Author's response to reviews

Title: Heterogeneous Bone Marrow Uptake on interim 18F-FDG PET scan for Lymphoma mimicking disease progression: a case report

Authors:

Martin H Cherk (m.cherk@alfred.org.au)
Sushrut Patil (S.Patil@alfred.org.au)
Paul Beech (p.beech3@gmail.com)
Victor Kalff (Victor.kalff@monash.edu)

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Author's response to reviews: see over
Authors Response To Reviewers

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Authors – Martin H Cherk, Sushrut Patil, Paul Beech, Victor Kalff

m.cherk@alfred.org.au
s.patil@alfred.org.au
p.beech3@gmail.com
victor.kalff@monash.edu

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Authors Response To Reviewers – See Over
Dear Journal of Medical Case Reports

Re: MS 2856543391308298 - Heterogeneous Bone Marrow Uptake on interim 18F-FDG PET scan for Lymphoma mimicking disease progression: a case report. Cherk et al.

Thank you for considering our manuscript for publication in your journal. We have addressed the editors and reviewers queries as follows.

**Editor Queries / Requests:**

1. Please change the description of the patient’s gender to ‘female’.
   
   **Done.**

2. Please include the Ethnicity of the patient in the Abstract and Case presentation sections.
   
   **Done.**

3. Please include three to ten keywords representing the main content of the article, after the Abstract section.
   
   **Done.**

4. Please change the ‘Background’ section header to ‘Introduction’.
   
   **Done.**

5. Please include a list of abbreviations used in the manuscript and their meanings after the Conclusions section.
   
   **Done.**

6. Please upload the figures as separate files via the online submission system. They should not be included within the main manuscript document.
   
   **Done.**

7. Please remove the Figure legends in the figure files. They should be included after the References list.
   
   **Done.**
Reviewer 1 Queries / Requests: Nil

Reviewer 2 Queries / Requests:

1. What was the site of the initial bone marrow biopsy?

   Right ilium.

   This information has been added to the Case presentation section of the manuscript.

   “A bone marrow aspirate and trephine of the right ilium at a site of increased FDG uptake on PET scan confirmed......”

   Was this site non-avid on the initial PET?

   This site was intensely FDG-avid on the initial PET in keeping with a site of active disease. This information has been highlighted in the case presentation section of the manuscript.

   “Heterogeneous increased FDG uptake was also seen in a right external iliac node and throughout the skeleton, most marked and intense in the trochanteric region of the right femur and right ilium consistent with marrow infiltration.....”

   Patchy bone marrow regeneration with a "flip-flop" phenomenon has been observed in high grade lymphoma and has been previously reported


   The “flip-flop” phenomenon has now been added to the discussion along with the two additional references provided.

   “.....PET scans which can result in a heterogeneous appearance where sites of successfully treated lymphoma which appear photopenic are interspersed with islands of more FDG-avid regenerating normal marrow. This ‘flip-flop’ phenomenon on PET scan has been previously described in cases of high grade lymphoma[12, 13].”

   It can be quite striking especially after the use of GCSF.

   A separate paragraph in the discussion section highlights how Pegfilgrastim (GCSF) likely exaggerates the heterogeneous appearance on interim and post therapy PET scanning.

   “At this time point, Pegfilgrastim was likely having its maximal stimulatory effect on granulopoiesis resulting in any residual islands of normal bone marrow appearing particularly FDG-avid further mimicking disease progression in the marrow[15, 16].”
A low grade non-metabolically activelymphoma involving the bone marrow appears to be the most likely explanation for the scan appearances, possibly resulting in a "partial flip-flop" variant. This possibility is not adequately explored in the discussion.

The following paragraph has been added to the discussion

“As our patient likely has mixed low and high grade lymphoma, the interim and post therapy PET/CT scan appearances possibly represent a ‘partial flip-flop variant’ with photopenic sites representing either sites of successfully treated disease or non FDG-avid less chemotherapy responsive lower grade lymphoma.”

A statement is made that there may be a "slightly" heterogenous appearance.

In fact, this appearance is often "significantly" heterogenous with cold areas of prior disease and very avid regenerating bone marrow.

‘Slightly’ has been changed to ‘significantly’ heterogeneous in the discussion section of the manuscript.

“The interim post 3rd cycle chemotherapy PET scan was most concerning for a mixed response to therapy, with the significantly heterogeneous appearance in the marrow highly suspicious for disease…..”

2. Figure 2 should be referenced in the text.

Figure 2 (now Figure 3) has been referenced in the case presentation section of the manuscript.

3. If possible, could you provide additional, more detailed images of the bone marrow. A midline sagittal view of the spine on the three PET scans (added to Figure 1) would be most helpful to view the bone marrow findings.

Midline Sagittal images of the spine from the baseline, interim and post completion PET scans have been provided. Due to the size of images, they were not combine with Figure 1 and a separate Figure 2 has been created.

4. Could you please add a very brief description of the initial scanning protocol: camera brand, injected dose, uptake period and if there were any significant changes to this protocol on the subsequent scans.
The following paragraph has been added at the end of the Case Presentation section of the manuscript:

“The baseline, interim and completion PET/CT scans were all performed on the same Phillips GEMINI PET/CT camera. Range of $^{18}$F-FDG dose and uptake time for the three PET/CT scans were 307-319 MBq and 60-65 minutes respectively suggesting differences between PET scan appearances were true changes and not due to variability in acquisition technique.”