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Case Report

Chronic Pneumocystosis: Differential Diagnosis of Pulmonary Cystic Lesions

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Abstract: *Pneumocystis jirovecii* pneumonia is an opportunistic fungal disease that typically presents with a subacute onset of fever, cough, and progressive dyspnea, accompanied by a characteristic diffuse bilateral ground-glass pattern on imaging. However, a minority of patients may have an indolent course and atypical radiological features, such as diffuse pulmonary cysts. Diagnosis should be suspected mainly in immunosuppressed individuals and relies on direct visualization of the fungus through bronchoalveolar lavage, sputum examination, or, less commonly, histopathology in uncertain cases. Although new diagnostic methods are under investigation, they remain costly, non-standardized, and difficult to access. Treatment consists of high-dose trimethoprim-sulfamethoxazole for 21 days, with corticosteroid therapy in selected cases (e.g., $PaO_2 < 70$ mmHg and increased alveolar-arterial gradient). This disease gained prominence during the HIV pandemic in the 1980s and 1990s. Most studies date from that period and are limited to case series and observational designs, lacking controlled randomized trials, which means treatment still relies on established clinical practice.

Keywords: Pneumocystosis; Pulmonary cysts; Human Immunodeficiency Virus; Trimethoprim-sulfamethoxazole; *Pneumocystis jirovecii*.

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1. Introduction

Pneumocystis jirovecii pneumonia classically presents with cough, fatigue, dyspnea, and hypoxemia, associated with a typical imaging pattern consisting of diffuse bilateral ground-glass opacities on chest computed tomography, which can rapidly progress to respiratory failure if not properly treated [6, 7]. The absence of these findings makes the diagnosis unlikely; however, a minority of cases have been described in literature with atypical radiological and histopathological features [2–4, 11]. Cavitations, nodules, and pulmonary cysts were reported in case series during the HIV pandemic, in addition to a more indolent course without clinical deterioration, with improvement following treatment with sulfamethoxazole-trimethoprim [2-4].

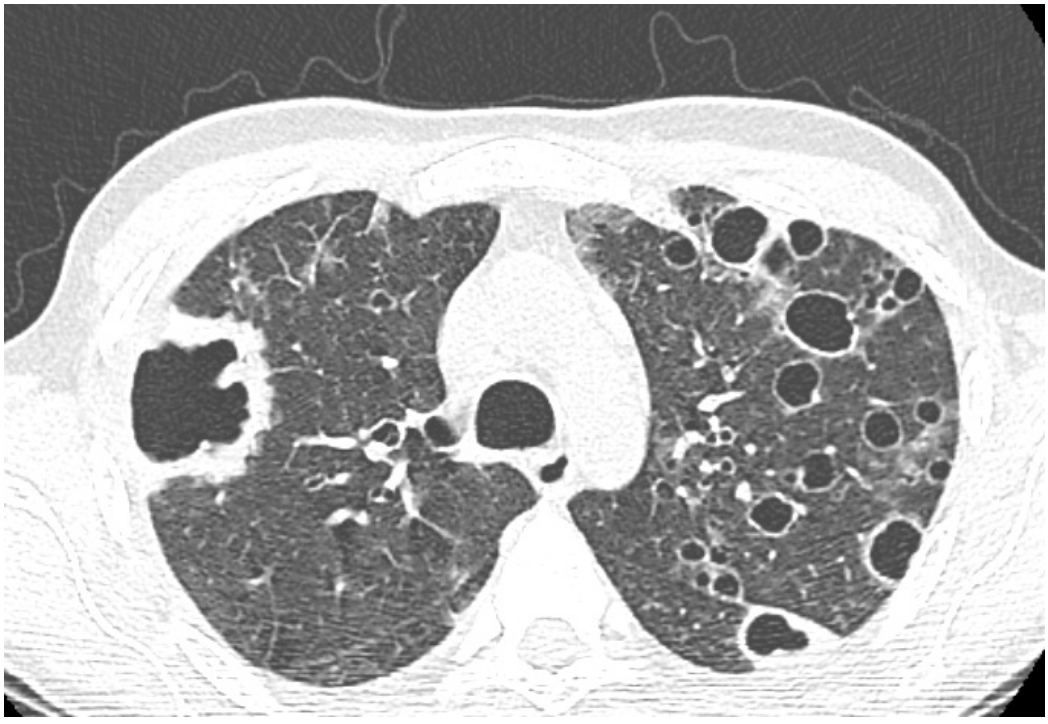
The objective of the following article is to present a case report of a young patient admitted to a tertiary hospital in Fortaleza with an indolent course of cough, fever, hemoptysis, and weight loss. Imaging studies revealed a predominantly cystic lung disease. During hospitalization, the patient was diagnosed with HIV infection, with a CD4 count of 32 cells/μL. Given the atypical presentation and inconclusive initial tests, the patient underwent segmentectomy of the right upper and lower lobes for histopathological examination, which confirmed the diagnosis of *Pneumocystis jirovecii* pneumonia [5,6].

2. Case Report

A 31-year-old young male patient with a history of an unexplained psychiatric disorder was admitted on April 13, 2024, to a tertiary hospital in Fortaleza, Ceará, due to unintentional weight loss over approximately four months, not quantified, associated with hyporexia. During the same period, he developed daily, unmeasured fevers without a specific pattern, as well as an initially dry cough that worsened before hospital admission, becoming productive with hemoptoic sputum, and progressive dyspnea on minimal exertion, which prompted him to seek medical care in the emergency department, leading to hospitalization for investigation. According to the anamnesis, the patient was single, born and residing in Fortaleza, and had never been employed. He had no history of alcohol consumption, active or passive smoking, illicit drug use, or significant environmental exposures. He denied previous pulmonary diseases and prior hospitalizations, as well as other comorbidities, chronic illnesses, or regular use of medications.

On admission physical examination, he was in fair general condition, febrile, and emaciated, but neither cyanotic nor jaundiced. Pulmonary auscultation revealed bilateral crackles without tachypnea, and peripheral oxygen saturation was 97%. Cardiac auscultation was unremarkable, heart rate was normal, abdominal examination was benign, and extremities showed no abnormalities. Given the clinical history and physical examination, general laboratory tests were requested, revealing normocytic normochromic anemia, leukocytosis with neutrophil predominance, and elevated C-reactive protein (CRP). A chest radiograph was also requested, which showed multiple circular images bilaterally, prompting a high-resolution chest computed tomography (HRCT) for better evaluation (Figure 1). Figures 1 and 2 show the HRCT findings at admission.

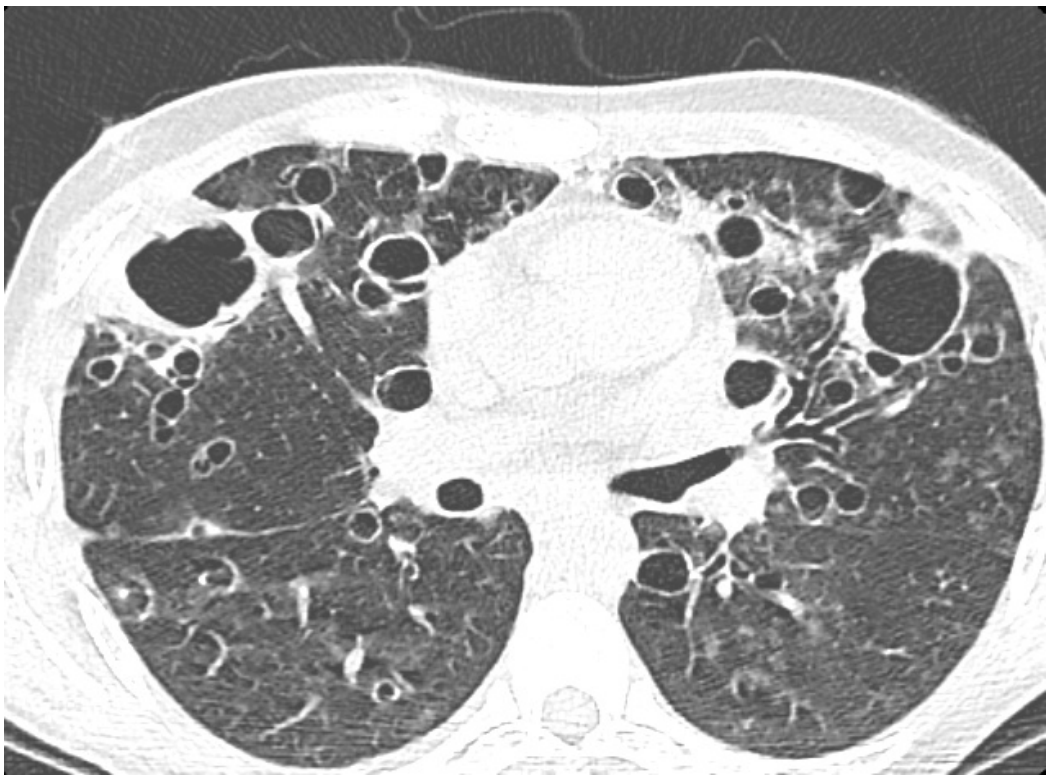
Figure 1. High-resolution chest CT image of the upper lobes demonstrating multiple thin-walled cystic lesions throughout the pulmonary parenchyma, as well as cavitations with thickened walls indicating active disease. Some cystic lesions show bronchial communication.



Considering a possible infectious process, empirical antibiotic therapy was initiated with ceftriaxone and moxifloxacin for 10 days, with clinical improvement after completing the regimen. To further investigate, sputum smear microscopy and molecular testing for tuberculosis were performed, both of which were negative. Iron profile confirmed iron-

deficiency anemia. Viral serologies were negative for hepatitis B and C; however, upon retesting, HIV infection was confirmed. Given these findings, the case was discussed in a multidisciplinary session including pulmonologists, thoracic surgeons, and pathologists. Based on imaging and laboratory results, several differential diagnoses were considered, including lymphocytic interstitial pneumonia, tuberous sclerosis, Langerhans cell histiocytosis, Sjögren's syndrome, light-chain disease, pneumocystosis, and neoplasia.

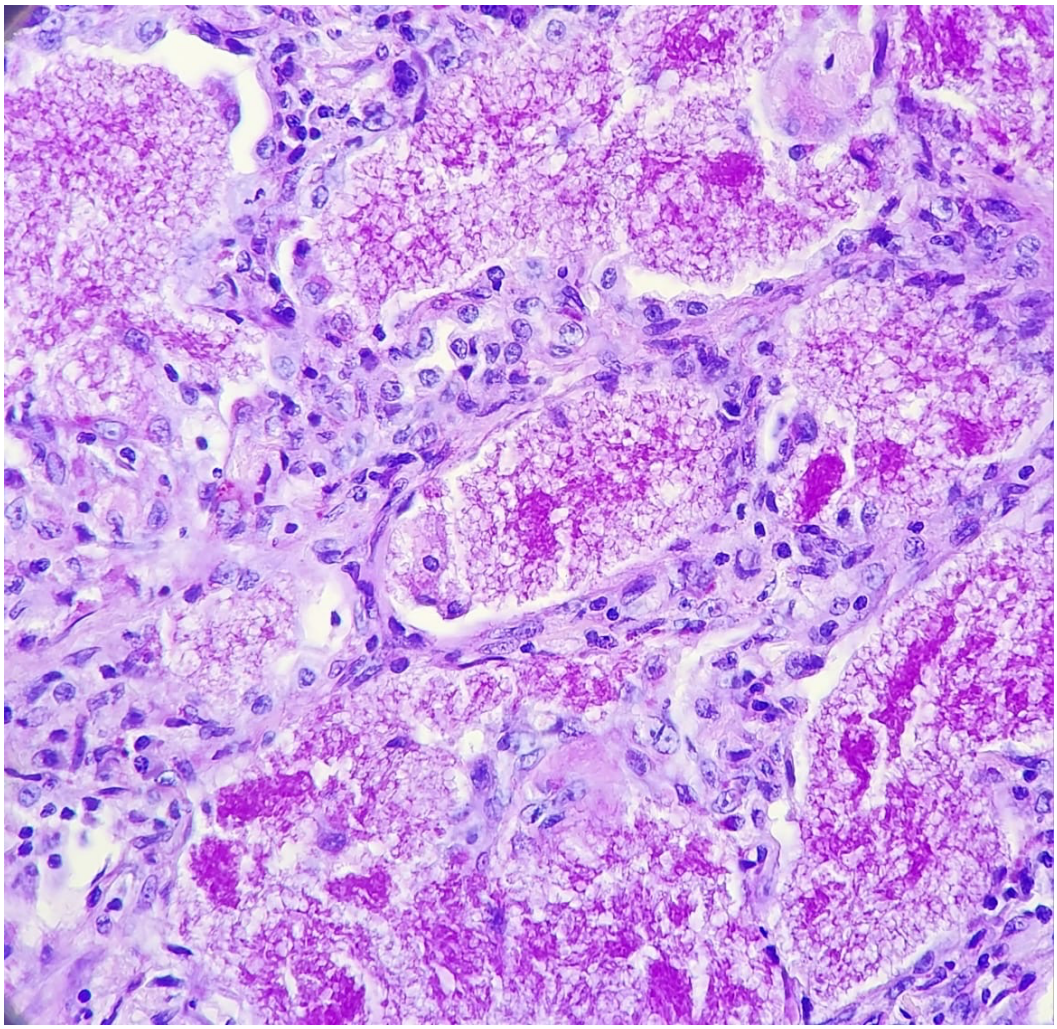
Figure 2. High-resolution chest CT image of the upper lobes showing multiple thin-walled cystic lesions throughout the pulmonary parenchyma, as well as cavitations with thickened walls indicating active disease. Some cystic lesions show bronchial communication.



Recommended procedures included cranial and abdominal contrast-enhanced CT (to investigate astrocytomas, angiomyolipomas, or other distant lesions), bronchoscopy with transbronchial biopsy, and collection of serum lactate dehydrogenase (LDH), in addition to HIV viral load and CD4 T-cell count. LDH was 519 IU/L (reference value <460 IU/L). Viral load was 720,000 copies/mL, with CD4 = 32 cells/μL. Cranial CT showed only age-appropriate findings, while abdominal and pelvic CT revealed no significant alterations. On April 17, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was performed, showing moderate mucoid secretions in the right upper lobe.

Cultures for pyogenic bacteria, fungal cultures, and fungal investigation were all negative. Tests for acid-fast bacilli (AFB) and rapid molecular testing for tuberculosis (TRM-TB) were also negative. Cytology of the bronchoalveolar lavage revealed a predominance of neutrophils (60% of the cellular composition), absence of atypia, and a negative result for neoplastic cells. The histopathological report was limited due to an insufficient tissue sample but described cartilaginous bronchiolar mucosa and alveolar spaces containing a nonspecific inflammatory infiltrate rich in neutrophils, rare eosinophils, and scattered multinucleated giant cells with a suppurative component (Figures 3 and 4). Immunofluorescence tests, beta-D-glucan, and PCR for *Pneumocystis jirovecii* were not available at the institution.

Figure 3. Histopathology of lung tissue showing interstitial mononuclear infiltrate, along with forms compatible with *Pneumocystis jirovecii*, and associated foci of alveolar proteinosis.



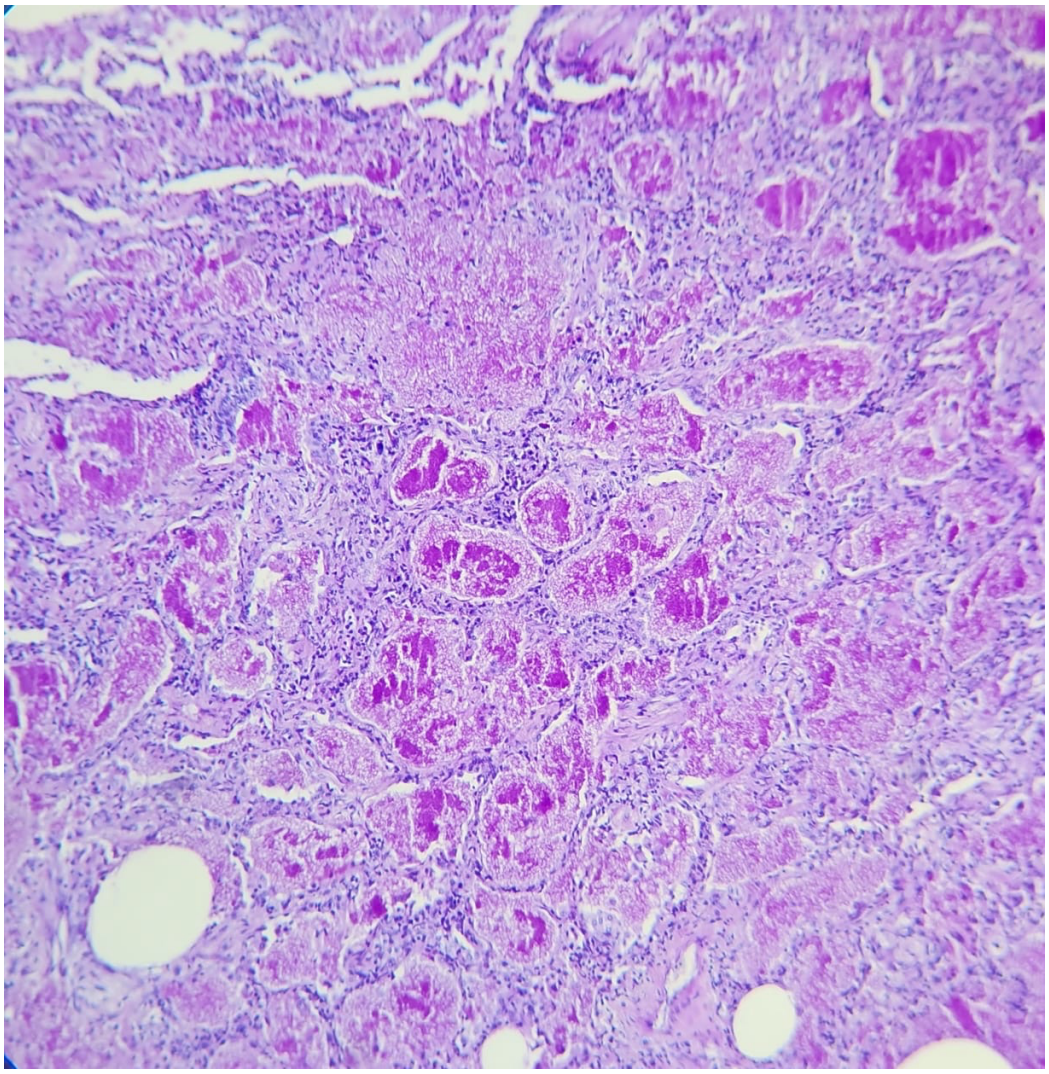
Based on the tests recommended at the first multidisciplinary meeting, the case was discussed again. Given the inconclusive biopsy and negative investigation for pyogenic, mycobacterial, and fungal pathogens in the bronchoalveolar lavage, a new biopsy was planned, this time via video-assisted thoracoscopic surgery (VATS). After consultation with the Hospital Infection Control Committee (CCIH), antiretroviral therapy (ART) was initiated, and the patient was instructed regarding prophylaxis due to the low CD4 cell count. On May 7, 2024, the patient underwent surgical biopsy of the right upper and lower lobes to collect material for histopathological examination and cultures.

The procedure proceeded without complications. The patient was transferred to the intensive care unit (ICU) already extubated, in the process of awakening, with a right-sided chest drain. He remained in the ICU for 24 hours and was then transferred to the ward. Post-procedure, the patient remained stable, afebrile, and without complaints, and was discharged with instructions to retrieve the histopathology report, maintain follow-up with an infectious disease specialist, and attend an early follow-up visit at the pulmonology clinic for clinical monitoring. Figures 3, 4, and 5 represent histopathology sections confirming the diagnosis of Pneumocystosis.

Following the issuance of the report, the patient was contacted and returned to the pulmonology follow-up clinic on August 28, 2024. He was in good general condition, afebrile, and without respiratory complaints. He was adherent to antiretroviral therapy (ART) and prophylaxis with azithromycin and sulfamethoxazole-trimethoprim (Bactrim).

At the end of the consultation, a therapeutic dose of sulfamethoxazole-trimethoprim was prescribed, adjusted to 15 mg/kg/day for 21 days. A new chest CT was also requested to assess radiological response to treatment, to be evaluated at a subsequent consultation.

Figure 4. Histopathology of the right lower lobe showing partially distorted pulmonary histoarchitecture due to cystic formations with dense accumulation of eosinophilic PAS-positive granular material within the alveoli. Xanthomatous macrophages and cellular debris are also observed, along with a clear demarcation between affected and normal pulmonary parenchyma.



After completing treatment, the patient returned to the outpatient clinic showing weight gain and, once again, no respiratory complaints. A follow-up chest CT (see Figures 6 and 7) demonstrated significant reduction of the previously observed pulmonary cavitations and cysts, with no evidence of recurrence or new lesions. Given the excellent clinical and radiological evolution, he was discharged from pulmonology follow-up.

3. Discussion

Pulmonary cysts are common findings on chest computed tomography (CT) scans and are sometimes identified incidentally. They may be associated with the absence of symptoms or with nonspecific presentations, such as cough and dyspnea, which makes their diagnosis challenging [1]. The classic definition consists of a rounded image with thin walls measuring less than 2 mm in thickness, low attenuation, and surrounded by

preserved pulmonary parenchyma. These cysts should be differentiated from cavities, which can be single or multiple but typically have a wall thickness greater than 4 mm [3].

Figure 5. Thoracoscopic biopsy image showing ovoid thick-walled yeast forms compatible with *Pneumocystis jirovecii* using Grocott staining.

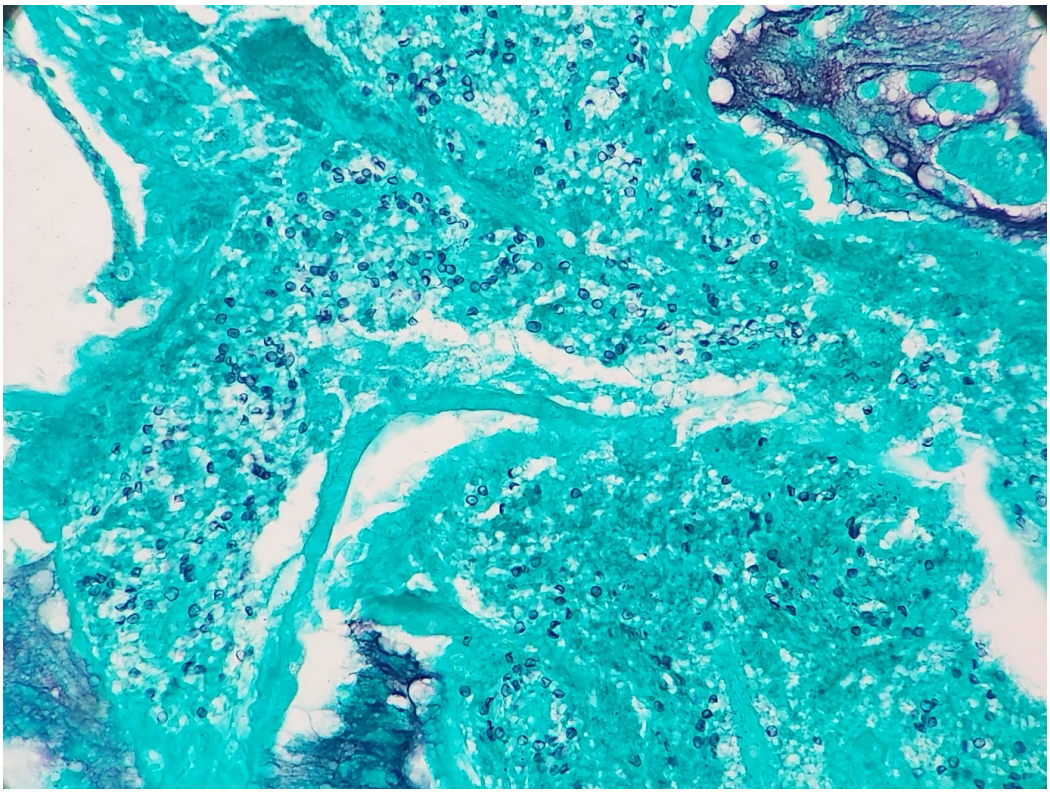


Figure 6. Chest CT image after completion of treatment with sulfamethoxazole-trimethoprim. Compared to the admission scan, a reduction in pulmonary findings is evident, indicating an ongoing improvement process.

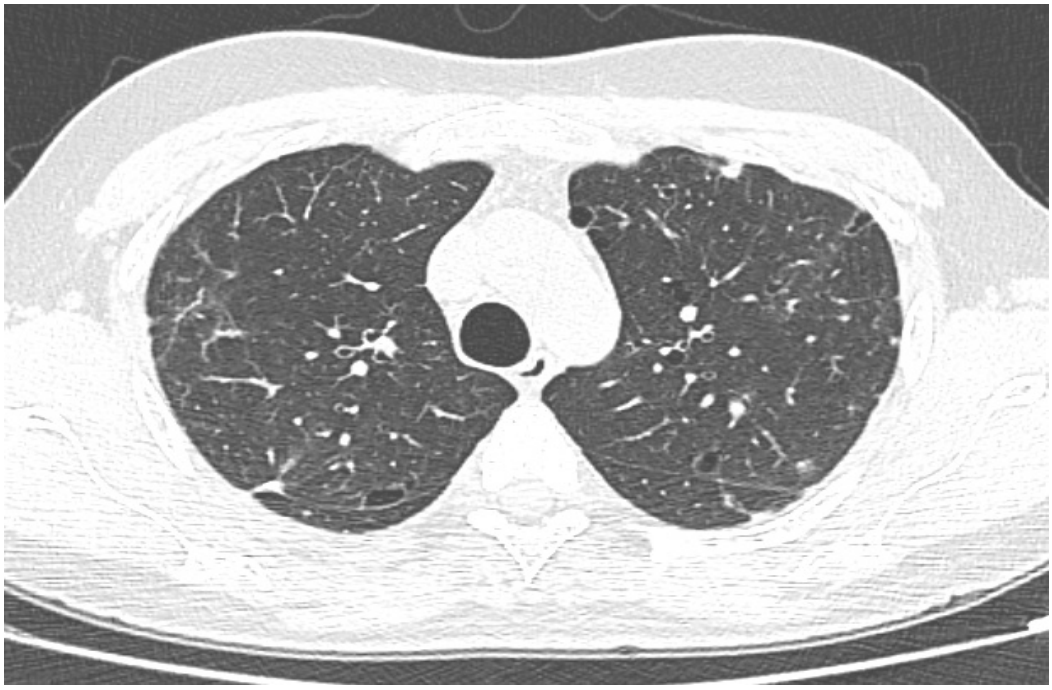
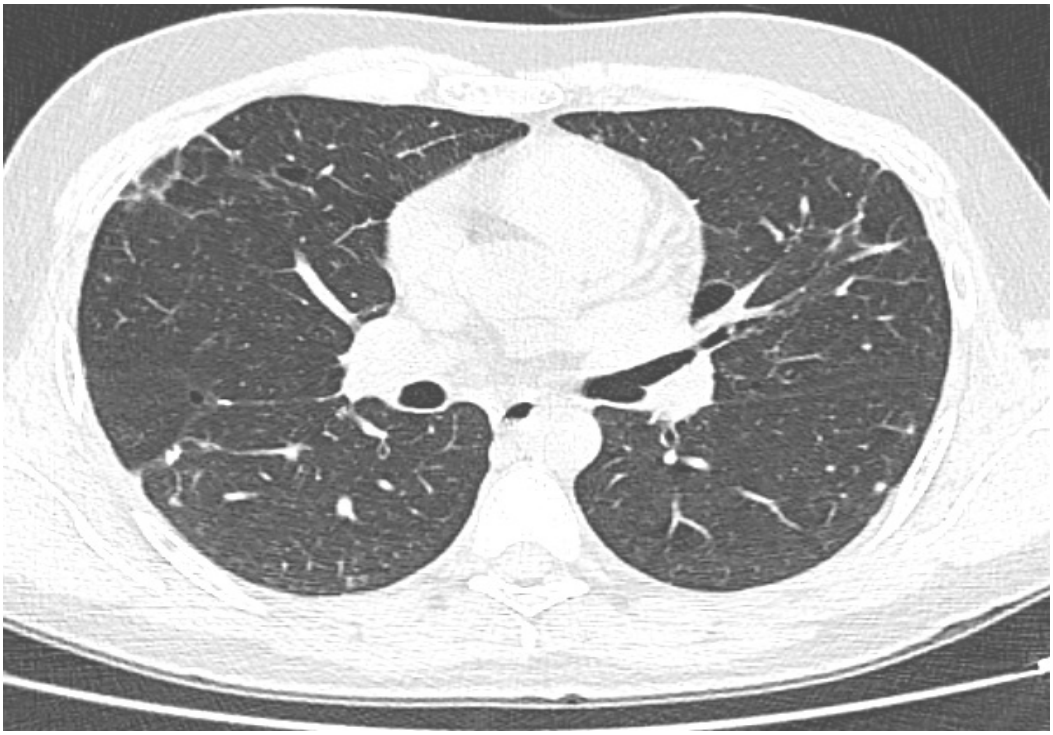


Figure 7. Chest CT image after completion of treatment with sulfamethoxazole-trimethoprim. Compared to the admission scan, a reduction in pulmonary findings is observed in the middle lobe and lingula, previously the most affected areas, indicating an ongoing improvement process.



Cysts can be classified according to their number, distribution, location, and association with other morphological changes, such as pulmonary nodules and ground-glass opacities. The association between ground-glass opacities and diffuse cystic images can include, in the differential diagnosis, various pathologies, among them *Pneumocystis jirovecii pneumonia* [2, 3, 8]. Pneumocystosis is an opportunistic fungal infection that may present as potentially fatal pneumonia. Transmission occurs through inhalation of aerosolized particles, with humans serving as the primary host. Immunocompromised patients are the most affected, including people living with HIV with a CD4 count < 200 cells/μL, transplant recipients (solid organ or bone marrow), and users of immunosuppressive therapies such as biologics, chemotherapy, or high-dose corticosteroids [5, 9].

The clinical presentation is highly variable and nonspecific. The combination of symptoms with medical history and suggestive imaging findings should guide diagnostic suspicion. The most frequent symptoms include cough, fever, fatigue, weight loss, chest pain, progressive dyspnea, and hypoxemia, generally presenting subacutely over 1–2 weeks. In more severe cases, it may progress to respiratory failure requiring ventilatory support. The presence of hemoptysis or the absence of exertional dyspnea are findings that make the diagnosis less likely [6]. On physical examination, patients generally present with tachycardia and tachypnea, but pulmonary auscultation is often unremarkable, representing a clinical–radiological dissociation [6, 7].

Regarding imaging, chest radiography may reveal interstitial or diffuse opacities and can even be normal in the early stages. In contrast, high-resolution computed tomography (HRCT) is more sensitive, with the typical finding of bilateral ground-glass opacities, predominantly in the upper lobes. A minority of cases have been described in literature with atypical radiological and histopathological features. Cavitations, pneumothorax, nodules, and pulmonary cysts have been reported in case series, especially during the HIV pandemic [2-4]. In these cases, the course tends to be more indolent, without significant clinical deterioration, and may be related to a more intense inflammatory process that favors

fungal persistence and chronicity of the condition. However, the exact mechanism is not yet fully elucidated, which is consistent with the previously described report.

Routine diagnosis of pneumocystosis is performed by detecting the fungus in bronchoalveolar lavage, which provides higher-quality samples [7, 13]. However, less invasive methods, such as induced sputum and nasopharyngeal swabs, can also be used. Pulmonary biopsy, despite being invasive, still has diagnostic value, as it allows direct visualization of the fungus in tissue and is indicated when conventional methods do not clarify the diagnosis [1, 7].

Recent studies demonstrate the superiority of direct and indirect immunofluorescence compared to traditional staining techniques. Diagnosis is confirmed by the presence of monoclonal antibodies directed against fungal cell wall antigens, with sensitivity and specificity reaching up to 100%, depending on the sample [13, 14]. Another diagnostic alternative is the use of nucleic acid amplification tests, particularly polymerase chain reaction (PCR), which employs specific primers targeting regions of the Pneumocystis jirovecii genome, allowing detection in samples such as bronchoalveolar lavage, induced sputum, and lung biopsies [13–15]. Although effective, PCR is expensive, non-standardized, and cannot differentiate colonization from active infection [14, 15].

Other tests used in clinical practice include beta-D-glucan (BDG) quantification, a polysaccharide present in fungal cell walls, which may indicate ongoing infection [7, 15]. Its levels correlate with fungal burden, disease progression, and treatment response. Lactate dehydrogenase (LDH) is also a useful and widely available test, functioning as a non-specific marker of pulmonary injury in this context [7]. Regarding the differential diagnosis of cystic lesions, the main hypotheses considered were lymphocytic interstitial pneumonia, Langerhans cell histiocytosis, and tuberous sclerosis, all of which were excluded after histopathological analysis of the pulmonary parenchyma [6, 7].

Lymphocytic interstitial pneumonia, the main alternative diagnosis considered in this case, may be associated with HIV infection. It manifests with randomly distributed cysts throughout the pulmonary parenchyma, ground-glass opacities, and centrilobular nodules. Treatment involves corticosteroids and, in some cases, immunosuppressants. Prognosis is unpredictable, with possibilities ranging from spontaneous resolution to progression to pulmonary fibrosis or lymphoma [6].

Langerhans cell histiocytosis is a rare condition, observed mainly in smokers aged 20–40 years. Radiological findings vary depending on the stage of the disease. When present, cysts are generally thin-walled, irregular, and bizarrely shaped [6]. Due to the absence of tobacco exposure or other risk factors, this hypothesis was ruled out. Tuberous sclerosis is an autosomal dominant genetic disorder with multisystem involvement. Pulmonary involvement occurs due to its association with lymphangioleiomyomatosis (LAM), which presents multiple bilateral cysts diffusely distributed and surrounded by preserved pulmonary parenchyma. In patients with tuberous sclerosis, the course tends to be milder than in sporadic forms of LAM [6].

The treatment of choice for *Pneumocystis jirovecii* pneumonia is sulfamethoxazole-trimethoprim, due to its cost-effectiveness, wide availability, proven efficacy, and cross-protection against other opportunistic pathogens [5, 7, 9]. The medication acts by inhibiting the biosynthesis of nucleic acids and essential proteins in the microorganism. The recommended therapeutic dose is 15–20 mg/kg/day of trimethoprim, administered orally or intravenously, divided throughout the day for 21 days [5, 9]. In moderate to severe cases with associated hypoxemia, adjunctive corticosteroid therapy is indicated. Prednisone should start at 40 mg orally twice daily for the first 5 days; 40 mg once daily from day 6 to day 10; and 20 mg once daily from day 11 to day 21 [9].

4. Conclusion

Pneumocystis jirovecii pneumonia is a common cause of persistent cough, dyspnea, and hypoxemia and should always be considered, even in more indolent cases and with atypical radiological presentations compared to the classic pattern of diffuse bilateral

ground-glass opacities, especially in immunocompromised patients, such as those on biologics, high-dose corticosteroids, chemotherapy, or living with HIV. Early diagnosis, combined with knowledge of both typical and atypical clinical presentations, is essential for initiating appropriate treatment and reducing associated morbidity and mortality.

Despite advances in less invasive diagnostic techniques, these methods remain poorly available in some institutions and lack standardization, in addition to being unable to differentiate infection from colonization. Moreover, they are costly. Therefore, pulmonary biopsy still maintains its role in clinical practice, as it allows direct visualization of the fungus in lung tissue and is indicated in doubtful cases where conventional methods fail to clarify the diagnosis.

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Research Ethics Committee Approval: We declare that the patient approved the study by signing an informed consent form and the study followed the ethical guidelines established by the Declarationof Helsinki.

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Conflicts of Interest: The authors declare no conflicts of interest.

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