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Dear Editor,

We thank you for considering our work and hope you will judge appropriate the revised form.

As requested, here are the answers to the questions asked by both reviewers.

Reviewer 1:

1. To diagnose suspected tuberculosis, SPOT test can be helpful.

You are right, SPOT test can be helpful. This test was unfortunately not done. The medical staff in charge of the patient considered empyema with purulent fluid as unlikely to be caused by *Mycobacterium tuberculosis*.

2. Why not drawn pleural fluid repeatedly if the volume is increasing? The quality of the fluid is also changing to become purulent.

We chose surgery instead of repeated pleural drawings, because local sepsis was not controlled nor bacteriologically documented

3. Why did you change the antibiotics after thoracentesis?

Treatment with metronidazole was added to cefotaxime after the surgery in order to cover anaerobic bacteria.

4. Why did the patient's condition deteriorate progressively after surgery when the purulent fluid was removed ? Typically, sepsis can be more easily controlled if the surgical site of infection was drained. Are there large transfusion or fluid loading

during operation? Which can cause fluid overload. Large volume transfusion may cause acute lung injury.

Unfortunately, the *L. pneumophila* stain identified in our patient was naturally resistant to all the antibiotics received.

As no massive transfusion was initiated during surgery and shock was the main matter, fluid overload could not explain the evolution in multiple organ failure.

5. What is the sensitive test for the bacteria ? Which antibiotics did it sensitive to ? If it was sensitive to the antibiotics that had been used, the infection may not be the cause of his death.

Because the *L. pneumophila* stain identified in our patient was naturally resistant to all the antibiotics received by our immunocompromized patient, we think likely the infection to be the cause of his death.

6. Suggest to report the SOFA score sequentially (to create a time line) with reference to the use of antibiotics, surgery and other important treatment strategy ; this may provide hints to why the condition deteriorated.

As the patient only stayed a few hours in our intensive care unit, it is hazardous to have a clear idea of SOFA score before intensive care admission day by day.

However, it is sure that after a slow unfavorable evolution during the ten first days of hospitalization, the patient's condition worsened brutally three days after surgical thoracocentesis leading to septic shock complicated of multiple organ failure.

7. Also need to consider why the patient got infected by the *Legionella pneumophila*.
Some risk factors?

Retrospectively, our patient presented the following risk factors: male sex, aged more than 50 years, chronic lymphocytic leukemia with history of immunocompromising treatments, chronic kidney failure, diabetes mellitus and weaned smoking.

8. In the conclusion section, the statement "pleural empyema of unknown cause" needs to be defined. Like the definition for fever of unknown origin (FUO), there is

specific diagnostic workup for the condition. So what did you mean by “pleural empyema of unknown cause”?

We consider pleural empyema with negative bacteriological standard culture and unresponsive to conventional antibiotherapy as pleural empyema of unknown cause.

9. Need several lines of discussion on the treatment of sepsis, cite a reference is helpful.

Early identification of sepsis and early administration of adapted antibiotherapy is now recommended by international clinical practice guidelines[14]. In our case report, identification of sepsis and its pleural origin was easy. Unfortunately, empirical antibiotherapy did not cover Legionellosis, and probably led to the patient's death.

14. Zhang Z, Smischney NJ, Zhang H. AME evidence series 001 – The Society for Translational Medicine: clinical practice guidelines for diagnosis and early identification of sepsis in the hospital. J Thorac Dis 2016 Sep; 8(9): 2654–2665 [PMID : 27747021 DOI : 10.21037/jtd.2016.08.03]

Reviewer 2 :

1. Is there a chance of a super infection or a co-infection with another microbial entity causing empyema ?

We believe that chances of super infection or co-infection with another bacterium are scarce. Patient indeed received broad spectrum antibiotics directed against common bacteria causing pleural empyema (including anaerobic bacteria, gram-negative bacillus, streptococci and staphylococci), and repeated standard bacteriological cultures remained negative.

Sincerely,

François Maillet.