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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
The authors report a case of a 67-year-old male with a past medical history of Alcoholism and Diabetes who 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.
Keywords: Disseminated Tuberculosis, Bone marrow, Biopsy, Diagnosis
INTRODUCTION

Tuberculosis is a highly prevalent disease in Portugal (incidence of 18.7 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 4-month history of anorexia, weight loss of 10kg (previous weight: 60kg), 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 cytocholestatic 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 /mm³ ) 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 (Figure 3,4).

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 per cent 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/mm$^3$ and after a few additional days to 18,000/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 was being decontaminated for mycobacterial growth culture. The patient was
started on a four drug therapy with isoniazid, rifampicin, pyrazinamid 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. Final diagnosis was disseminated tuberculosis with miliary bone marrow,
abdominal and thoracic involvement.

DISCUSSION
Disseminated Tuberculosis, especially miliary form, accounts for less than 2 per cent
of all cases and up to 20 per cent of all extra-pulmonary cases in various clinical
series.\cite{1} Classic presentation is seeding in the lung, as evidenced on chest
radiography or computed tomography scan. But individual organ involvement,
although unusual, is possible \cite{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
\cite{2,3,4,5,6} 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\% \cite{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 the 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 per cent. 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.

CONCLUSION

In conclusion, milliary 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.

CONFLICT OF INTEREST

The author declares no conflicts of interest

AUTHOR’S CONTRIBUTIONS

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Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data

Group 2 - Drafting the article, Critical revision of the article

Group 3 - Final approval of the version to be published
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Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

Patricia Raimundo Cachado

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Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

REFERENCES


FIGURE LEGENDS

Figure 1: Thoracic x-ray showing unilateral right sided effusion

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

Figure 3: Non-enhanced Chest CT scan showing unilateral right sided pleural effusion with small mediastinal right-sided lymphadenopathy and cardiomegaly

Figure 4: Non-enhanced Abdominal CT scan showing moderate free-fluid ascites
Figure 1: Thoracic x-ray showing unilateral right sided effusion
Figure 2: Abdominal ultrasound identified moderate ascites with a normal-sized homogeneous texture liver
Figure 3: Non-enhanced Chest CT scan showing unilateral right sided pleural effusion with small mediastinal right-sided lymphadenopathy and cardiomegaly.

Figure 4: Non-enhanced Abdominal CT scan showing moderate free-fluid ascites.