Reviewer’s report

**Title:** Thyroid Rosai-Dorfman disease with infiltration of IgG4-bearing plasma cells associated with multiple small pulmonary cysts

**Version: 0 Date: 28 Dec 2018**

**Reviewer:** Or Kalchiem-Dekel

**Reviewer's report:**

We read with great interest the case report by Gienella et al describing a female patient diagnosed with a rare form of histiocytosis (Rosai-Dorfman disease) involving the thyroid gland and the respiratory tract. Overall, the case presentation is well-written, and the case discussion is concise and focused. The figures are very illustrative and clear. As delineated by the authors, pulmonary involvement in Rosai-Dorfman disease is indeed a rare occurrence; moreover, parenchymal lung disease. As is also evident from the authors’ discussion and reference list, previous reports exploring chest radiographic findings in thoracic Rosai-Dorfman disease mainly describe mediastinal lymph node or other mediastinal structure involvement, conducting airways involvement (thickening, narrowing etc.), lung parenchymal findings in the form of septal lines and consolidative nodules/masses, and pleural disease (thickening, effusion). Pulmonary cyst formation, as also mentioned by the authors, is described in two previous publications: (a) in the case series by Cartin-Ceba et al from Mayo Clinic (Resp Med, 2010), one out of nine patients had evidence of lower-lobe predominant cystic disease and it is not clear from the report whether causal relation to Rosai-Dorfman disease was confirmed via lung biopsy. Another patient in this series with biopsy-proven pulmonary Rosai-Dorfman disease, had some solitary cysts, however her main pulmonary manifestations were lower-lobe predominant ground-glass infiltrates, reticular opacities, and traction bronchiectasis, consistent with fibrosing ILD; (b) In the case report published by Campana et al (Sarcoid Vasc Diffuse Lung Dis, 2015), cystic lung disease has developed over time in a patient, who also developed other radiographic findings of consolidative nodules, pleural thickening, septal lines, and mediastinal lymphadenopathy. The diagnosis of pulmonary Rosai-Dorfman disease was established by open-lung biopsy. From these two publications, it seems that while cyst-formation is possible in pulmonary Rosai-Dorfman disease, it is (1) very rare indeed; and (2) likely to be accompanied by other pulmonary radiographic findings, suggestive of ILD.

Another interesting aspect of Rosai-Dorfman disease is the overlap with IgG4-related lung disease, mainly with regards to the presence of IgG4-positive plasma cells upon histologic examination of the inflammatory infiltrate of excised lesions. Indeed, as mentioned by the authors, differentiation between the two conditions may sometimes be difficult also due to the similar distribution of both conditions within the lungs. Indeed, some authors suggest that the
two conditions may share similar pathogenetic features and may represent a spectrum (Zhang et al, Am J Clin Pathol, 2013), whereas others suggest differentiating between the two based on higher degree of IgG4-positive infiltrates and higher IgG4:IgG ratio in IgG4-related lung disease (Liu et al, Am J Clin Pathol, 2013). Emperipolesis, however, seems to be a shared feature of both conditions, once again delineating the overlap between the two (Shrestha et al, Am J Surg Pathol, 2009).

Major comments:

a) Our main comment with regards to this manuscript is related to the authors' hypothesis about a causal relation between thyroid/mediastinal, biopsy-proven, Rosai-Dorfman disease and pulmonary cysts. We tend to agree with the authors' statement regarding a unifying diagnosis. Furthermore, the diagnostic work-up performed in this case, has elegantly ruled out other major causes of cystic lung disease. However, given the very rare occurrence of cystic disease as a manifestation of Rosai-Dorfman disease and in the absence of histologic lung evidence of pulmonary Rosai-Dorfman disease nor any pulmonary/pleural parenchymal radiographic findings other than the cysts in the presented case, it is difficult to ascertain that the cystic lung lesions are indeed a result of pulmonary Rosai-Dorfman disease. We would therefore advise being more guarded and cautious with regards to this association and revise the title and text accordingly. While the thyroid gland was involved with likely extension into the trachea, lung involvement by cysts, in the absence of other compelling evidence, while possible is definitely not probable.

b) Title: consider revising to Inflammatory thyroid infiltration with emperipolesis

c) P3, Line 51: as mentioned earlier, emperipolesis is not pathognomonic for Rosai-Dorfman disease and can be seen in multiple other conditions, most notably Erdheim-Chester disease and HLH. Nevertheless, we agree that emperipolesis is a prominent feature of the Rosai-Dorfman disease and greatly supports the diagnosis when appears in combination with specific histiocyte markers, as mentioned by the authors. Please consider revising as well as mentioning which cells were seem to be engulfed by histiocytes in this case. This should also be mentioned in the legend of Figure 3A.

d) P4, Lines 6-8: please clarify this statement as it is not supported by the citations provided.

e) P4, Line 16: please clarify the term severe sub-acute dyspnoea.

f) Apparently, the patient presented with mainly respiratory symptomatology, however, no effort was made in the discussion to explain the cause of this symptomatology. One can assume it was related to tracheal compression by the thyroid-originating mass as evident
from the CT image, but this is not specifically addressed by the authors. More complete results of pulmonary function tests and especially any evidence of large airway abnormality as reflected by morphology of the flow-volume loop would be beneficial in this regard.

g) Please clarify whether the resected specimen was investigated for infectious etiology.

h) P4, Lines 55-57: the patient was diagnosed with nodal and extranodal Rosai-Dorfman disease, however, no evidence for nodal involvement was provided. Were resected lymph nodes positive for hystiocytic inflammation as well? Please clarify. Again, reconsider the phrase probably lung as the pathologic specimen obtained does not provide evidence of lung involvement.

i) In the histologic description the authors initially state that the final diagnosis was Rosai-Dorfman disease, but then also suggest a diagnosis of IgG4-related disease. Consider rephrasing the paragraph to reflect the one final diagnosis that was assigned and perhaps briefly explain why the other was dismissed. Alternatively, a histophtologic description can be provided with further clarification of the final diagnosis in the discussion.

j) P5, lines 14-18: if you read carefully and as mentioned above, there were two patients with cysts mentioned in this case series, but only one was described as such in the Table. Consider revising.

k) P5, lines 20-22: please provide reference to support this statement.

l) Please apply all revisions to the abstract where appropriate.

Minor comments:

a) P4, line 14: please clarify if the patient was current non-smoker at presentation or a lifetime never-smoker.

b) P4, line 22: when describing results of physical examination, it is customery to use the term non-tender. Pain is a subjective feeling.

c) P4, line 42: provide normal range for VEGF-D

d) P5, line 32: this cyst distribution is atypical for PLCH, but not other cystic lung diseases.

e) P6, line 26: this statement is redundant.
f) Figure 1A: the asterisk is not mentioned in the legend.

g) Figure 1B: arrows should be more prominent. Consider switching to white.

h) Figure 2: there is no asterisk on the image.

i) Figure 3A: legend mentions the tracheal wall, however, that is not clearly seen or delineated in the image. Also, stain is not mentioned.

General comments:

This manuscript would benefit from professional English language editing. Some spelling and grammar mistakes are notable throughout. Here are some examples:

a) P4, line 22: on room air

b) P4, lane 28: walls instead of wall

c) P4, line 38 and P5, line 42: and instead of and/or?

d) P4, Line 46: 3,5 should be 3.5

e) P6, line 2: contain is not an appropriate word.

f) Figure 4 legend requires English editing.

When using abbreviations, the first mentioning should be unabbreviated. For example:

a) P4, line 26: CT

b) P4, line 40: TSH, VEGF-D

c) P4, lines 42-43: ECG, FEV1, TLC etc.

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

Unable to assess

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

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