

Disseminated tuberculosis: Challenges in diagnosis

**Catarina Assis Cardoso, Teresa Filomena Garcia,
Patricia Raimundo Cachado**

ABSTRACT

Introduction: Disseminated tuberculosis is difficult to identify and probably underdiagnosed. Its prevalence in non-HIV patients is rising and a high index of suspicion must always be present, especially when other diseases are present, because there is usually considerable signs and symptoms overlap between them. Also, difficulties in obtaining adequate tissue specimens and body fluids is frequent not only because the patient may not be able to undergo some procedures but also adequate biological samples amount and material processing in high quality laboratories is needed to reach a definitive diagnosis.

Case Report: A case of a 67-year-old male with a past medical history of alcoholism and diabetes presented with cachexia, right pleural effusion, abdominal ascites and bilateral leg edema. Isolated thrombocytopenia was present. Heart failure was first diagnosed, but thrombocytopenia worsening led us to a high suspicion for tuberculosis. A series of factors such as heart failure treatment and restraints on adequate tissue biopsy specimens for histopathological and microbiological evidence delayed diagnosis. Bone marrow biopsy was the key for a conclusion. However, despite therapy, the patient's condition did not improve and he passed away. Post-mortem examination revealed the extension of the disease.

Conclusion: Late diagnosis and treatment is one of the reasons why disseminated tuberculosis has such high rate mortality, so our aim is to raise awareness for its early identification with appropriate use of invasive procedures and also provide an example of some restraints that might preclude diagnosis, which physicians should pay attention to.



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CASE REPORT

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key for a conclusion. However, despite therapy, the patient's condition did not improve and he passed away. Post-mortem examination revealed the extension of the disease. **Conclusion:** Late diagnosis and treatment is one of the reasons why disseminated tuberculosis has such high rate mortality, so our aim is to raise awareness for its early identification with appropriate use of invasive procedures and also provide an example of some restraints that might preclude diagnosis, which physicians should pay attention to.

Keywords: Bone marrow, Biopsy, Diagnosis, Disseminated tuberculosis

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INTRODUCTION

Tuberculosis is a highly prevalent disease in Portugal (incidence of 187 per 100,000 population) but disseminated form is rare (1%), especially in non-HIV patients. Although there have been some unusual case presentation reports, it is probably underdiagnosed in most of the patients and means a challenge for physicians because symptoms and signs may overlap other diseases,

sometimes with difficulties in establishing the diagnosis due to the fact that patients may not be able to undergo some invasive procedures.

CASE REPORT

A 67-year-old man born in Mozambique with Goa ancestry, living in Portugal for 30 years without any abroad trips, currently unemployed, with a past medical history of alcoholism, type 2 diabetes under control with metformin 850 mg twice daily and stage three chronic kidney disease, was admitted in the emergency department with a four-month history of anorexia, weight loss of 10 kg (previous weight: 60 kg), adynamia and dry cough. On physical examination the patient was emaciated. Lung auscultation revealed diminished sounds in the lower right hemithorax and the abdomen showed shifting dullness to percussion. There was discrete bilateral leg edema and doubtful hepatojugular reflux. Blood laboratory workup revealed chronic renal failure (creatinine 1.54 mg/dL, urea 87 mg/dL) a cyto-cholestatic pattern without hyperbilirubinemia (aspartate aminotransferase/alanine aminotransferase 70/89 U/L respectively, alkaline phosphatase 312 U/L), discrete International Normalized Ratio elevation to 1.5 and thrombocytopenia ($78,000/\text{mm}^3$) without additional cytopenias.

Thoracic X-ray showed a unilateral right effusion (Figure 1). We decided to hospitalize the patient for further investigation.

We considered the following differential diagnosis: neoplasia, tuberculosis or chronic hepatic disease.

Infectious serologies, namely HIV and hepatitis were non-reactive. Tuberculin test was negative.

Blood smear did not show significant abnormalities.

Imaging exams such as abdominal ultrasound showed no signs of chronic hepatic disease but moderate ascites was noticed (Figure 2).

Non-enhanced (due to renal failure) chest and abdominal computed tomography scan revealed mediastinal perihilar right adenopathies with a unilateral moderate right pleural effusion, cardiomegaly and moderate ascitic fluid (Figures 3 and 4).

Thoracentesis and closed pleural biopsy were not possible at the same time so they were scheduled in the following week. Meanwhile, transthoracic echocardiography revealed global hypokinesia with severe left systolic dysfunction, low ejection fraction of 17% with impaired right ventricle function. Brain natriuretic peptide was strongly elevated with 1,200 pg/mL. We considered a heart failure diagnosis, so treatment with diuretics, beta blockers, angiotensin II receptor blockers and small dose digoxin were started.

There was a gradual improvement of both pleural effusion and ascites, but on the other hand, a progressive decrease in thrombocytopenia to $55,000/\text{mm}^3$ and after a few additional days to $18,000/\text{mm}^3$ was noticed without additional explanation. Thoracic X-ray showed a marked

decrease in right pleural effusion making closed pleural biopsy a high risk procedure, even with coagulopathy correction, so it was not performed. Meanwhile, a second abdominal ultrasound also showed very small ascites with significant diffuse bowel distension making the patient unfit for paracentesis.

Bone marrow biopsy was performed and few epithelioid non-caseous granulomas were identified with a negative acid-fast bacilli smear. Unexpectedly, myeloculture and blood culture showed the presence of a nosocomial bacteria *Serratia marcescens*, which contaminated the sample for mycobacterial growth. We decided to treat this infection with piperacillin-tazobactam according to antimicrobial susceptibility testing.

A second bone marrow biopsy attempt was made and this time significant stromal fibrosis due to Langhans giant cell granulomas, one with caseous necrosis, was identified.

Considering the patient's history and bone marrow findings, disseminated tuberculosis was very likely, so we decided to add anti-tuberculosis drugs while the sample



Figure 1: Thoracic X-ray showing unilateral right-sided effusion.

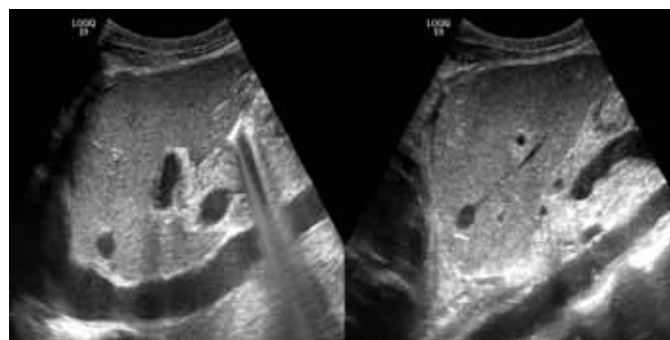


Figure 2: Abdominal ultrasound identified moderate ascites with a normal-sized homogeneous texture liver.

was being decontaminated for mycobacterial growth culture. The patient was started on a four drug therapy with isoniazid, rifampicin, pyrazinamide and ethambutol. Eventually there was a discrete improvement on platelets counts, but the patient died due to progressive malnutrition after one week of therapy.

Post-mortem examination revealed green ascites with identification of yellowish granulomas present in mesentery and subdiaphragmatic peritoneum. Mediastinal adenopathies were present bilaterally. Liver had a granular surface texture. Acid-fast bacilli were identified with Ziehl-Neelsen technique in granulomas, adenopathies and liver myeloculture was positive for mycobacterium tuberculosis. Final diagnosis was disseminated tuberculosis with miliary bone marrow, abdominal and thoracic involvement.

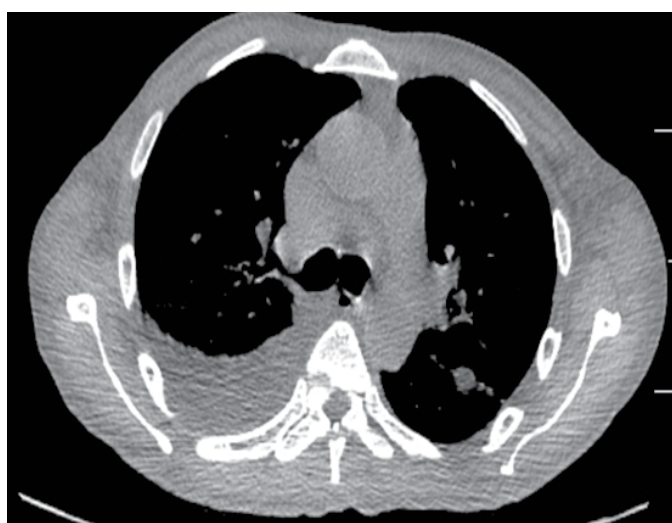


Figure 3: Non-enhanced chest computed tomography scan showing unilateral right sided pleural effusion with small mediastinal right-sided lymphadenopathy and cardiomegaly.



Figure 4: Non-enhanced abdominal computed tomography scan showing moderate free-fluid ascites.

DISCUSSION

Disseminated tuberculosis, especially miliary form, accounts for less than 2% of all cases and up to 20% of all extra-pulmonary cases in various clinical series. Classic presentation is seeding in the lung, as evidenced on chest radiography or computed tomography scan. But individual organ involvement, although unusual, is possible [1].

Also, it is more difficult to diagnose. Conventional acid fast bacilli smears have low sensitivity and require a long time for *Mycobacterium tuberculosis* to become evident during culture. As a result, diagnosis mostly depends on histological evidence.

Our case is different from other reported disseminated tuberculosis diagnosis [2–6] because we had to endure considerable difficulties on acquiring biological material for the final diagnosis. Heart failure first diagnosis and treatment decreased pleural and ascitic fluid, which together with coagulopathy made closed pleural biopsy a high risk procedure. Moreover, even if we tried paracentesis in a small amount of ascitic fluid, acid fast stained smear has a disappointingly low yield and not only the frequency of a positive culture is less than 20% [7, 8] but we also need to consider the usual four to six weeks delay of microbiological culture results.

Since the key to diagnosis was finding a few caseating granulomas in bone marrow histopathology. We call attention for bone marrow biopsy as a high profitable and less prone for complications invasive procedure whenever disseminated tuberculosis is suspected, especially when cytopenias are present [8].

Another problem was the identification of *Serratia marcescens* in myelocultures, which precluded mycobacteria growth. As far as literature reviews, no case of bone marrow culture with nosocomial bacteria isolation has been reported. Positive cultures from bone marrow have a low yield as described in literature [1, 9] but they remain the gold standard for tuberculosis diagnosis, especially in an era of multidrug resistance disease.

Mortality, in disseminated tuberculosis, is high in the range of 50 to almost 100%. Certain factors are thought to contribute to the variable outcome such as disease severity and underlying comorbidities, but delay in initiation of appropriate treatment is probably the most important. These two latter conditions were indeed present in our patient; he was extremely malnourished and treatment was started in a disease probably present for more than four months [10].

CONCLUSION

In conclusion, miliary tuberculosis still faces diagnostic difficulties. Our aim is to show and discuss diagnostic issues in acquiring appropriate tissue and body fluids since they must be obtained in the first place with

adequate amount and appropriate analysis in high quality laboratories whenever tuberculosis is to be considered.

Author Contributions

Catarina Assis Cardoso – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Teresa Filomena Garcia – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Patricia Raimundo Cachado – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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