Author's response to reviews

Title: Acute tubulointerstitial nephritis complicating Legionnaires' Disease: a case report.

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

We thank the reviewers for their comments on the manuscript “Acute tubulointerstitial nephritis complicating Legionnaires' Disease: a case report”. We think we were able to respond to the concerns of both reviewers, and this improved our manuscript.

Here is our point-by-point response.

Sincerely,
Dr Aurélie Daumas.

Reviewer 1

Minor revision. Please add the following information in the text.

Comment 1: Discussion Section
-The urine antigen test is highly specific, provides rapid results, and is particularly useful because the fact that test positivity can persist for days even during administration of antibiotic. Specificity of sputum culture is high, however, obtaining an adequate sputum specimen can be difficult. The test for serum antibodies to Legionella has a high specificity, but the lowest sensitivity. To date, clinical experience has not shown PCR to be more sensitive than culture, and therefore the Centers for Disease Control and Prevention (CDC) does not recommend the routine use of genetic probes or PCR for the detection of Legionella in clinical samples.
Ref:

→ The following text was added in the discussion section:

“The urine antigen test is highly specific, provides rapid results, and is particularly useful because positive Legionella antigenuria can persist for days even during administration of antibiotics [...]. Sputum culture has a high sensitivity and specificity and allows the identification of all types of Legionella, but obtaining an adequate sputum specimen can be difficult, as in our patient [1-5]. The test for serum antibodies to Legionella has a high specificity, but the lowest sensitivity, a 4-fold increase in antibody titers being necessary for the assessment of seroconversion, which may not be detectable until 4 to 12 weeks after infection [3]. To date, clinical experience has not shown PCR to be more sensitive than culture, and thus the American Center for Disease Control and Prevention (CDC) does not recommend the routine use of genetic
Comment 2: Discussion section
-The mechanism of renal failure associated with Legionnaires’ disease is mostly multifactorial. Histological examination of renal biopsy usually shows tubulointerstitial nephritis and/or acute tubular necrosis in patients with acute renal failure [1]. Among possible factors, those associated with dehydration or shock, rhabdomyolysis, endotoxemia and direct microbial toxicity. In one previous report, the existence of Legionella bacteria was found by electron microscopy [2]. Therefore, recent reports describing the mechanism of renal dysfunction seem to point to direct renal toxicity from the Legionella organism or a systemic manifestation of Legionnaires’ disease [2].
-In the lung, the organism is phagocytosed into respiratory epithelial cells, where it replicates and induces cellular injury [3]. It is possible that the same process occurs in renal epithelial cells, both at the tubular epithelial cells and at the glomeruli.

Ref:
“The mechanism of renal failure associated with LD is mostly multifactorial: in addition to functional AFR (hypovolemia), acute tubular necrosis (shock or rhabdomyolysis) and drug toxicity, Legionella pneumophila has also its own renal toxicity [7-14]. The mechanism of renal dysfunction could be a direct nephrotoxicity of the microorganism, but the presence of Legionella bacteria in renal tissue was documented by electron microscopy in 3 cases only [8]. In the lung, the organism is phagocytised into respiratory epithelial cells, where it replicates and induces cellular injury. The same process may occur in renal epithelial cells [9]. In our observation, bacterial antigen was not found in renal tissue. The most likely explanation for the systemic manifestations of the LD, including ARF is the presence of a circulating endotoxin responsible for vasoconstriction or occlusion of the microvasculature of various organs [10]. Histological examination of renal biopsy in patients with AFR in a context of LD usually shows tubulointerstitial nephritis (TIN) and/or acute tubular necrosis [7-14].

The references were added (references [14], [10] and [9] of revised manuscript).
The report includes a nice summary of the case along with investigations (biochemistry and renal biopsy) and the treatment the patient received. Although they intend to show that this is a case Legionella associated with AIT, I have a few worries about this case.

1. They have not fully convinced us that the said patient had Legionella infection:
   A patient with that degree of lung involvement will have sputum positive test which has been shown to have better sensitivity and specificity at diagnosing Legionella than other tests (see: Roig J, Rello J. Legionnaires' disease: a rational approach to therapy. J Antimicrob Chemother. 2003 May;51(5):1119-29)

   → A sputum samples could not be obtained from the patient, who had a dry and irritative cough. We specified it in the case presentation section: “No sputum could be obtained for culture...” and added in the discussion section “Sputum culture has a high sensitivity and specificity and allows the identification of all types of Legionella, but obtaining an adequate sputum specimen can be difficult, as in our patient.”

   → The reference by Roig et al was added (reference [4] of the revised manuscript).

Could the urine test for Legionella antigen be false-positive?

→ The patient reported no recent infection, and had no rheumatic disease. We added in the discussion section: “A risk of false-positive results has been reported in
patients receiving anti-thymocyte or in those with rheumatoid-like factors in urine."

Was a source of Legionella infection founded? If yes, then it should be clearly stated.

→ No source of Legionella infection could be found for our patient. We specified it in the case presentation section: “Investigation of Health Services did not find the source of Legionella contamination”.

2. We found no other tests to exclude other possibilities for AIT. There are no serologies for other infectious diseases or especially there were no tests for a systemic disease.

→ Because it was not clear enough in the text, we moved the section on differential diagnosis so that it appears earlier in the revised manuscript: “Blood cultures were normal, bacterial and viral serologies negative (leptosiriosis, HIV, Hepatitis B Virus, Hepatitis C Virus), the search for tuberculosis and for auto-immunity was negative (normal complement level, negative antinuclear antibodies and anti-SSA/SSB), and eye examination was normal. We thus attributed this acute TIN to Legionnaires’ Disease.”

3. The normal reference ranges for some values provided in the text should be provided.

→ Normal reference ranges were provided in the text.