Reviewer’s report

Title: Bone pathologic fracture revealing an unusual association: Coexistence of Langerhans cell histiocytosis with Rosai-Dorfman disease Case report and a literature review

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Reviewer: Ronald Jaffe

Reviewer's report:

1. There is a problem with the diagnosis of "combined" histiocytic lesions. It is generally thought that combined lesions have two (or more) areas, zones or populations that, if micro-dissected, would each qualify for a different histiocytosis. Thus, in this case, an image could be produced of an area of Langerhans Cell Histiocytosis (LCH) and another area of Rosai-Dorfman disease (RDD). It specifically does not refer merely to an admixture of cell types since there is cytologic and phenotypic overlap. In particular, emperipolesis by itself is not diagnostic of RDD but individual cells with emperipolesis can be seen in a number of other situations. In the Case Presentation there is a description of the large histiocytes with emperipolesis but no description or image of an area or zone, that, taken by itself, would be diagnostic of RDD. In addition, the phenotype of the RDD-type elements is incomplete since S100 that should be selectively and strongly expressed is only very weakly positive with the comment that the nitric acid decalcification might be to blame. It would appear to be critical in diagnostic pathology for the positive controls to be described, in this instance using the S100 antibody on a known 'positive control' tissue that had been subjected to nitric acid decalcification. All is not lost even if this is the case, Fascin is also selectively expressed by RDD cells and could be substituted (given appropriate controls). In the Discussion the authors reference O'Malley (4) and Cohen-Barak (5) for the pathology of combined lesions, however it is O'Malley's large series that speaks to and clearly illustrates 'zones or areas' of LCH and RDD. Cohen-Barak's case had each at a different site, bone (LCH) and skin (RDD) not an admixture but "two separate anatomic and physiologic systems".

Since this is an instructive case of the difficulty in defining 'combined lesions', the authors could include a paragraph that highlights an issue that is not well aired anywhere else. It would make the diagnosis of RDD more tentative, but still worth the discussion.

2. The radiologic image might be instructive and consideration should be given to including it.

3. In the Background, the authors refer to LCH as representing abnormal Langerhans cells. There is abundant contemporary literature to suggest that LCH cells are bone-marrow derived myeloid cells that are very different from Langerhans cells. The importance is that
having myeloid histiocytes (clonal and others) at the same site opens the discussion of 'combined lesions' to a different dimension (See Beres ML et al, J Exp Med 2014;211:669-83).

3. A little more detail on treatment and follow-up (if available) might be of use. Was the "osteosynthesis" (? by pinning) the definitive treatment, no curetage, no follow-up systemic treatment?

Images: Figure 1 is not sharp nor particularly informative in the context of this report. Fig 2 is taken at the power that could represent two distinct zones or areas, if they exist. But if not, it is representative of the diagnostic problem in this case. Fig 3 is not convincing, nor helpful when compared to fig 4 that appears to show a diffuse LCH component on the CD1a immunostain. Fig 4A, if representative, would be evidence for diffuse LCH. Fig 4B does little for the case. Fig 5, CD68 could be construed as paranuclear LCH staining, though the distribution differs somewhat from that of Fig 4 that was more diffuse. The clone should be stated (KP-1, PGM-1 etc) since some monoclonals, like KP-1 also stain myeloid precursors. The large cell is not in sharp focus. In bone lesions of any kind, osteoclast-like giant cells will stain for CD68. Presumably the claim here is that the giant cell represents emperipolesis, but is not convincing of that phenomenon. CD68 in a RDD cell is of little diagnostic value though, only S100/fascin would help support the diagnosis. Fig 6 is not convincing; LCH has nuclear/cytoplasmic S100 that should be in the same distribution as the CD1a (even if it is light) and should selectively highlight the cells with emperipolesis.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

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