Author’s response to reviews

Title: Acute illness associated with Ehrlichia sp. Panola Mountain from Atlanta, Georgia, USA: a case report

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Author’s response to reviews: see over
Reviewer: Michael Rosenblum
This is a persuasive presentation for a potential new cause of ehrlichia in humans. You have made it plain that the patient's symptomatology may have been the result of another causative agent that went unrecognized and this is of utmost importance. In the laboratory section of the presentation, the DNA sequences are not going to be significant for the majority of readers and should be removed to create a more concise abstract. The specifics of the testing though important do not need to be discussed at such length or specificity.

Response:
DNA primer sequences have been deleted.

Reviewer: Laurel Garrison
General Comments:
A very nice case report of the first ever documented human infection with the Panola Mountain Ehrlichia. However, the argument would be stronger had the tick been appropriately preserved for testing and tested positive as well.

Revisions necessary for publication:
1.) To my knowledge, this is the first report to use the name â##Ehrlichia sp. P-Mtnâ## to describe the Panola Mountain Ehrlichia. I would suggest using the name â##Panola Mountain Ehrlichiaâ## for consistency, or including a statement about the different name.
2.) This case does not technically meet the CDC surveillance case definition for infection with Ehrlichia sp. It meets the laboratory criteria, but fails to meet the clinical criteria. If using the 2000 case definition, fever or rash is required, and if using the 2008 case definition, fever is required. Re-phrase the last sentence of the introduction to state that this case meets the laboratory criteria only.
3.) The table is not necessary since the patientâ##s CBC results were all within normal limits.

Response:
1) Changed to “the Panola Mountain Ehrlichia sp.” to be more consistent with other manuscripts on this agent. “Ehrlichia sp. P-Mtn” is the designation for the GenBank entries.
2) Rephrased to “laboratory confirmation” and updated reference to the newly released 2008 case definition.
3) We agree that the CBC was within reference ranges and would be willing to remove it if the editorial staff desires. However, the other reviewers appear to want this information included, so we have left it in.

Reviewer: Karen Bloch
The authors report a case of a patient with ehrlichiosis caused by a newly described species that has never previously been reported in humans, with the diagnosis confirmed by PCR of whole blood. This is an interesting & novel report. Substantiative comments on the content are below:
1. While it is notable that no Rickettsial DNA was amplified from pts blood, PCR is notoriously poor for diagnosis of RMSF, and serology is the gold standard. Were R. rickettsii titers performed? If not, how can the authors be sure this wasn't RMSF responsive to doxy?
2. No discussion is made of the genetic relationship between this newly described organism & other Ehrlichia spp. Is this phylogenetically close to chaff? Ewingii? This has potential bearing on serologic cross-reactivity.
3. There needs to be a more complete discussion of the significance of this finding for clinicians...lower threshold for empiric therapy and if so, in what pt population? Increased need for whole blood PCR in pts with possible tick-borne disease? What are the implications of this new human pathogen???

Response:
1) We recognize that we cannot conclusively rule out other tick-borne diseases and have already addressed this limitation in the discussion. Serology for other tick-borne diseases was performed, was negative for all agents tested, and was previously omitted from the manuscript in the interest of brevity. We have added this information back in. We would also like to point out that A. americanum does not transmit RMSF.
2) The phylogenetic status of this agent was reported in reference #4 but has been summarized briefly in the conclusion for readers of this paper.
3) Added a sentence underscoring the value of PCR testing of whole blood for diagnosis. Thresholds for empirical therapy, patient populations, etc., are interesting questions but beyond the scope of a case report.

Specific comments to improve the case report:
Abstract:
1. Only 2 spp. of Ehrlichia cause dz in the US--sennetsu causes human infection in Japan. Clarify or correct.
2. The authors allude to a "sore neck"--on exam was this felt to be nuchal rigidity? Musculoskeletal? A better clinical exam would be helpful here.
3. Recommend including a sentence that paired serology was performed and was inconclusive.

Introduction:
1. Cite the sentence about treatment abrogating serologic response
2. I am confused by the sentence “Only E chaff is available for serologic...increasingly relies on PCR”. These seem like 2 true but unrelated facts. Clarify or separate into 2 sentences.

Case:
1. Was the male previously healthy? Any immunodeficiency? Steroids?
2. Awkward phrasing, suggest "USA presented with a complaint of neck soreness for 3 weeks."
3. More historical details & PE would be useful. Was there photophobia? Nuchal rigidity? Reproducible tenderness with palpation of SCM or trapezius? Focal neuro exam? Was any bloodwork done prior to starting doxy? Imaging?
4. The time frame of 48-60 hours seems sort of random. More typically would go by 24hr increments (48-72 hours).
Lab testing:
1. I would recommend putting the CBC results in the case presentation. They are out of place in lab testing.
2. Recommend putting IgG before "32 (15 Oct).

Response:
Abstract #1: The abstract states that “two species of Ehrlichia are known to cause human illness”. This refers to E. chaffeensis and E. ewingii and is a factual statement. Sennetsu is not an Ehrlichia; it was formally moved to Neorickettsia in 2001 (Dumler 2001).
Abstract #2: The sore neck was believed to be musculoskeletal. Added into case presentation.
Abstract #3: Added.
Introduction #1: We realized that the reference for this statement was not already in the paper and we had reached our limit for references, so we deleted the statement.
Introduction #2: Since serology and PCR are the most commonly used methods of diagnosis, they are related – but PCR is replacing serology, especially when acute diagnosis is critical or appropriate antigen is not available. Clarified this issue in the text.
Case #1: Male was previously healthy with no known immunosuppressive factors.
Case #2: Done.
Case #3: Unfortunately, this information is not available. The patient did not report photophobia. All work was done at a small outpatient clinic, and a focal neuro exam or imaging were not performed.
Case #4: The patient reported significant improvement after 4-5 doses of doxycycline, which were spaced 12 hours apart: 48-60 hours.
Lab Testing #1: CBC is not a presentation, but is performed by a laboratory.
Lab Testing #2: Done.

Reviewer: John Goldman
One of the best manuscripts I have seen submitted to this journal. It was well written, well thought out, and persuasive. I think you made a convincing case for infection with a newly reported Ehrlichia species.
The only criticism I would have was that I thought the level of detail on the specific laboratory tests done were more appropriate for a basic science journal. For example I would not include the specific PCR primers.
I would suggest putting in slightly less detail to make the description of the laboratory tests more appropriate for a clinical journal.
I thought it was very well done.

Response:
DNA primer sequences have been deleted, as well as the recipe for PCR reactions.