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A 40-Year-Old Male Farmer from Peru With Chronic Cough and Weight Loss

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Clinical Presentation

History

A 40-year-old farmer from the Peruvian Amazon is referred to a hospital in the capital, Lima, with a 4-month history of chronic productive cough and chest pain. The patient reports dyspnoea on exertion and weight loss of about 20 kg. He denies diarrhoea, fever or night sweats.

Three and half months earlier, the patient was hospitalized at a regional hospital in the Peruvian Amazon for similar complaints. During the hospitalization, three sputum smears for acid-fast bacilli (AFB) were reported negative. No tuberculin skin test was performed. The chest radiograph was described as abnormal but no report is available and the patient does not have the film. A diagnosis of pulmonary tuberculosis (TB) was made based on clinical presentation and abnormal chest radiographic findings. The patient received first line TB therapy consisting of isoniazid, rifampicin, pyrazinamide and ethambutol.

In the following months, despite adherence to treatment, he showed no clinical improvement and reported persistence of productive cough with streaking of blood in the sputum. He was then referred to Lima with a suspected diagnosis of multi-drug resistant TB (MDR TB) for further work-up.

The patient had been found to be HTLV-1-positive 10 years previously. A recent HIV ELISA test was negative. The patient denies recent travels.

Clinical Findings

A 40-year-old man appears fatigued and cachectic. Temperature 37.2°C (98.96°F), blood pressure 120/75 mmHg, pulse 70 bpm regular, respiratory rate 15 breaths per minute. On inspection, few cervical and retroauricular lymph nodes are palpable, which are small, mobile, soft and non-tender. Lungs: crackles and rhonchi bilaterally. No hepatosplenomegaly. The rest of the physical examination is normal.

Laboratory Results

Platelets: 1093×10^9/L (reference range: 150–450); the rest of the full blood count is within normal limits.

Questions

1. What are your differential diagnoses?
2. How would you approach this patient?

Discussion

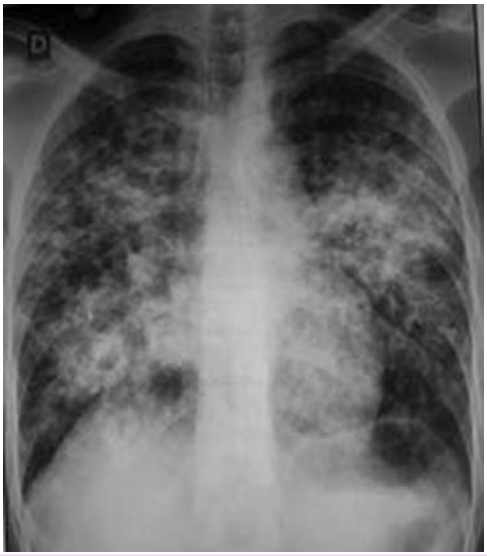
A male farmer from the Peruvian Amazon presents with a history of chronic cough and weight loss. After 3 months of TB treatment for a presumptive diagnosis of pulmonary tuberculosis, he shows no clinical improvement. The patient is cachectic with cervical lymphadenopathy and abnormal pulmonary auscultation. Laboratory investigations show thrombocytosis.

Answer to Question 1

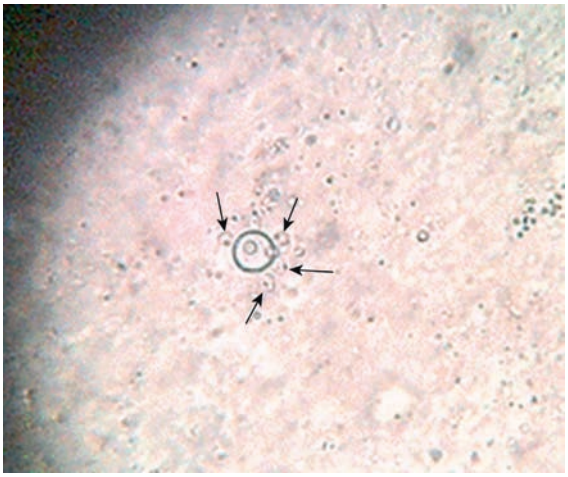
What Are Your Differential Diagnoses?

The most important differential diagnoses in the given setting are MDR TB, histoplasmosis and paracoccidioidomycosis. TB is highly endemic in Peru and MDR TB is an increasing issue. TB and MDR TB almost always need to be considered when clinical symptoms and evolution, as in this case, are suggestive of the disease. What would be unusual about this patient is his origin from a rural area in the central Peruvian Amazon where MDR TB is still uncommon in comparison with underprivileged districts of Lima and other big cities of Peru.

Histoplasmosis can present with recurrent or progressive pulmonary symptoms that can mimic TB. However, his presentation would suggest a chronic form that is more often seen in individuals with preexisting chronic obstructive pulmonary disease, which this patient does not have. The patient's age, gender, occupation, origin and clinical symptoms with a pulmonary focus are all typical of the chronic form of paracoccidioidomycosis and make this diagnosis the most likely of the three. Co-infection of TB (non-MDR)



• **Fig. 55.1** Chest radiograph showing bilateral confluent reticulonodular infiltrates predominantly in the central and upper zones of both lungs. Cavities are seen in the right lung. There is no hilar lymphadenopathy.



• **Fig. 55.2** Large budding yeast (range: 8–40 μm) with multiple surrounding smaller buds around (arrows) seen on KOH preparation of the patient's sputum.

and paracoccidioidomycosis are not uncommon and should also be kept in mind as a possible differential. Parasitic infections such as paragonimiasis or pulmonary hydatid cyst are also possible diagnoses, though less common. Imaging (chest radiography and CT scan) will help identifying the typical lesions of these infections.

Answer to Question 2

How Would You Approach this Patient?

The first step in this patient is to evaluate him for MDR TB. Initial investigations should include chest radiography (the patient should also be asked to bring the initial chest x-ray and report for comparison), tuberculin skin test (PPD) and repeated AFB sputum smears and sputum-PCR (Xpert MTB/RIF) for *M. tuberculosis.* Mycobacterial culture should complete the evaluation and, if positive, culture-based drug sensitivity testing should be added. Locally endemic fungal infections (e.g. histoplasmosis and paracoccidioidomycosis) should be evaluated by direct examination of sputum with wet mount potassium hydroxide (KOH) preparation and cultures. Depending on chest radiographic findings, local availability and costs, a CT scan of the chest could be considered as well as bronchoscopy with biopsy if less invasive diagnostic evaluation is unrevealing. The thrombocytosis should be confirmed on a smear.

The Case Continued…

The tuberculin skin test was negative as were two AFB smears. The chest x-ray showed bilateral confluent reticulonodular infiltrates and multiple cavities in the right lung (Fig. 55.1).

TABLE 55.1 Differences Between the Main Clinical Forms of Paracoccidioidomycosis

Paracoccidioidomycosis	Chronic (Adult) Form	Acute (Juvenile) Form
Epidemiology	>90% of cases	<10% of cases
Infected Population	Men >30 years old (male:female ratio 14:1)	Children and young adults, both sexes HIV patients (rare)
Clinical Characteristics	Chronic Slow progression Reactivation years after initial exposure Lung (always) Dissemination to liver and lymph nodes can occur Mucocutaneous lesions (~70%) (face, nasal and oral cavity)	Acute or sub-acute Rapidly progressive Develops after recent exposure Systemic disease of reticuloendothelial system with dissemination from lung to liver, spleen, lymph nodes and bone marrow Mucosal lesions (rarely) *HIV patients: similar plus cutaneous lesions and severe pulmonary involvement*
Differential Diagnoses	Mimics other chronic fungal infections and pulmonary TB	Mimics leukaemia, lymphoma, severe disseminated TB
Treatment	Azoles (itraconazole) Co-trimoxazole	Azoles (itraconazole) Amphotericin B (HIV or severe disease)

Examination of his sputum (KOH preparation) revealed the characteristic yeast forms of *Paracoccidioides brasiliensis* (Fig. 55.2). Culture grew *P. brasiliensis.*

A diagnosis of chronic (adult) paracoccidioidomycosis was made. The thrombocytosis was considered reactive to the underlying chronic infection. Given the extensive pulmonary lesions and HTLV-1 co-infection, the patient was started on amphotericin B followed by itraconazole (as opposed to itraconazole alone). TB treatment was discontinued.

Our patient was HTLV-1 positive. His symptoms were confined to the lungs as in the chronic adult form of paracoccidioidomycosis (see Summary Box), but his pulmonary lesions were unusually extensive. His long-term prognosis depends on the extent of pulmonary fibrotic sequelae.

SUMMARY BOX

Paracoccidioidomycosis

Paracoccidioidomycosis is a systemic fungal infection endemic only to the moist tropical regions of Latin America. The infection is caused by the thermally dimorphic fungus *Paracoccidioides brasiliensis,* which grows as mould in the environment and as yeast in tissue and at 37°C. Humans are infected through the inhalation of aerosolized conidia (spores) from the soil. In endemic areas, initial exposure occurs in childhood and the majority of primary infections remain asymptomatic or subclinical. In those who develop disease, two main clinical forms are observed (Table 55.1). The chronic adult form is characterized by pulmonary symptoms that slowly develop over months, typically in middle-aged men living in rural endemic areas, which are often accompanied by mucosal lesions. Women of fertile age are rarely affected, probably because of a protective effect of oestradiol preventing the transformation of the fungus into the yeast stage. The acute juvenile form is seen in children and young adults of both sexes and presents as an acute systemic disease of the reticuloendothelial system. Adult patients with advanced HIV infection present a more aggressive acute disease similar to the juvenile acute form with extensive pulmonary involvement.

Diagnosis is confirmed by visualization of *P. brasiliensis* (yeast form) on wet preparation of specimen and/or isolation in fungal culture. The identification of *P. brasiliensis* is more difficult in sputum than in skin lesions or material from lymph nodes. The yeast is easily observed on KOH preparation but its isolation in culture is difficult and takes 20 to 30 days. Serological testing is useful for antibody detection and diagnosis, assessing disease severity and monitoring treatment response. Molecular methods could be used instead of culture to confirm the diagnosis but are not yet widely available in resource-limited endemic areas.

Treatment includes azoles for mild and moderate cases. Itraconazole (200 mg/day for 12 months) is considered the drug of choice. Voriconazole and co-trimoxazole are alternatives; the latter is commonly used in Brazil. Amphotericin B (cumulative dose of 1–2 g) is indicated for severe and extensive disease. However, the drug is not curative and should be followed by an azole or co-trimoxazole to complete 12 months' treatment.

Cure is determined based upon four criteria: clinical (i.e. absence of symptoms), mycological (i.e. negative testing), radiological (i.e. stability of lung lesions on x-ray for 1 year) and immunological (i.e. decrease of specific antibodies).

Recently case reports of severe and unusual extrapulmonary manifestations of paracoccidioidomycosis have been described in HTLV-1 infected patients and the two conditions might be associated.

Further Reading

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4. Mendes RP, Cavalcante RS, Marques SA, et al. Paracoccidioidomycosis: Current Perspectives from Brazil. Open Microbiol J 2017;11: 224–82.
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