Reviewer’s report

Title: Host-specific Factors Affect the Pathogenesis of Adverse Reaction to Metal Debris

Version: 0 Date: 24 Jan 2019

Reviewer: Pat Campbell

Reviewer’s report:

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This study aimed to investigate whether host-specific intrinsic factors affecting the pathogenesis of ARMD could be identified in a cohort of 33 patients with bilateral failed ASR metal-on-metal total hips. The larger parent ASR cohort has used in previous studies and many of the methods that apply to this study were cited from those studies. There were 5 bilateral hip resurfacings, 14 bilateral totals and presumably the remaining patients had one of each. A previously published, multi-part histological grading system was used.

This is a well-written paper of a good study design that addressed a topical and important clinical question. The study rationale is explained and the methods are appropriate.

Specific comments:

Figure 1 seems unnecessary as the information is provided in the text.

Figure 2. for ease of reading, the axis should be labeled "difference in total volumetric wear".

Line 133 - for completeness, add that the remaining 24 patients had mixed resurfacing / total bilateral hips.

Line 179 - It may seem obvious, but include the word microscope here as readers may think this is a camera. By normal light, do the authors mean "transmitted light" here - please clarify.

Line 210 - Provide citations for the homogeneity test and McNemar tests

Line 234. Do the authors mean that in some patients there was heavy infiltration of macrophages and lymphocytes - were there cases with just heavy macrophages or just heavy lymphocytes? This description could be expanded.
Line 235. It is stated that the majority of patients had no plasma cells, diffuse lymphocytic infiltration, germinal centers or granulomas. Table 5 lists the statistics for these features for symmetry between hips which implies that these features were commonly present. Furthermore, granulomas are included in the discussion about features that are a response to the number of particles, but this seems not to be the case if most patients lacked this feature. This is confusing and needs a footnote or amended text.

Line 248 - this is a little unclear. Do the authors mean that when a granuloma was present on one side only, it was always on the higher wearing side?

Line 251. Have the authors considered looking at the histological data only considering the features that were found within the majority of the cohort i.e. without plasma cells, diffuse lymphocytic infiltration, germinal centers or granulomas? It seems that the description of the results in this section includes symmetry of the absence of some features. If the description was about macrophages and lymphocytes and necrosis only, how might this change the interpretation of the findings?

Line 264. Intriguingly, it seems that the authors' data may provide an amount of wear that is linked to pseudotumor formation but that information is not in Table 7, which just lists the differences between the sides. Can the wear data for pseudotumors vs non-pseudotumors be included in the results?

Line 272. As noted above, perhaps it is appropriate to add the word "key" here i.e majority of the patients had similar findings on both hips in several KEY histological variables.

Line 276. It isn't clear what "differences" are being referred to - please reword for clarity.

Line 301. When discussing the findings of these other papers, it would be more informative to include which histological features were found to be symmetrical with particular reference to the key features noted in this study (macrophages, lymphocytes and necrosis).

Line 333. For clarity, this could be rearranged as We hypothesized that components of the innate response (macrophages, granulomas, necrosis) are more closely related to extrinsic factors, such as wear volume and components of the adaptive response (lymphocytes, germinal centers and plasma cells) to intrinsic factors such as [genetic predisposition to metal hypersensitivity].

Line 368. Please provide a citation for the statement about high bearing wear leading to trunnion wear.

L370. The word bilateral should be included here as this is the biggest group of bilateral MM hips published with histology and wear data to date.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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