Title: Retinal vasculitis with Chronic Recurrent Multifocal Osteomyelitis: a case report and review of the literature

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Author’s response to reviews:

Dear Dr. Gaffo,

RE: Retinal vasculitis with Chronic Recurrent Multifocal Osteomyelitis: a case report and review of the literature (BRHM-D-18-00087)

Thank you for reviewing the attached manuscript for possible publication in the BMC Rheumatology. We have responded to reviewer comments below. Edits are highlighted in yellow in the manuscript.

1. Title: Suggest the title be changed to include CRMO as intermittent sternoclavicular pain is too nonspecific.

Title has been changed as requested to: Retinal vasculitis with Chronic Recurrent Multifocal Osteomyelitis: a case report and review of the literature
2. **Abstract:** remove “at the request of the ophthalmologist” since I am not sure what it adds to the case

Phrase has been removed as requested.

3. **Background:** Please add references to the table with the differential diagnosis of retinal vasculitis. There is not much information on the pathophysiological link between retinal vasculitis and CRMO

References added as requested

4. **Case presentation:** Suggest starting the manuscript with the clinical case rather than the background as the information is currently the manuscript is hard to follow

This change has been made as requested

5. **Differential diagnosis:**
   a. Suggest rephrasing of the first sentence “A 37-year old woman presented with retinal…”

This change has been made as requested

b. Bony and Boney are both used – please correct spelling

Spelling has been corrected throughout manuscript.

c. Why did the authors start discussing sarcoidosis first – is that the most common disease that causes both CRMO and retinal vasculitis

Introductory paragraph to differential has been reworded. For the purposes of this review and discussion, we will focus on diseases that are known to cause both lytic/sclerotic bone lesions and retinal vasculitis.

d. Authors state more than 60% of patients with sarcoid uveitis have … however the case described is about retinal vasculitis. Is there data on how often ACE is elevated, or how often CXR shows characteristic changes of sarcoid.

Phrase changed to sarcoid eye disease. Reference provided.

e. Line 2 on page 11 – authors point out that the sclerotic and lytic lesions noted are not typical for sarcoidosis, but on page 5 they say the opposite.
Mixed sclerotic and lytic lesions are not typical for sarcoidosis

f. To my knowledge the HLAB27 is not a diagnostic test for ankylosing spondylitis, so its absence does not exclude the etiology

Sentence reworded: In this case, HLA-B27 testing was negative, essentially excluding the HLA-B27-associated arthropathies as an etiology.

g. Suggest providing more references for the information presented in the tuberculosis section

Additional references have been added.

h. How was tuberculosis ruled out

Sentence added: This patient had a negative QuantiFERON-TB gold screening test and no other systemic findings of tuberculosis.

i. How was primary lymphoma of the bone ruled out

Primary lymphoma of the bone was ruled out following the bone marrow biopsy

j. Was bone specific alkaline phosphatase obtained

This test was not done.

k. Why discussion of management of CRMO was included in the differential diagnosis section

This has now been moved to the discussion section for better continuity of the manuscript.

l. How was multiple myeloma ruled out

Multiple myeloma was ruled out following the bone marrow biopsy

m. The authors don’t explain why a primary ocular disease could not be the etiology of the patient’s symptoms.

Throughout the manuscript we do explain that the focus of discussion is related to diseases that can cause both eye involvement and mixed lytic and sclerotic bone lesions.

A primary ocular disease would not have caused the bone lesions that were seen in this case.

n. Why the authors chose to highlight some but not all the conditions described on the first two columns of table 1.
For the purposes of this review and discussion, we have only focused on diseases that are known to cause both lytic/sclerotic bone lesions and retinal vasculitis.

- Clinical course information is more like an additional evaluation information

Title of this section changed to DIAGNOSTIC TESTING

- Bone marrow biopsy: What is CD138 marker for and how about CD56 – a casual reader may not know the significance of these markers.

CD138 is a marker of plasma cells and multiple myeloma cells. CD56 is a marker of NK cells. These have been clarified in the text.

- Where there any special stains performed on the bone marrow biopsy

The description includes the reports of all the additional testing done on the bone marrow biopsy.

- Diagnosis: No need to capitalize chronic recurrent multifocal osteomyelitis

This change has been made as requested

- How long was the patient treated with prednisone

Treatment is ongoing. Section re-worded

- On what basis was TNFi therapy used

Section reworded: After completion of lactation she continued to have elevated inflammatory makers and significant pain and swelling at the sternoclavicular joint. She was commenced on TNF-α inhibitor therapy with adalimumab (Humira®) and prednisone was slowly tapered

- Was there any follow up imaging

Follow up imaging was not performed since the patient was improving and it was not deemed to be clinically indicated.

- Is there any pathophysiologic link between retinal vasculitis and CRMO

This is unknown. Conclusion has been expanded.

6. Conclusion: Can the authors provide a bit more detail in the conclusion paragraph and include the why of this diagnosis

Expanded as requested: The final diagnosis in this case was that of chronic recurrent multifocal osteomyelitis with retinal vasculitis. Inflammatory eye syndromes including episcleritis have
previously been reported in association with CRMO spectrum disorders (39). However, in this case we describe a novel report of retinal vasculitis with confirmed evidence of CRMO on bone biopsy adding to the literature of the association between CRMO spectrum disorders and inflammatory eye disease.

7. Figure 2A: There are some other regions of uptake on the PET – is that expected? A casual reader might not be familiar with PET results as it is still not very commonly used diagnostic test.

The other regions of uptake are physiologic, the following was added to the figure legend: Normal physiologic tracer uptake is present in the brain, heart, salivary and parotid glands, adenoids and palatine tonsils, and vocal cords. There is also physiologic urinary clearance of the tracer into the renal collecting system.

8. Table I: Some infectious etiologies are presented based on etiologic agent and some are not – suggest consistency

This change has been made as requested.

9. Table 2 – why the authors included the first 2 columns

The first two columns were included to clarify the causes of isolated sclerotic bone lesions, the causes of isolated lytic bone lesions and the causes of mixed lytic and sclerotic lesions.

10. Table 3: are there any results from the original presentation

Results are not available from the original presentation.

11. What was the albumin and PTH

The albumin was normal (4.2), PTH was not tested.

12. Authors present multiple negative autoantibody results – not sure if this is necessary

See comment below – OK to move to supplemental data if there is insufficient room.
13. Figure 1: There seem to be some abnormalities around the optic disc, should they be labelled?

Legend for figure 1 has been changed to: Figure 1: Fluorescein angiogram of the left eye demonstrating regions of retinal vascular staining and leakage near the optic nerve and in the peripheral retina (arrows).

Reviewer 1:

14. Consider leading with the case description and eliminating the small background paragraph and from the case transition to differential of retinal vasculitis, differential of mixed sclerotic… followed by the specific diseases

This change has been made as requested

15. Page 2, line 5 replace “as well as” with “and”. Gramatically, the term “both” precedes and it should read “both lytic/sclerotic bone lesions and retinal vasculitis”

This change has been made as requested (note section moved)

16. The case description can be consolidated. Condense the review of systems into 1-2 sentences and include in HPI

Review of systems consolidated as requested

17. Include medications in HPI as current treatment for chest/sternal pain

This has been changed as requested

18. Family and allergies not necessary – would delete

Deleted as requested

19. Physical exam is rather specific – report the vitals as “Vital signs, including BMI were normal”
This section was changed as requested.

20. Consider adding headers to the disease categories under differential diagnoses descriptions (e.g. autoimmune, infection, etc.)

This has been done as requested.

21. Under TB there is no mention of the TB screening being negative to rule out. All the other sections state why that disease was eliminated (which was great)

This has been added.

22. Page 17, Line 2 need sources added to support the treatment options

Reference added to support current treatment options for CRMO.

23. Consider deleting table 3. Everything except the inflammatory markers was unremarkable. All pertinent labs were addressed in the text.

Authors recommend retaining – OK to move to supplemental table if insufficient room in print, but most cases of this kind would include such a table.

Thank you for reconsidering this revised manuscript for publication.

Yours sincerely,

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