33

A 53-Year-Old Man from Malawi With a Chronic Cough

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Clinical Presentation

History

A 53-year-old Malawian man presents to a local hospital with a productive cough and whitish sputum for 3 months. He also reports night sweats and some weight loss, which he is unable to quantify.

Two months earlier he presented to a health centre with the same complaints. He was given presumptive antimalarials and amoxicillin for 5 days, but to no avail.

The patient is not aware of any tuberculosis (TB) contacts. He is currently not on any medication and his past medical history is unremarkable. He is a subsistence farmer. He has never worked in a mine or in the construction industry. He is a non-smoker. He is married with five children; all are well.

Clinical Findings

53-year-old man, slightly wasted. Temperature 38.8°C (101.8°F), blood pressure 100/80 mmHg, pulse 88 bpm, oxygen saturation 97% on ambient air. He appears mildly anaemic. On inspection of his mouth there is no oral thrush, no Kaposi's sarcoma and no oral hairy leukoplakia. His chest is clear and there are normal heart sounds without any murmurs. There is no lymphadenopathy; liver and spleen are not enlarged.

Investigations

The HIV-test is reactive. His further laboratory results are shown in Table 33.1.

Chest Radiography

His chest radiograph on admission shows a prominent hilar region bilaterally but is otherwise normal (Fig. 33.1).

TABLE 33.1 Laboratory Results on Admission

Parameter	Patient	Reference
WBC ($\times 10^9$/L)	3.2	4–10
Haemoglobin (g/dL)	9.8	13–15
MCV (fL)	90	80–98
Platelets ($\times 10^9$/L)	305	150–350
CD4 count (cells/μL)	54	500–1200
Sputum for AFB	2 × negative	Negative
Malaria RDT	Negative	Negative
Thick smear for *Plasmodium* spp.	Negative	Negative

• **Fig. 33.1** Chest radiograph on admission showing a prominent hilar region.

Questions

1. What is your suspected diagnosis?
2. How would you approach this patient?

Discussion

A 53-year-old Malawian man presents with chronic cough and constitutional symptoms. A course of oral antibiotics did not yield any improvement. The patient is not aware of any TB contacts. On admission he is newly diagnosed with HIV-infection and advanced immunosuppression. His sputum microscopy is negative for acid-fast bacilli (AFB). Chest radiography shows a prominent hilar region but is otherwise normal.

Answer to Question 1

What is Your Suspected Diagnosis?

In all HIV-positive patients with cough and weight loss who do not respond to antibiotic therapy, tuberculosis is top of the list of differential diagnoses. In this case the most likely diagnosis is smear-negative pulmonary TB.

TB in patients with advanced immunosuppression often presents with a clinical picture that is very different from immunocompetent individuals: sputum smear-negative TB, which is uncommon in HIV-negative patients, is commonly seen in HIV-infected patients, particularly if immunosuppression is advanced as in this case. The slightly prominent hilar region seen on the patient's chest radiograph is compatible with the intrathoracic lymphadenopathy: typical though not specific for TB. Physical examination of the chest is normal in about half of HIV patients with pulmonary TB.

The fact that the patient does not report any TB contact should not be overvalued. Firstly, TB in immunosuppression is often a consequence of reactivation and the primary infection may have been decades ago. Secondly, in resource-limited countries, practically everyone is exposed to TB – this could occur during a ride on an overcrowded minibus or when congregating with friends and family in someone's small home.

Given the fact that our patient is in an advanced stage of immunosuppression and has not taken any co-trimoxazole prophylaxis, an alternative or possibly co-existing diagnosis to consider is *Pneumocystis jirovecii* pneumonia (PCP). A concomitant bacterial chest infection is possible but unlikely to explain the whole 3 months of illness.

Kaposi's sarcoma (KS) of the lung is another differential diagnosis to consider, but patients with pulmonary KS usually have manifestations of KS elsewhere (skin, oral mucosa). On chest radiography of patients with pulmonary KS, patchy infiltrations are commonly seen in the lower lung zones. Neither was the case in our patient, which makes this diagnosis unlikely.

Pulmonary malignancy or pulmonary sarcoidosis, which would be high on the list of differential diagnoses in industrialized countries, are much less likely than an infectious cause in the given setting.

Apart from chest infections, Gram-negative sepsis secondary to invasive non-typhoidal *Salmonellae* (iNTS) needs to be considered in this febrile and anaemic patient with advanced immunosuppression.

Answer to Question 2

How Would You Approach This Patient?

Induced sputum should be examined for acid-fast bacilli. Real-time PCR-based tests such as XPert MTB/RIF are easy to use, more sensitive than microscopy and also help detect rifampicin resistance. Thanks to an endorsement by WHO and international donor support, XPert MTB/RIF is increasingly available even at remote hospitals in rural areas.

Mycobacterial cultures of the sputum should be done but results will take several weeks, too long to guide the clinician's imminent decision.

Ideally, bronchoscopy with bronchoalveolar lavage should be done and material assessed for *M. tuberculosis* (PCR, culture, microscopy) and *Pneumocystis jirovecii* (PCR, microscopy). Pulmonary Kaposi's sarcoma could also be diagnosed on endoscopy.

Urine lipoarabinomannan (urine-LAM) is a simple lateral-flow assay helpful to look for TB in patients with advanced immunosuppression (CD4 $<100/\mu l$). A positive test indicates disseminated TB with renal involvement.

Ultrasound is also very useful and simple to look for signs of extrapulmonary/disseminated TB in patients with advanced immunosuppression. Simple and very useful algorithms have been published to guide clinicians not ultrasound-experienced in the diagnosis of TB.

If none of these investigations is available, it is well justifiable to empirically start the patient on antituberculous treatment, because sputum smear-negative TB is common and fatal if untreated. Adding prednisolone for the first 4 weeks of antituberculous treatment has been shown to reduce the incidence of immune-reconstitution inflammatory syndrome (IRIS).

Additional antibiotic treatment should be considered in this febrile patient with advanced immunosuppression. If available, blood cultures should be taken in any febrile patient before starting antibiotic treatment. Also, adding high-dose co-trimoxazole to antituberculous therapy as presumptive treatment for PCP has to be considered if the patient does not clinically improve. The optimal timing to initiate antiretroviral therapy (ART) is within the first 8 weeks of starting antituberculous treatment and within the first 2 weeks for patients who have CD4 cell counts <50 cells/μl.

The Case Continued…

Induced sputum results came back negative for AFB and there was no sputum PCR available. The patient's exercise test (walking down the hospital corridor three times at a fast pace) showed oxygen saturation of 98% as opposed to 97% at rest, and was therefore negative.

The patient was treated for a possible bacterial chest infection, covering also for Gram-negative bacteria. He received ceftriaxone 2 g IV od and erythromycin 500 mg qid for 5 days. It was decided not to treat him for PCP and he received the prophylactic dose of co-trimoxazole (480 mg bid according to local national guidelines). Nonetheless, his fever persisted, even though the cough subjectively improved slightly.

On day 7 in the hospital, the patient was started on empirical treatment for smear-negative TB with four antituberculous drugs (Isoniazid (H), Rifampicin (R), Pyrazinamide (P) and Ethambutol (E). After the first week of treatment, he started to feel better. His fever went down and the cough gradually settled. He was discharged home. Three weeks into the TB treatment he was seen at the HIV clinic. He was doing well and had started antiretroviral therapy.

• **Fig. 33.2** Chest radiograph of a patient with miliary TB.

TABLE 33.2 Clinical Presentation of TB in Patients With and Without Immunosuppression

	HIV-negative or high CD4 count (>200/μL)	Low CD4 count (≤200/μL)
Cough and sputum production	Severe, productive	Often mild, small amounts of whitish sputum
Haemoptysis	Common	Rare
Chest radiography appearance	Cavities, upper lobe infiltrates and destruction	No cavities Infiltrates Hilar lymphadenopathy Miliary pattern May be completely normal
Sputum smear result	Often positive	Often negative
Extrapulmonary and disseminated TB*	≤20% of TB cases	Common, about 50%

*Disseminated = involving two or more non-contiguous organs concomitantly.
(After Harries, A.D., et al., 2004. and Sharma, S.K., et al., 2005.)

SUMMARY BOX

Tuberculosis in HIV-Infected Patients

TB and HIV infection are the most important 'tropical' diseases in adults in many parts of sub-Saharan Africa. Co-infection with HIV and TB is common and poses a particular challenge to the clinician.

Clinical presentation of TB changes with declining peripheral CD4 counts (Table 33.2).

Cavitating smear-positive pulmonary TB, as seen classically in HIV-negative individuals, is uncommon in advanced immunosuppression. Instead, patients more commonly present with sputum smear-negative pulmonary TB. CXR may be completely normal and clinical symptoms are often discrete; patients may produce little sputum and haemoptysis is rare.

HIV-positive individuals are also more likely to present with extrapulmonary TB manifesting as pleural effusion, pericardial disease, lymph node TB, abdominal TB, TB meningitis and miliary disease or a combination of these (Fig. 33.2). Severe anaemia is a common clinical clue to a co-infection with HIV/TB and reflects bone marrow involvement.

When treating HIV/TB co-infected patients, pharmacokinetic interactions between rifampicin and antiretroviral drugs have to be considered. Adding prednisolone during the first 4 weeks of antituberculous treatment may help decrease the risk of immune-reconstitution inflammatory syndrome (IRIS).

Further Reading

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