American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2026; 27: e953438
DOI: 10.12659/AJCR.953438

Received: 2026.03.15
Accepted: 2026.06.24
Available online: 2026.08.07
Published: 2026.XX.XX

Pulmonary Actinomycosis Diagnosed via BALF mNGS in a 53-Year-Old Nonsmoking Man With Pneumoconiosis and Penicillin-Induced Thrombocytopenia: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Financial support: This work was supported by the National Natural Science Foundation of China (NSFC82202544) and the Guangxi Key Research and Development Program (2024AB17061)

Conflict of interest: None declared

Patient: Male, 53-year-old

Final Diagnosis: Pulmonary actinomycosis

Symptoms: Cough and hemoptysis

Clinical Procedure: —

Specialty: Laboratory Diagnostics • Infectious Diseases • Pharmacology and Pharmacy

Objective: Unusual clinical course

Background: Pulmonary actinomycosis is an uncommon infection with nonspecific clinical and radiologic features that can be difficult to distinguish from lung malignancy, tuberculosis, and other chronic pulmonary diseases. This report describes a patient with pneumoconiosis in whom bronchoalveolar lavage fluid (BALF) metagenomic next-generation sequencing (mNGS) provided important microbiologic evidence to support the diagnosis of pulmonary actinomycosis after inconclusive conventional evaluation.

Case Report: A 53-year-old nonsmoking presented with a 1-month history of cough and hemoptysis. Chest computed tomography showed bilateral upper-lung masses, multiple nodules, and lymphadenopathy; he initially underwent right upper lobectomy because malignancy was suspected. Histopathologic examination showed necrotizing granulomatous inflammation with carbon deposition, but no specific pathogen was identified. Empirical antituberculosis treatment was ineffective. After transfer to our hospital, bronchoscopy was performed. Routine BALF culture and staining results were negative, whereas mNGS detected *Actinomyces israelii*. Intravenous ampicillin/sulbactam led to clinical and radiologic improvement, but severe thrombocytopenia developed. Platelet counts decreased again after subsequent penicillin exposure, supporting probable penicillin-induced thrombocytopenia. After discontinuation of penicillin and joint evaluation by respiratory physicians and clinical pharmacists, omadacycline was administered, followed by oral doxycycline. The patient displayed clinical improvement, platelet counts normalized, and follow-up imaging showed lesion absorption.

Conclusions: This case illustrates the diagnostic difficulty of pulmonary actinomycosis in a patient with pneumoconiosis and suggests that BALF mNGS can be helpful when routine studies are unrevealing. It also indicates that omadacycline is a feasible alternative when penicillin-associated thrombocytopenia prevents continuation of first-line therapy.

Keywords: Pneumoconiosis • Thrombocytopenia • Actinomycosis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/953438

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Introduction

Pulmonary actinomycosis is an uncommon chronic bacterial infection caused by *Actinomyces* species, most commonly *Actinomyces israelii*. Its clinical presentation and computed tomography (CT) findings are often nonspecific; the disease may be difficult to distinguish from lung cancer, tuberculosis, or other chronic pulmonary infections [1,2].

The diagnosis of pulmonary actinomycosis can be challenging. Conventional culture has limited sensitivity because *Actinomyces* species are fastidious anaerobes, and prior antibiotic exposure may further reduce microbiologic yield [3]. Histopathologic examination and microbiologic confirmation remain important, but bronchoalveolar lavage fluid (BALF) metagenomic next-generation sequencing (mNGS) can provide additional pathogen information in selected patients when routine studies are unrevealing [4].

Penicillin-based therapy is the standard treatment for pulmonary actinomycosis [4]. However, severe drug-induced thrombocytopenia may require interruption of first-line therapy and selection of an alternative antimicrobial agent [5]. This report describes a patient with pneumoconiosis and a pulmonary actinomycosis diagnosis supported by BALF mNGS, whose treatment course was complicated by probable penicillin-induced thrombocytopenia. It highlights the diagnostic contribution of BALF mNGS in a clinically challenging case of pulmonary actinomycosis, along with the use of omadacycline after penicillin was discontinued because of severe thrombocytopenia.

Case Report

A 53-year-old nonsmoking man presented with a 1-month history of cough and hemoptysis. He had initially been treated at a local clinic for presumed pneumonia with cefuroxime and levofloxacin, but his symptoms did not improve. Further evaluation showed negative results for serum 1,3-β-D-glucan, galactomannan, cryptococcal antigen, T-cell testing for tuberculosis infection, autoantibodies, and human immunodeficiency virus screening. Initial sputum and blood culture findings also were negative. Chest CT showed masses and nodules in both upper lobes with mediastinal lymphadenopathy (**Figure 1A**). Pulmonary tuberculosis was initially considered, and scar carcinoma could not be excluded. Thus, the patient underwent right upper lobectomy with lymph node dissection.

Postoperative histopathologic examination of the surgical specimen showed necrotizing granulomatous inflammation

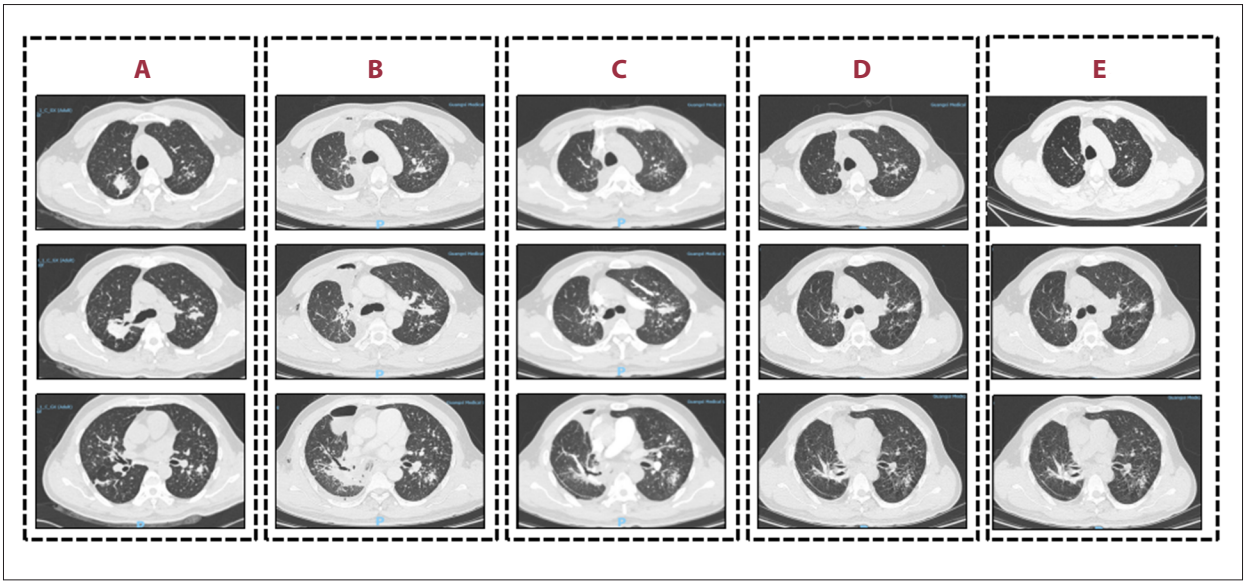

Figure 1. Chest computed tomography (CT) findings at various clinical stages. (**A**) Before surgery: CT images show irregular contrast-enhanced soft-tissue masses in the bilateral upper lungs, multiple bilateral solid nodules, and enlarged lymph nodes in the right supraclavicular fossa and mediastinum. (**B**) After surgery and 2 weeks of antituberculosis therapy (isoniazid, rifampin, ethambutol, and pyrazinamide): CT images show postoperative distortion of the right lung architecture, right hydropneumothorax, persistent bilateral solid nodules without appreciable interval resolution, and persistent lymphadenopathy in the right supraclavicular fossa and mediastinum. (**C**) After 12 days of treatment with penicillin sodium: CT images show prominent resolution of the pulmonary lesions compared with previous images. (**D**) After 2 weeks of omadacycline treatment: CT images show further interval resolution of the pulmonary lesions. (**E**) After 4 weeks of omadacycline followed by 6 months of doxycycline treatment: CT images show continued resolution and improvement of the pulmonary lesions.

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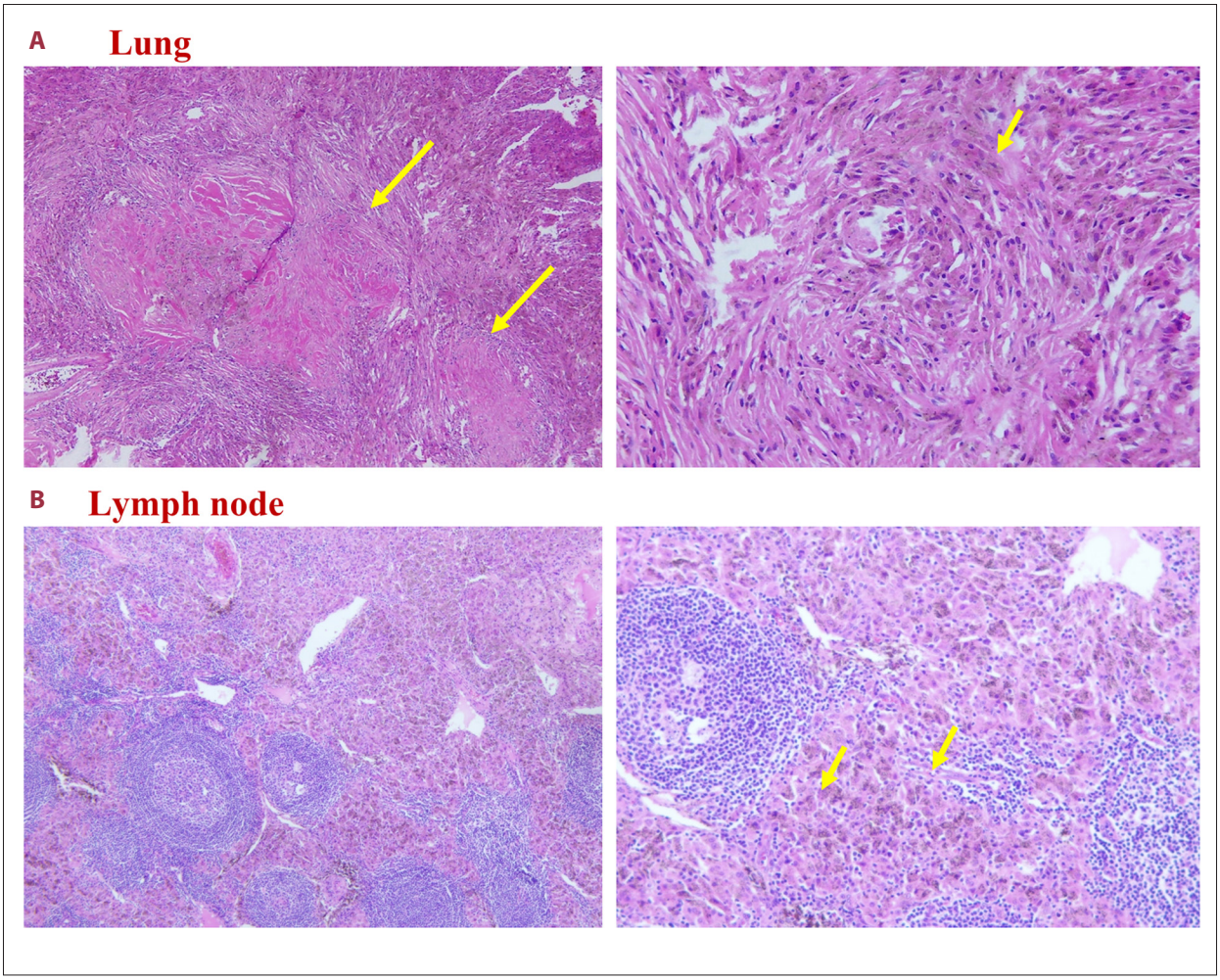
with carbon dust deposition (**Figure 2A, 2B**). Periodic acid-Schiff (PAS), PAS with diastase (PAS-D), and acid-fast staining results all were negative. On the basis of the pathologic findings and occupational history, pneumoconiosis with possible pulmonary tuberculosis was considered; empirical antituberculosis therapy with isoniazid, rifampin, ethambutol, and pyrazinamide was initiated. However, the response was poor. Two weeks later, the patient was admitted to our hospital because of worsening cough and new-onset yellow sputum production.

According to the patient, he had no smoking history and had worked in spray painting for 10 years. He also reported a history of eating wild bamboo rats. He had no recent travel history and had not taken any other medications before visiting the hospital. On admission, laboratory testing showed a white blood cell count of 14.28×10^9/L (reference range, 3.5-9.5 × 10^9/L), neutrophil proportion of 88.5% (reference range, 40%-75%), C-reactive protein level of 47.18 mg/L (reference range, 0-10 mg/L), and erythrocyte sedimentation rate of 75.2 mm/h (reference range, 0-15 mm/h). The CD3+CD4+ T-cell count was 396/μL (reference range, 550-1400/μL). Repeat chest CT showed a postoperative right-sided pneumothorax with persistent pulmonary nodules and lymphadenopathy (**Figure 1B**). Because the clinical course was inconsistent with an effective response to antituberculosis therapy, the initial working diagnosis was reconsidered.

Bronchoscopy was performed. BALF smear and culture results were negative. On admission day 15, BALF mNGS detected *A. israelii* (**Figure 3A**). Given the clinical course, imaging findings, and lack of evidence supporting tuberculosis or other common pathogens, the patient was diagnosed with pulmonary actinomycosis in the setting of pneumoconiosis. Antituberculosis therapy was discontinued.

Subsequently, the patient was given intravenous ampicillin/sulbactam. After 1 week, his symptoms improved, the C-reactive protein level returned to normal. However, the platelet count abruptly fell to 11×10^9/L (reference range, 125-350 × 10^9/L). He was urgently treated with platelet transfusion and recombinant human interleukin-11, and the platelet count gradually stabilized. On admission day 30, antimicrobial therapy was



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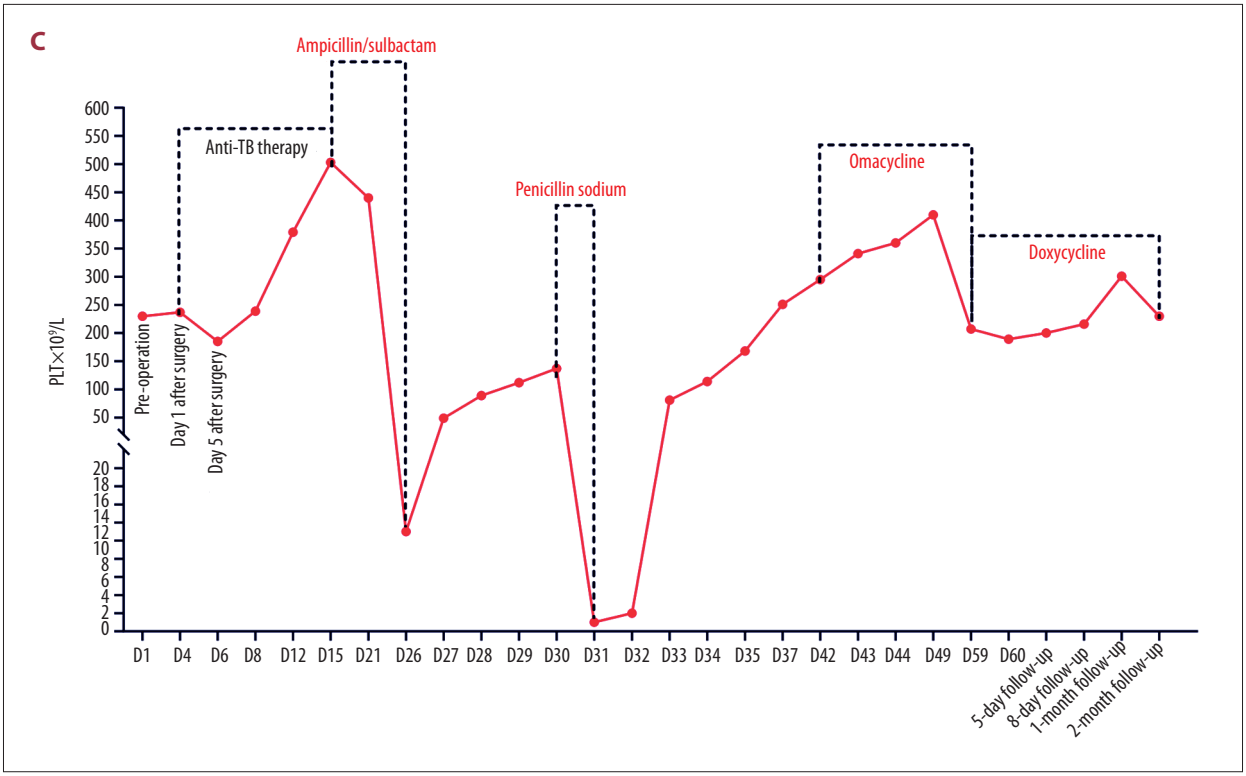

Figure 2. Histopathologic and hematologic findings. (**A, B**) Histopathologic examination of the surgical lung and lymph node specimens showed necrotizing granulomatous inflammation with carbon deposition and numerous macrophages containing carbon particles. (**C**) Changes in platelet count during the treatment course. Abbreviations: PLT, platelets; TB, tuberculosis.

changed to intravenous penicillin sodium. After this change, the platelet count fell further to 1 × 10^9/L, and petechiae developed on the extremities. Nevertheless, follow-up CT showed a reduction in pulmonary nodule size (**Figure 1C**).

A multidisciplinary clinical review was then undertaken. Sepsis, disseminated intravascular coagulation, autoimmune disease, and hematologic malignancy were excluded. The adverse drug reaction was assessed using the Naranjo scale, with a score of 8 (**Table 1**), supporting a diagnosis of penicillin-associated thrombocytopenia. Because penicillin could no longer be used, an alternative regimen was required. Considering the relatively low hematologic toxicity of tetracycline-class agents, omadacycline was initiated. After the change in treatment, the patient's symptoms improved, and the platelet count remained stable. After 2 weeks of omadacycline, follow-up chest CT showed further radiologic improvement of the pulmonary lesions (**Figure 1D**). Treatment was then stepped down to oral doxycycline, and the patient was discharged.

At the 6-month follow-up, chest CT showed continued improvement of the pulmonary lesions (**Figure 1E**). The platelet count remained within the normal range (**Figure 2C**), and no recurrent life-threatening thrombocytopenia occurred. On January 10, 2025, BALF was sampled again for mNGS, which continued to detect *A. israelii* (**Figure 3B**). Doxycycline therapy was therefore continued, and the patient's respiratory symptoms greatly improved. The clinical timeline of diagnosis and treatment is summarized in **Figure 4**.

Discussion

Pulmonary actinomycosis remains a difficult clinical diagnosis because its symptoms, imaging findings, and even histopathologic features are often nonspecific [3]. Patients may present with cough, sputum production, hemoptysis, fever, mass-like lesions, nodules, cavitation, or lymphadenopathy; these findings can overlap with those of tuberculosis, lung cancer, or other chronic pulmonary infections [4]. Reported data indicate that the initial diagnostic accuracy is less than 4% to 7%; more than 25% of cases are misdiagnosed as lung cancer, and many others are misdiagnosed as tuberculosis [4,6,7]. In the present case, bilateral upper-lung masses and nodules with lymphadenopathy, along with necrotizing granulomatous inflammation on histopathology, initially raised concern regarding pulmonary tuberculosis and possible scar carcinoma. The diagnosis was further complicated by the patient's pneumoconiosis, which contributed underlying structural lung disease and carbon dust deposition to the histopathologic background.

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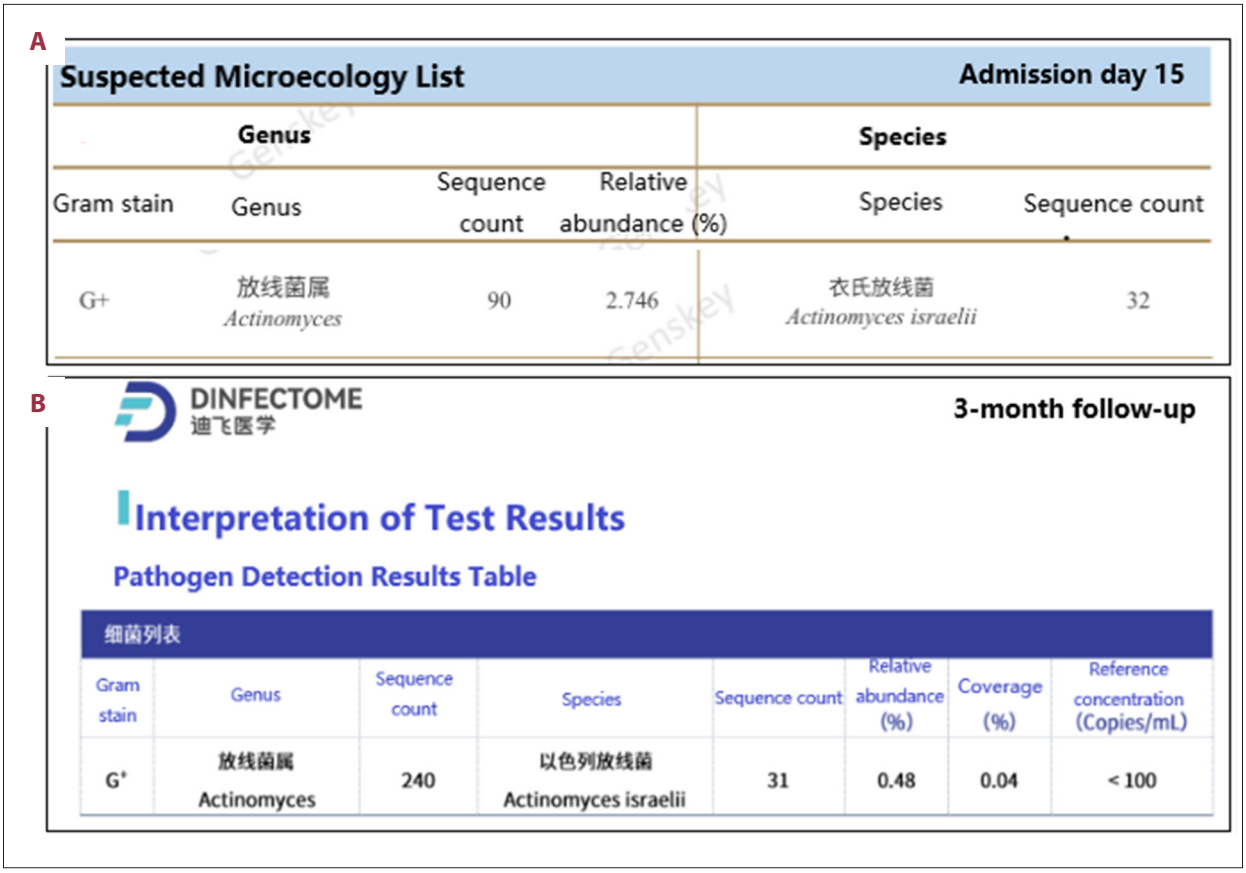

A

Suspected Microecology List — **Admission day 15**

Genus				Species	
Gram stain	Genus	Sequence count	Relative abundance (%)	Species	Sequence count
G+	放线菌属 *Actinomyces*	90	2.746	衣氏放线菌 *Actinomyces israelii*	32

B

DINFECTOME 迪飞医学 — **3-month follow-up**

Interpretation of Test Results

Pathogen Detection Results Table

细菌列表

Gram stain	Genus	Sequence count	Species	Sequence count	Relative abundance (%)	Coverage (%)	Reference concentration (Copies/mL)
G+	放线菌属 Actinomyces	240	以色列放线菌 Actinomyces israelii	31	0.48	0.04	< 100

Figure 3. Serial BALF mNGS results. Image shows BALF mNGS findings from admission day 15 (**A**), and 3-month follow-up (**B**). In panel A, *Actinomyces israelii* was identified as a suspected pathogenic microorganism, with 32 sequence reads. In panel B, *Actinomyces israelii* was identified as a pathogenic microorganism, with 31 sequence reads. Abbreviations: BALF, bronchoalveolar lavage fluid; mNGS, metagenomic next-generation sequencing.

A central lesson from the present case is that pulmonary actinomycosis can remain unrecognized when routine microbiologic and histopathologic findings are nondiagnostic. In our patient, sputum culture, blood culture, BALF smear, BALF culture, and multiple serologic test results were negative. Histopathology showed necrotizing granulomatous inflammation, but special stains did not identify a specific pathogen. Although *Actinomyces* infection is typically confirmed by histologic sulfur granules, anaerobic culture, or tissue-based microbiologic testing, these findings are not always obtained in routine practice—particularly after prior antibiotic exposure or when clinical specimens are limited [6,7]. Accordingly, molecular methods such as mNGS may be useful when routine studies do not provide a definitive diagnosis [8]. In the present case, BALF mNGS provided an important diagnostic clue by detecting *A. israelii*. This finding was not interpreted in isolation but was considered along with the patient's clinical course, the lack of evidence supporting tuberculosis or other common pathogens, and the subsequent response to anti-*Actinomyces* therapy. Thus, our case illustrates the practical value of mNGS as an adjunctive diagnostic tool when conventional studies are unrevealing and the diagnosis remains uncertain.

The diagnosis of pneumoconiosis also warrants attention [9]. Our patient had a 10-year occupational history of spray-painting work, postoperative histopathology showed carbon dust deposition, and the imaging findings were consistent with chronic structural lung disease. These factors supported the diagnosis of pneumoconiosis and likely contributed to the diagnostic complexity [9]. Chronic lung injury and impaired local clearance may create a setting in which uncommon infections are more difficult to distinguish from malignancy, mycobacterial disease, or postoperative changes [1]. In our patient, pneumoconiosis was both a comorbidity and a contributing factor to diagnostic uncertainty early in the clinical course.

Another important feature of the present case was the treatment-limiting adverse drug reaction. Penicillin-based therapy remains the standard treatment for actinomycosis; our patient initially showed clinical, laboratory, and radiologic improvement after ampicillin/sulbactam. However, the abrupt

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Table 1. Naranjo scale.

No.	Question	Score				
		Yes	No	Do Not Know	Ampicillin/ Sulbactam	Penicillin G
1	Are there previous conclusive reports of this reaction?	**+1**	0	0	+1	+1
2	Did the adverse event appear after the suspected drug was administered?	**+2**	-1	0	+2	+2
3	Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	**+1**	0	0	+1	+1
4	Did the adverse event reappear when the drug was readministered?	+2	-1	**0**	0	0
5	Could alternative causes have caused the reaction on their own?	-1	+2	0	+2	+2
6	Did the reaction reappear when a placebo was given?	-1	+1	**0**	0	0
7	Was the drug detected in blood or other fluids at concentrations known to be toxic?	+1	0	**0**	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	**0**	0	0
9	Did the patient have a similar reaction to the same or similar drugs during any previous exposure?	**+1**	0	0	+1	+1
10	Was the adverse event confirmed by any objective evidence?	**+1**	0	0	+1	+1
Total score					**8**	**8**

Total score	Interpretation
≥ 9	Definite
5 to 8	**Probable**
1 to 4	Possible
< 0	Doubtful

decline in platelet count after β-lactam exposure, followed by a more severe recurrence upon administration of penicillin sodium, strongly suggested a drug-related cause. Other potential causes of thrombocytopenia (eg, sepsis, disseminated intravascular coagulation, autoimmune disease, and hematologic malignancy) were excluded during multidisciplinary evaluation. The Naranjo score was 8, supporting a probable drug-induced reaction [5]. In this context, continued penicillin therapy was inappropriate, and an alternative antimicrobial regimen was required.

Tetracyclines are recognized alternatives for the treatment of actinomycosis. In the present case, omadacycline, an aminomethylcycline, was selected after penicillin discontinuation because ongoing antimicrobial therapy was still required and additional hematologic toxicity was a major concern. Its selection was supported by several practical considerations [10-12]: preserved tetracycline activity despite common resistance mechanisms involving efflux pumps and ribosomal protection, in vitro activity against anaerobic gram-positive organisms, the absence of a clear association with thrombocytopenia in available clinical data, and the convenience of both intravenous and oral administration without routine renal or hepatic dose adjustment.

After omadacycline had been initiated, the patient's respiratory symptoms improved, platelet counts remained stable, and follow-up imaging showed continued radiologic improvement. He was subsequently transitioned to oral doxycycline and remained clinically stable during follow-up. Although no broad

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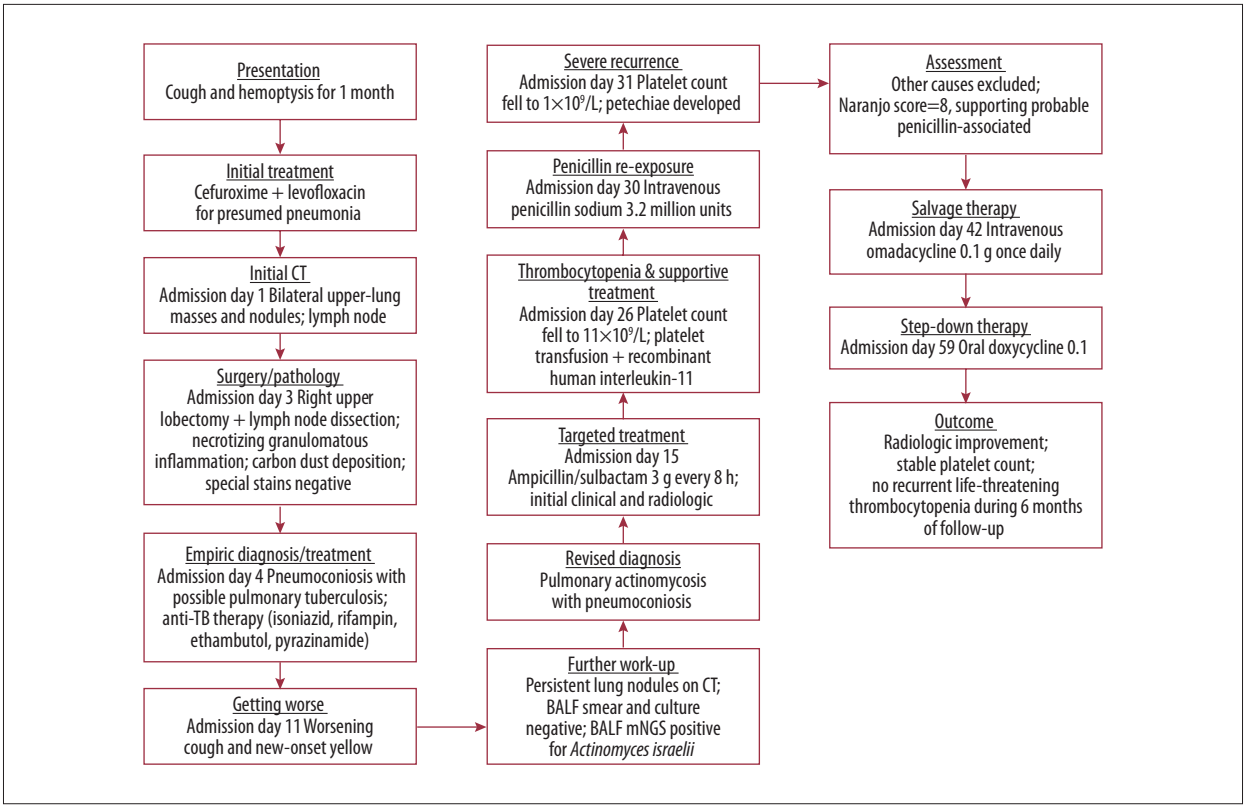

Figure 4. Clinical timeline of diagnosis and treatment. Abbreviations: BALF, bronchoalveolar lavage fluid; CT, computed tomography; TB, tuberculosis.

treatment recommendation can be made based on a single case, the present clinical course suggests that omadacycline is a reasonable alternative for selected patients with pulmonary actinomycosis when penicillin cannot be continued because of severe thrombocytopenia.

The present case also highlights the value of multidisciplinary management in complex infectious diseases. Final diagnosis and treatment decisions were not based on a single test result or the opinion of a single specialty. Instead, the case required integration of respiratory assessment, histopathology, microbiologic testing, adverse drug reaction evaluation, and antimicrobial decision-making. Collaboration between treating physicians and clinical pharmacists was particularly important after the onset of severe thrombocytopenia, when balancing antimicrobial efficacy and drug safety became the central management challenge. In this setting, multidisciplinary review strengthened the diagnostic reasoning and facilitated safer transition of antimicrobial therapy.

Some limitations should be acknowledged. First, this is a single case report, and its findings cannot be generalized. Second, the diagnosis of pulmonary actinomycosis was supported by BALF mNGS rather than by culture isolation or demonstration of sulfur granules; notably, the result was consistent with the overall clinical context and treatment response. Third, detailed antimicrobial susceptibility data were unavailable. Finally, although the temporal association and Naranjo score supported penicillin-associated thrombocytopenia, drug-specific immunologic testing was not performed.

In summary, the present case demonstrates that pulmonary actinomycosis in a patient with pneumoconiosis can present a serious diagnostic challenge when routine studies are inconclusive and more common conditions are initially favored. It also suggests that BALF mNGS may provide useful adjunctive diagnostic evidence in such settings and that omadacycline may be considered when penicillin therapy must be discontinued because of severe thrombocytopenia.

Conclusions

Pulmonary actinomycosis should be considered in patients with chronic pulmonary lesions when routine microbiologic study findings are negative and the clinical course is inconsistent with the initial diagnosis. In the present case, BALF mNGS provided useful adjunctive diagnostic evidence. When penicillin therapy could not be continued because of severe thrombocytopenia, omadacycline was successfully used as salvage therapy.

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Department and Institution Where Work Was Done

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Patient Consent

The patient provided written informed consent for publication of this case report and accompanying images.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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