Title: Unusual cardiovascular complications of brucellosis: a case series

Authors:

Nikolaos K Gatselis (ngatsel@med.uth.gr)
Konstantinos P Makaritsis (makarits@med.uth.gr)
Ioannis Gabranis (forestgab@in.gr)
Aggelos Stefos (agstefos@hotmail.com)
Konstantinos Karanikas (bpthkos@yahoo.gr)
George N Dalekos (dalekos@med.uth.gr)

Version: 2 Date: 21 October 2010

Author's response to reviews: see over
Attention to:
Professor Michael Kidd
Editor-in-Chief, Journal of Medical Case Reports

Dear Professor Kidd,

Thank you very much indeed for your two e-mail messages dated September 2 and 9, 2010 concerning our manuscript by Gatselis et al entitled “Unusual cardiovascular complications of brucellosis: two case reports and review of the literature” your Ref No: MS: 1178346931376342 that is kindly been recommended for revisions in the Journal of Medical Case Reports.

Today we submit our revised manuscript with all changes precisely indicated in the text (additions in red; deletions are also obvious). Also, I have uploaded an unmarked version of the revised manuscript.

We are very grateful to you and the assessors for the helpful and thoughtful recommendations and for your willingness to consider a revised manuscript. We believe that we addressed most of them satisfactorily. All of us feel that our paper has now been significantly improved. A co-author who substantially contributed to the preparation of the revised version has now been added (A. Stefos).

Our point-by-point responses, to each of the reviewers’ comments/suggestions, are as follows (with respect to the marked revised version of the manuscript):

Reviewer #1 (Christopher Coulter):

1. “General comments: The authors title their paper as a case series. However two cases do not make a ‘series’. These cases are not unique as other authors in recent years have also made the same point: that cardiac involvement with brucellosis is rare and even more so in the absence of concomitant endocarditis. However as the number of cases in the literature is numerically very low, the present two cases are worthy of publication but revisions to the paper are required”.

   Reply: We have followed the recommendation of the reviewer and the title has now been changed accordingly.

2. “There are quite a few grammatical errors throughout the paper which should be addressed. Some words do not translate well into English for an academic paper. For example the word "cookers" [Discussion, paragraph 2] would better be termed "food handlers" or similar”.

   Reply: We have followed your suggestion (see page 7). In addition, several reconstructions in the whole new text have now been done by a native speaker of English (please see additions/deletions throughout the text).

3. “Introduction: Sentence two - the use of the word 'as' implies that the generalized and systemic symptoms of brucellosis are due to the fact that almost every organ can be affected, whereas using the word "and" would be more accurate”.

   Reply: According to your suggestion we have changed the text (page 3).
4. “Case 1. This case is presented as a case of pericarditis complicating brucellosis. In fact none of the cardinal features of acute pericarditis were present i.e. there was no chest pain, no ECG changes and pericardial friction rub. There are no features of chronic pericarditis. This is a case of pericardial effusion presenting with acute brucellosis. It is unclear whether this is a direct infection of the pericardium or an immunological phenomenon, as no invasive diagnostic procedure was performed (acknowledged by the authors). While pericarditis may well be the cause of the pericardial effusion, this patient did not have any clinical or ECG evidence of pericarditis. I suggest the authors change their paper to reflect that they are describing a case of asymptomatic pericardial effusion. The word “New” in second last sentence of case 1 report is not necessary”.

Reply: I absolutely agree with your comment. Therefore, we have changed in the new version the word “pericarditis” with “asymptomatic pericardial effusion” throughout the text in order to reflect precisely what we are describing (Page 2, abstract; Page 3, introduction; Page 5; Discussion, pages 8, 9 and 10). Also, the word “new” in the second last sentence of case 1 (page 5) has now been deleted.

5. “Points on microbiological diagnosis (cases 1 and 2). If the authors are wishing to attribute these rare manifestations to a particular species of Brucella, it is important that some reference is made to how the laboratory confirmed the diagnosis. While the local epidemiology would make the pre-test probability of the species being B. melitensis likely, accurate speciation is problematic in a routine microbiological laboratory. Were the isolates identified in a reference laboratory and what methods were used? The serological agglutination test is not species specific for B. melitensis”.

Reply: This issue is a valid critique raised by the reviewer. Thank you very much indeed. You have absolutely right and of course we are not able to identify particular species of Brucella in our routine practice (similarly to the reported previous publications of my group e.g. ref. 7-9). Therefore, we have now deleted this statement which has mistakenly been reported in our previous version of the paper (Pages 4 and 6).

6. “The authors refer to high titre ELISA tests. These assays are usually not reported as a quantitative titre, unless specific control standards have been used. There may have been a high signal to cut off ratio detected by the laboratory but this is not usually reported as it can be problematic comparing values from different runs.

Reply: I can realize the concerns raised by the reviewer. Therefore, we have now provided the precise characteristics of the method which was used according to the instructions of the manufacturer with the exact upper normal limits in U/ml for IgG and IgM antibodies against Brucella (pages 4 and 6).

7. “Case 2. In the second sentence the use of the word “referred” would be better replaced by “described” or “complained of”. In the third sentence replace the word “as” (a common cold) with “for a”. In addition consideration could be given to using “upper respiratory tract infection” instead of “common cold”. No ‘e’ required for troponin. Suggest add “wall” after the word “ventricular” [para 3 sentence 4 of case 2]. Suggest delete “so far” at the end of the final paragraph describing case 2”.

Reply: We have followed all your suggestions in the new version (page 5, Case 2; page 6, 2nd paragraph and page 7 1st paragraph).

8. “Discussion/ Conclusion. Other publications are referenced to back up the assertion that cardiac complications, without endocarditic are rare. It would be useful if any clinical information on presentation from other cases could be summarised though there may not be sufficient detail in the papers to make this possible”.

Reply: According to your recommendation we have now added a Table presenting the published data in the English literature between 1984 and 2010 on this issue (Brucella-related pericardial effusion, pericarditis and myocarditis in adult patients in the absence of concomitant Brucella-related endocarditis). In addition, we have added a comment concerning this Table in the discussion section (page 8), while the appropriate new references (ref. 21-25).

9. “The authors make the case that pericardial and myocardial manifestations of brucellosis may be under-diagnosed due to the lack of routine use of echocardiography. While this is possible, both cases presented showed evidence of their cardiac involvement on routine tests i.e. chest radiograph (case 1) and ECG (case 2). It would be reasonable to emphasize the use of these tests in assessing febrile patients, especially where brucellosis is clinically and/or epidemiologically suspected.
Echocardiography can be used where such abnormalities are detected. If the authors go on to complete and publish their planned study where routine echocardiography of all cases provides useful information which changes clinical management, then broader recommendations may be appropriate”.

Reply: This is also a valid comment. Thank you. I absolutely agree with you and therefore, we have now changed the respective text accordingly (page 9, 2nd paragraph and page 11, lines 1-4).

10. “Quality of written English: Needs some language corrections before being published”.

Reply: The whole revised manuscript has now been corrected by a native speaker of English (please see additions/deletions throughout the text).

Reviewer #2 (Georgios Pappas):
1. Valuable presentation, well documented Two things needed: “Polishing of grammar and syntax- it is surprising (at least for the final author's track) to see some awkward use of English”.

Reply: Please see my responses No. 1 and 10 to Reviewer # 1.

2. A short comment on the rationale of 3-month treatment duration (compared to the typical 6 weeks in uncomplicated disease)

Reply: I can realize the concern raised by the reviewer. However, from our experience treating more than 30-45 patients with diverse manifestations of brucellosis annually, we believe that these cases cannot be considered safely as “uncomplicated” disease. Therefore, we made a comment on this issue to satisfy the reviewer (Discussion, page 10, lines 9-17).

Reviewer #3 (Javier Solera):
1. “GENERAL COMMENT: The authors describe two cases with unusual manifestations in patients with acute brucellosis. The cases are well described but they do not provide relevant diagnostic clinical or physiopathological information. A literature review would be useful if a detailed description of previous cases was provided along with the cases reported by the authors. In such review besides the epidemiological data described in the discussion they should include a detailed description of the clinical findings, ECG, echocardiography, and other imaging tests, laboratory data including myocardial damage parameters, treatment and outcome”.

Reply: Please see my response No. 8 to Reviewer # 1.

2. –“The title can be misleading because just two cases are not a “a case series”.

Reply: Please see my response No. 1 to Reviewer # 1.

3. “Case I: Pericarditis and pericardial effusion as isolated finding in the echocardiogram has been described previously. This patient had no characteristic chest pain, nor pericardial friction rub and no ECG changes, therefore the patient had a pericardial effusion as a finding in the echocardiogram. Information about immunological alterations in laboratory data could be interesting e.g.: immunoglobulins, complements, rheumatoid factor, protein C reactivity, since the patient could have a pericardial effusion of immunological nature related or not to the bacteria”.

Reply: Please see my response No. 4 to Reviewer # 1. In addition, in our previous version we had stated clearly the abnormal laboratory findings of the cases (this means that the remaining tests e.g. hematological, biochemical and autoimmune serology, are within normal ranges). By the way, in order to further satisfy the reviewer we have now added the whole laboratory work-up (page 4 last line; page 5, lines 1-3 and page 6, lines 6-7).

3. “Case I: In relation to the treatment, it should be clarified if the patient received NSAID or corticosteroids. The discussion should comment why the patient received treatment with three antibiotics and during three months, despite the fact that endocarditis was not found”.

Reply: We have now made clear that the patient (actually both patients) did not receive NSAID or corticosteroids (page 5, lines 7-8; page 7, line 1 and Discussion section, page 10, lines 9-10). Concerning the treatment schedule please see my responses No. 2 to Reviewer # 2.

4. “CASE II: Treatment should be clearly explained i.e: dosis, duration, route of administration. Did the patient receive corticosteroids or NSAID?. Were the “mild regional motion abnormalities” detected by echocardiography resolved?”. 
Reply: We had stated in our previous version clearly in an attempt to have a brief description of our cases that the second patient received similar treatment (triple therapy with the same doses and duration) as the first one. By the way, we have now presented the data as you like precisely in the revised version (page 7, 1st par). Concerning NSAIDs and corticosteroids: Please see my response No. 3 to your comment No. 3 above. The motion abnormalities did resolve as we have also stated in our previous version (page 7, 1st par).

5. “DISCUSSION: The three first paragraphs of the discussion can be suppressed since they do not provide new information and it is not focused on the cardiological manifestations of brucellosis”.
Reply: According to the reviewer’s suggestion we have shortened the three first paragraphs of the discussion (page 7).

6. “DISCUSSION: A table summarizing clinical characteristics of the few reported cases would be useful for clinicians”.
Reply: Please see my response No. 8 to Reviewer # 1.

7. REFERENCES: There are some relevant references missing that can be found in Medline searching for “pericarditis” and “brucellosis”
Reply: Please see my response No. 8 to Reviewer # 1.

8. “Quality of written English: Needs some language corrections before being published”.
Reply: Please see my responses No. 1 and 10 to Reviewer # 1.

Reviewer #4 (Charalambos Gogos):

Interesting case reports and a well written review.
Minor comments: A figure of cardiac U/S should be presented. One of the patients had elevated LFTs. What about the other one? Was the presence of other systemic manifestations suspected, e.g. hepatic granulomas, splenic disease? Any signs of skeletal disease, e.g. spondylitis?
Reply: With all of my respect to the reviewer I do not know why an echocardiographic study showing pericardial effusion is important for publication of these cases and the extensive review (I really think is too much for case reports; besides I can assure you that very few reports after my extensive review show a figure with pericardial effusion). By the way, in case of final acceptance if the editorial staff insists we can provide the respective figure. Detailed information on the LFTs of the second patient is now given (page 6, lines 6-7). Concerning the potential presence of other manifestations of the disease: we have now clearly added the respective data (page 4, line 1; page 5, lines 4-5; page 6, line 2 and lines 2-4 from the bottom).

Once again, I would like to thank you and the referees for your helpful suggestions and for giving us the opportunity to submit a revised manuscript. I do hope now that our revised manuscript will be found suitable for publication in the Journal of Medical Case Reports.

Kind regards,
Yours sincerely

George N. Dalekos, MD, PhD
Professor and Chairman