Author's response to reviews

Title: Disseminated tuberculosis presenting with polymorphonuclear effusion and septic shock in an HIV-seropositive patient: a case report

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Author's response to reviews: see over
Dear Editor,

We would like to submit the revised version of our manuscript entitled “Disseminated tuberculosis presenting with polymorphonuclear effusion and septic shock in an HIV-seropositive patient” for publication in Journal of Medical Case Reports. We describe the case of a young HIV patient who presented with pleural and abdominal polymorphonuclear effusions and a quickly developing septic shock due to disseminated *Mycobacterium Tuberculosis* infection leading to multiple organ failure and death. Tuberculous lymphocytic pleural effusion is a common presentation but the association of polymorphonuclear effusion and septic shock due to *Mycobacterium tuberculosis* is an exceptional clinical presentation making the diagnosis of this aggressive situation challenging. This association has not been reported previously in the literature to our knowledge.

Neither this work nor any part of its essential substance (tables or figures) have been or will be published or submitted to another scientific journal or is being considered for publication elsewhere. If and when it is accepted for publication, the authors automatically agree to transfer the copyright to the publisher. The authors have no conflict of interest with this study. All authors have seen and approved the manuscript.

All changes have been highlighted in yellow in the revised manuscript. Furthermore, here are our answers to the first reviewer:
Major points:

In the end of the discussion section the authors are making a description of the types of effusions encountered in TB cases. It is unclear why these definitions need to be reminded and how this fits with the discussion of our case.

*Answer:* *The definition of the different effusions types encountered in Tb is reminded because we consider that it could be useful for the non specialized physicians reading this article and to emphasize the challenging diagnosis of this pathology. We feel it would be useful to keep this definition, however, if the Editor also thinks it should be removed, we are ready to do so.*

In is unclear why the authors present shortly the TB empyema. Empyema is defined by the gross appearance of fluid and not only by the presence of pleural fluid neutrophils.

*Answer:* *We agree with this point and we suppressed the term empyema in the abstract and removed the paragraph concerning this topic in the discussion.*

Also a more thorough discussion on the fact that a neutrophilic fluid may be present in early TB pleuresia is needed.

*Answer:* *We spent a whole paragraph in the discussion section about this topic. We feel that the discussion about this point is sufficient for a case report article. However, if the Editor thinks this section should be even more detailed, we are ready to do so.*

In the end of the discussion section the authors state that „Early pleural fluid direct examination by Ziehl-Neelsen staining, cultures and pleural biopsies are necessary to confirm the appropriate diagnosis”; this is partially true since only about 5% direct pleural fluid examination
are positive for Acid Fast Bacilli and no more than one case in three are culture positive. Some may infer that examination of pleural fluid may be sufficient for exclusion of TB diagnosis. Cultures from pleural biopsies are much more frequently positive (up to 80%). Please rephrase and document with appropriate references.

*p: Answer: We agree with your comments and we rephrased the paragraph and added the percent of positive smear and culture and quoted new references.*

The authors also state in the conclusion that early death is the illustration of the “aggressiveness of some forms of this disease” (i.e. TB). This should be rephrased since death in TB generally relate to late or inappropriate therapy (either due to drug resistance or inappropriate treatment protocol or poor compliance). Early treatment even in severe immunosuppressed patients generally results in cure.
The authors should emphasize the need for early treatment. Also a blood marrow examination (if available would be useful to be presented because this is frequently positive both at direct examination and culture.

*p: Answer: We agree with your comment and changed the last sentence of the discussion. The blood marrow was unfortunately unavailable.*

Minor

Introduction line 1-2: it is unclear today if the DOTS strategy has resulted in a huge decrease in incidence. Moreover in all developed countries the decrease in tuberculosis incidence has been observed long before implementation of the DOTS strategy. I would suggest to link the decrease of TB incidence to correct treatment of all cases and increase in welfare.
Answer: We agree with your comment and changed the first sentence of the introduction.

Introduction second paragraph: the statement „Because a substantial number of patients present with few or atypical symptoms” is correct only for people with immunosupression (of any kind). In general immunocompetent patients have a classical picture albeit it is not always very evident clinically. Moreover this patient has presented some symptoms as an inmate but which have been probably disregarded (which unfortunately happens frequently).

Answer: We agree with the fact that the atypical presentation is mostly seen by immunocompromized patient and we added it in the introduction. However, the abstract quoted (cf Ref. 1), reported as high as 30 percent of patients without typical symptoms even in non immunocompromized patients.

In the “Case presentation” section
Second paragraph: please number tables and figure (1 to n) even if only one is presented.

Answer: The table has been numbered.

In the sentence “Blood and urine were sent for bacteriology cultures and returned negative” please state after how much time. Because in some modern blood culture systems culture for M. Tuberculosis is systematically done (especially in HIV + patients).

Answer: the delay of culture’s result has been added.
Please be more precise than "cardiac echography was normal except for a moderate, inhomogeneous impairment of the left ventricular ejection fraction; which segments were involved, what was the global ejection fraction etc.

Answer: The description of cardiac echography has been precised as requested.

Please specify how "cytomegalovirus or herpetic infections" were excluded;

Answer: standard histological examination did not show any suggestive viral inclusion in the different tissues. Immunohistochemistry was not performed, since the type of inflammation clearly oriented to a bacterial origin. The Text has been modified in the case presentation section.

The authors state that "All tissue cultures remained negative for other bacterial infection": did they culture the tissues taken at autopsy? It is generally difficult to get aseptic specimens at autopsy. Generally this is limited for blood, Cerebrospinal fluid or sometimes tissue sampled very rapidly after death.

Answer: Autopsy was performed less than 3 hours after death, and the samples (tracheal aspirate, lung tissue and omentum) were taken in sterile conditions. These post-mortem samples were only cultured for mycobacterial infections, and not for other bacteria.

The term “septicaemia” should be replaced by bacteraemia (when proved by positive blood culture);

Answer: We agree with the comment and modified the term septicaemia by bacteraemia.
It is not correct to state that only seven cases of TB related septic shock have been described in the literature; a few short series exists and probably the reported cases are more than 100 in total.

**Answer:** We modified the text accordingly and added new reference (cf 2nd paragraph of discussion).

The consent paragraph should be very much shortened.

**Answer:** the consent paragraph has been shortened. If requested by the Editor, we are ready to shorten it even more.

Please be more descriptive about ”pyogranulomatous” nodules. The correct term is generally that of granuloma with or without necrosis (with the description of the type of necrosis). Why the term of Pyo was employed ? Does it contain polymorphonuclears ?

**Answer:** Pyogranulomatous nodules means that the necrotizing granulomas were very rich in polymorphonuclears, unlike usual mycobacterial granulomas, which demonstrate caseous necrosis. This somewhat unusual histology correlates with the polymorphonuclear effusion observed clinically just before death. In the text, the term ”pyogranuloma” has been changed, and a more descriptive terminology has been employed (cf last paragraph of case report and discussion).

We feel that these modifications improved our paper and we hope it is now suitable for publication.

Yours sincerely,

Olivier Nançoz, MD