment. Although the image of *Nocardia* terpene and *Pneumocystis jirovecii* infections lack specificity, they exhibit distinctive features. Should fever and skin lesions reoccur post-effective anti-infective therapy, it is imperative to explore non-infectious causes and expedite autoantibody testing.

Keywords: co-infection, *Nocardia* terpene, *Pneumocystis jirovecii*, anti-synthetase syndrome, anti-Ro-52 antibody, anti-Jo-1 antibody

Case Presentation

A 51-year-old male who was admitted to the hospital due to fever, asthma, cough, and sputum production for 3 days. The body temperature was not measured with no obvious and no chills. There were wheezing, coughing, and white purulent sputum. Occasionally there were dark red blood streaks in the sputum, accompanied by right side chest pain. There was no other symptoms. In 2022, The patient was diagnosed with non-infectious uveitis and was treated with methylprednisolone and cyclosporine.

On admission, Physical Examination revealed temperature of 38.9°C, heart rate of 130 beats/min, and respiratory rate of 20 breaths/min. He has a moon face, muscle atrophy of limbs and less subcutaneous fat. No rashes or ulcers were found on the skin and mucous membranes of the whole body. Percussion in the right lower lung showed solid sounds and coarse breath sounds, and wet rales were heard in both lower lungs. The muscle strength and tone of the limbs were unremarkable.

The laboratory tests after admission showed the The white blood cells of $10.62 \times 10^9/L$ and the neutrophil percentage of 82.9%; T lymphocyte count: CD3+CD4 percentage 12.52%, CD4+/CD8+: 0.34, absolute total lymphocyte count 45, suppressor/cytotoxic T lymphocyte count 11, helper/induced T lymphocyte absolute count 32 individual. Human immunodeficiency virus (HIV) antibody test, Serum Aspergillus galactomannan test, Aspergillus IgG antibody, Candida mannan antigen, and Candida IgG antibody results were all negative. Collect the patient's bronchoalveolar lavage fluid (BALF) and send to our microbiological laboratory for smear and culture and sent to Wuhan Kangsheng Zhenyuan Medical Laboratory Co., Ltd. (Wuhan, China) for the pathogenic microorganism metagenomic detection (mNGS). The mNGS analysis identified 73406 sequence reads corresponding to the *Nocardia* terpene genome, with 51.61% coverage and 538 sequence reads corresponding to the *Pneumocystis jiroveci* genome, with 0.38% coverage. Gram stain of sputum smear: Gram-positive bacilli; sputum culture: *Nocardia* terpene (Figure 1A–1D). Drug susceptibility test showed: amikacin, ciprofloxacin, linezolid, sulfamethoxazole(SMX)/trimethoprim(TMP), tobramycin, gentamicin sensitive, amoxicillin/clavulanic acid resistant. Chest computed tomography (CT) showed the both lung fields was unevenly reduced, showing mosaic changes, interstitial thickening, solid nodules, ground glass nodules, and halo signs around some parts. And the right lung There were flake-like high-density shadows with rough edges in the lower leaves, and patchy low-density necrosis, smooth inner walls of the cavities were seen inside. Multiple nodular high-density shadows of varying sizes were seen in each lobe of both lungs. Cord shadows in the left upper lung. An arc-shaped watery density shadow was seen on the right side of the chest (Figure 2A–2C). Fiberoptic bronchoscopy showed congestion and edema in the posterior basal mucosa of the right lower lobe (Figure 3). Then the patient was given

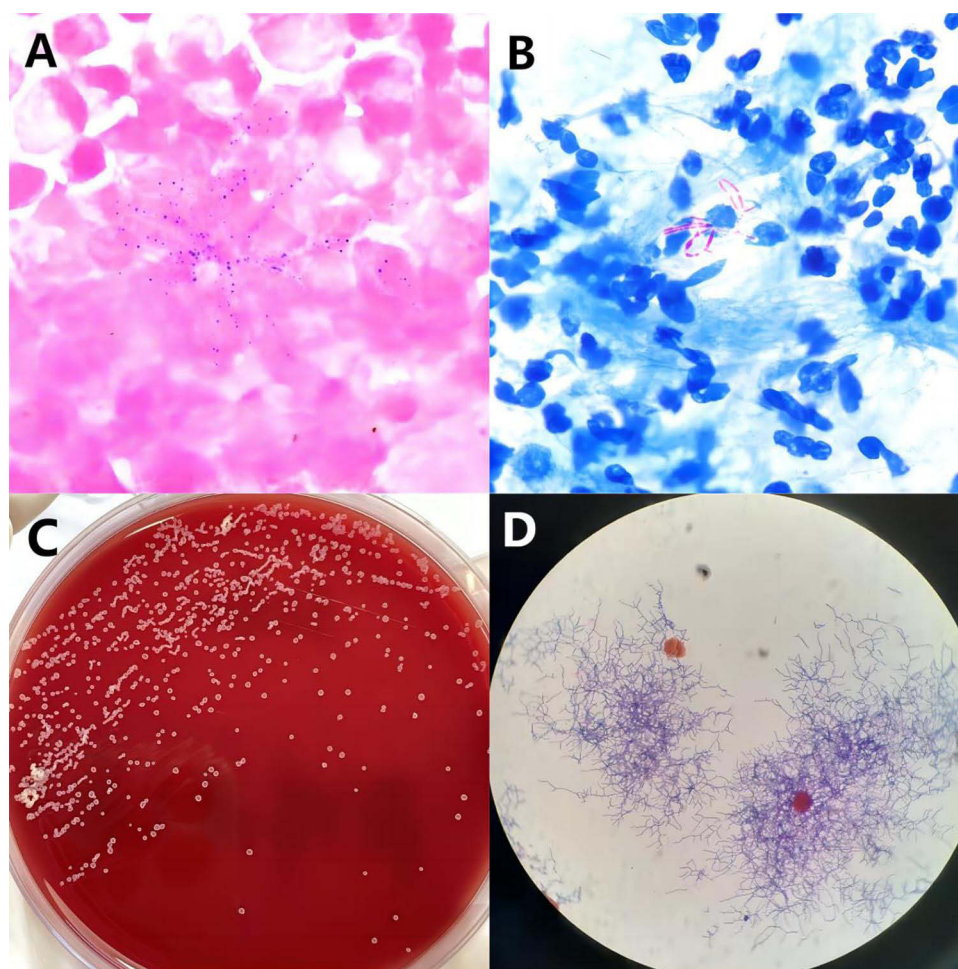


Figure 1 (A) A Microscopic examination of sputum smears with Gram stain. (B) Microscopic examination of sputum smears with weak acid-fast stain. (C) Colony morphology observed on blood agar plates after 48 hours of incubation. (D) Gram stain microscopic examination of direct smears of bacterial colonies.

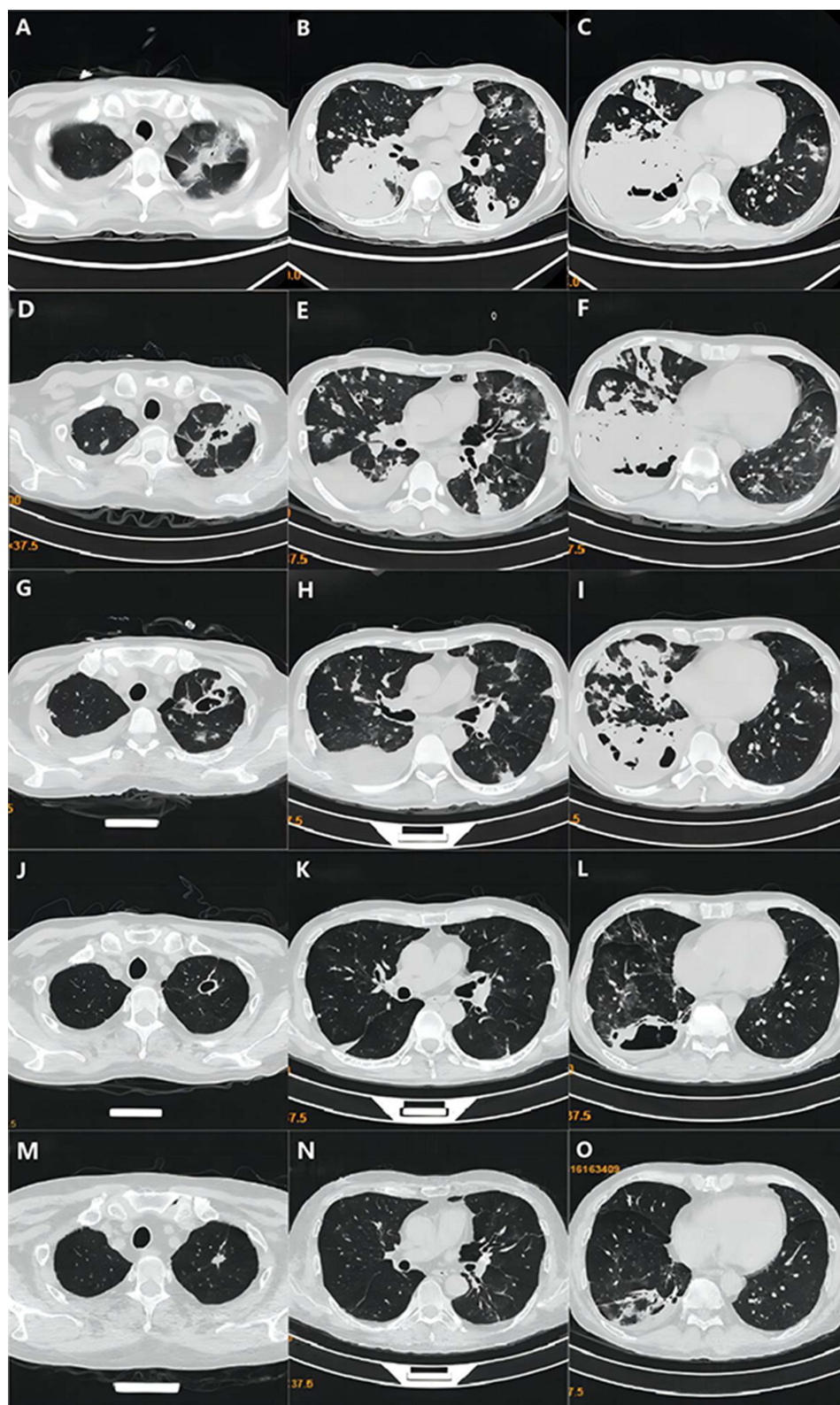


Figure 2 Chest CT imaging changes of the patient. (A–C) The imaging result on March 30 shows the both lung fields was showing mosaic changes, interstitial thickening, solid nodules, ground glass nodules. The right lung There were pleural effusion and flake-like high-density shadows with cavities inside. Striped shadow in the left upper lung. (D–F) The imaging result was on April 3. (G–I) The imaging result after 2 days after treatment (April 25). (J–L) The imaging result after treatment (June 7). (M–O) The imaging result after treatment (August 17) shows that the Lesion was further reduced.

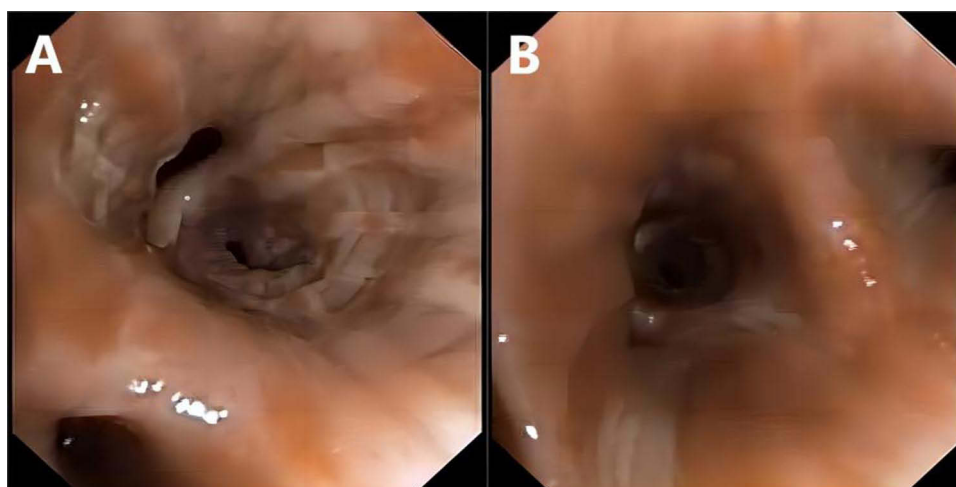


Figure 3 (A and B) Bronchoscopy showed congestion and edema in the mucosa of the basal segment of the right lower lobe.

imipenem-cilastatin 1 g qid, SMX-TMP 4 tablets qid, linezolid 0.6 g bid, caspofungin 50 mg qd for anti-infection, and methylprednisolone 80 mg qd for anti-inflammatory treatment. After 3 days, the patient's symptoms improved and his temperature became normal. However, after the prednisone was reduced to 20 mg, the patient developed fever again. Painful ulcers appeared on the tongue and tip of the tongue, and red rashes were scattered on the neck and chest (Figure 4). Chest CT showed that the cavity in the lesion in the lower lobe of the right lung was more obvious than before (Figure 2D–2F). Relevant examination tips are improved: rheumatoid factor, direct antiglobulin test, anti-Sm antigen, anti-keratin antibody, anti-nuclear antibody ANA, anti-double-chain antibody Antibodies to dsDNA, vasculitis-related antibodies, and gamma-interferon autoantibodies were all negative. The serum was sent to Wuhan Kangsheng Zhenyuan Medical Laboratory Co., Ltd. (Wuhan, China) For the dermatomyositis tests. It showed: anti-Jo-1 antibody, anti-Ro-52 antibody, and anti-RNP A antibody were positive. Electromyogram showed myogenic damage to the left biceps brachii, right deltoid muscle, and bilateral quadriceps muscles. Immunoglobulin 7.5 g qd, methylprednisolone 8 mg bid and cyclosporine 20mg bid were added to the original anti-infection treatment plan. After 2 days, the patient's symptom were relieved. Repeat chest CT showed that the nodular, patchy, and cord-like high-density shadows in both lungs were reduced compared with before (Figure 2G–2I).

Confirmed diagnosis: *Nocardia terpenae* combined with *Pneumocystis jirovecii* infection, along with overlap syndrome including NIU and anti-synthetase syndrome (ASS).



Figure 4 (A and B) Red and scattered rash on the patient's neck and chest.

Following discharge, treatment with oral methylprednisolone and cyclosporine was continued and gradually reduced. A follow-up chest CT on June 7 showed a reduction in nodular, patchy, and cord-like high-density shadows in both lungs, as well as absorption of high-density lesions and effusion in the right pleural cavity (Figure 2J–2L). Subsequent chest CT on August 17 revealed further reduction in shadows and cavity in the right lung, with no effusion in either pleural cavity. Methylprednisolone and cyclosporine were then discontinued (Figure 2M–2O). The patient's condition has remained stable with no recurrence of respiratory symptoms, oral ulcers, rash, or limb weakness since follow-up.

Discussion

Nocardia and *Pneumocystis jirovecii* are opportunistic pathogens known to cause infections. Clinically, fever and cough are frequently observed symptoms. The occurrence of nocardiosis is primarily associated with immune deficiencies resulting from conditions such as diabetes, HIV infection, and connective tissue diseases. However, it is important to note that there are also cases where patients do not have any underlying diseases. Patients with Pulmonary nocardiosis (PN) usually present with purulent sputum, while those with *Pneumocystis carinii* pneumonia (PCP) often have a dry cough. *Nocardia* typically leads to acute or chronic purulent or granulomatous changes, while *Pneumocystis jirovecii* often causes interstitial plasma cell pneumonia, with purulent changes being uncommon. The clinical symptoms, signs and CT images of *Nocardia* and *Pneumocystis jirovecii* infections are non-specific, requiring etiological examination for diagnosis. *Nocardia* is significant when found in clinical samples. Sputum smear microscopy demonstrated branched Gram-positive bacilli being engulfed by leukocytes (Figure 1A). Weak acid-fast staining of the bacterial smear was positive (Figure 1B). Following 48 hours of sputum culture, small dry off-white colonies were observed on the blood agar plate (Figure 1C). By 72 hours, the colonies had grown larger with dry, wrinkled surfaces. Direct microscopic examination revealed slender, curved branching hyphae (Figure 1D). *Nocardia* was confirmed through positive weak acid-fast staining and MALDI-TOF-MS identification. mNGS can offering a sensitive method for rare disease identification.¹

ASS is a type of idiopathic inflammatory myopathy (IIM) characterized by positive anti-aminoacyl-tRNA synthetase (ARS) antibodies, particularly anti-Ro-52 and anti-Jo-1 antibodies, etc. often appear together. ASS often presents with interstitial lung disease (ILD), with imaging findings commonly showing non-specific interstitial pneumonia (NSIP) or NSIP-organizing pneumonia (OP). Common imaging features include ground-glass opacities, reticular opacities, traction bronchiectasis, and consolidation, while honeycomb opacities are less frequent.^{2,3}

In this case, the patient tested negative for HIV but showed significantly reduced CD4⁺ and CD8⁺ T lymphocyte counts, possibly due to long-term use of hormones and cyclosporine for immunosuppression related to UIN. This led to infections with *Nocardia* and opportunistic infections with *Pneumocystis jirovecii*. Following treatment with hormones and effective anti-infectives, the patient's respiratory symptoms and fever showed significant improvement, along with a decrease in inflammatory indicators. Nevertheless, the patient experienced a recurrence of fever and rash upon tapering steroids, prompting consideration of non-infectious factors such as drug-induced fever and rheumatic diseases. Based on the patient's positive ARS and electromyography results, the diagnosis of ASS was considered. Unfortunately, during the diagnosis and treatment process, a biopsy of the patient's rash and lung was not performed to determine the pathological changes of the disease.

To date, there have been no documented cases of uveitis co-occurring with ASS or positive combinations of anti-Jo-1 and anti-Ro-52 antibodies in the existing literature. The specific mechanism underlying the development of ASS remains unclear. However, a study has suggested that respiratory tract infections could elevate the risk of IIM.⁴ It is hypothesized that infections might instigate local inflammation, heighten the overall inflammatory load, or activate the immune system, potentially leading to the onset of IIM through the stimulation of autoreactive lymphocytes and autoantibody production.^{5,6}

Treatment for *Nocardia* and *Pneumocystis jirovecii* typically involves SMX-TMP.^{7–10} *Pneumocystis jirovecii* treatment consists of SMX-TMP at a dose of 15 mg/kg/day for 3–4 weeks, followed by 10 mg/kg/day for 3–4 months. For PCP treatment, glucocorticoids are administered before SMX-TMP and then SMX-TMP at a dose of 15 mg/kg/day for 21 days.¹¹ A case study of an immunodeficient patient diagnosed using mNGS showed improvement with anti-infective, antifungal, and anti-inflammatory treatment. Regarding ASS, glucocorticoids are usually the initial treatment for patients

without contraindications. The initial treatment dose is typically continued for 4–12 weeks until clinical symptoms improve and muscle enzyme concentrations decrease, after which the dose is gradually tapered.¹² Most ASS patients also require concurrent immunosuppressive therapy.¹³ In cases of refractory myositis, biological agents or intravenous immune globulin (IVIG) can be considered as additional treatment.¹²

Conclusion

This case emphasizes the importance of clinicians investigating the underlying causes of low immune function when encountering significantly low CD4+/CD8+ levels or co-occurring opportunistic infections. Utilizing mNGS proves to be highly effective in diagnosing co-infections caused by *Nocardia* terpene and *Pneumocystis carinii*. Additionally, in cases where ILD, rash, and recurrent fever persist despite anti-infective treatment, consideration should be given to non-infectious causes such as autoimmune diseases for early detection and intervention. If feasible, conducting pathological biopsies of skin and lung tissue can provide further insights into the disease's pathological changes. Treatment with SMX-TMP demonstrates efficacy against *Nocardia* terpene and *Pneumocystis carinii* infections, while a combination of hormones and immunosuppressants plays a critical role in ASS treatment, necessitating careful evaluation of drug selection, dosage, and duration based on individual patient conditions.

Abbreviations

ASS, anti-synthetase syndrome; BALF, bronchoalveolar lavage fluid; mNGS, microorganism metagenomic detection; SMX, sulfamethoxazole; TMP, trimethoprim; CT, computed tomography; PN, Pulmonary nocardiosis; PCP, *Pneumocystis carinii* pneumonia; NSIP, non-specific interstitial pneumonia; NSIP-OP, non-specific interstitial pneumonia-organizing pneumonia; IVIG, intravenous immune globulin.

Ethics Approval and Informed Consent

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent to have the case details and any accompanying images published has been provided by the patient.

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Disclosure

The authors report no conflicts of interest in this work.

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