Author’s response to reviews

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

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Author’s response to reviews:

PULM-D-18-00531: A case report of Rosai Dorfman disease: thyroid infiltration with emperiploesis and increased IgG4-positive plasma cells associated with multiple pulmonary cysts

Response to Reviewers:

We thank all three reviewers for their overall very helpful and constructive comments. Please find below a detailed point-to-point reply taking all concerns into consideration. We revised the manuscript accordingly and strongly believe that the revision has substantially strengthened the quality of our manuscript and that it is now acceptable for publication. All modifications are highlighted in yellow in the manuscript.

Dirk Theegarten (Reviewer 1)

The authors describe a case of Rosai-Dorfman-disease (RDD) with interesting features. A simultaneous manifestation of RDD within the thyroid and the lung is very rare. The case report is written adequately.

1. Figures are demonstrating the findings. Some improvement can be done: Fig. 3a includes a dust particle, Fig. 3b has no adequate color balance.
2. There is one other report in pubmed concerning manifestations in the thyroid and lung (Ben Ghorbel I et al.; Rev Med Interne. 2005 May;26(5):415-9). This should be mentioned.

The suggestions of the reviewer have been taken into consideration, Fig.3a and Fig3b were improved accordingly and the reference (Ben Ghorbel I et al, 2005) is now cited (new ref 7).

E Radzikowska (Reviewer 2)

The authors presented very interesting case of Rosai-Dorfman disease (RDD) with possible lung involvement. The manuscript touches very rare and difficult clinical problem, however the diagnosis requires supplementations.

1. Only few cases of cystic lung lesions in the course of RDD have been presented in the literature. All of them were proved by open lung biopsy and CT pattern was different than in presented case. Harlander et al showed the nodular lesions with thickening of the pleura and lung cysts. Cartin-Ceba et al showed bilateral, subpleural reticular opacities, bilateral scattered areas of ground glass attenuation, mild traction bronchiectasis in the bases, and a few tiny cystic lesions were present in the upper lung fields, but no honeycombing was present. In described case only small tiny cyst, probably without special distribution, was shown. There were no lymph nodes enlargements, nodules, reticular changes and pleural thickening.

We agree with the reviewer that the observed cystic lung lesions cannot be attributed to RDD with certainty without the results of a lung biopsy. Therefore, we interpret our observation with more caution by stating that the cystic pulmonary lesions are possibly a lung manifestation of RDD in analogy to other histiocytic disorders. Lung manifestations of RDD are rare and vary as pointed out by the reviewer, however, cases with small cystic lesions have been reported. This notion has now been revised in the discussion. Unfortunately, we could not find the reference of Harlander.

2. It is impossible to rule out the LAM, even though there was no AML or lymphangioleiomyoma and low concentration of VEGF-D (the lung lesions in this case are not prominent, and usually in LAM cases with this type of changes the level of VEGF-D is low).

We agree with the reviewer that it is impossible to rule out LAM with certainty. However, follow up of several years revealed no functional or radiological worsening. Following clinical reasoning, we tried to find a unifying diagnosis and interpret the lung cysts in a patient with biopsy-proven nodal and thyroid RDD to be a manifestation of the same rare disease and dismissed an additional diagnosis of LAM, another extremely rare disease.
3. In addition Birt-Hogg-Dube syndrome should be excluded by the genetic testing. Since the distribution of the cysts was not suggestive and there were no other elements such as renal cancer for Birt-Hogg-Dube syndrome, genetic testing was not performed.

4. I think that lung lesion requires more precise diagnostic: BAL examination, transbronchial biopsy (cryobiopsy) or open lung biopsy.

We agree with the reviewer that a biopsy would be of great interest to assure the association of RDD and the lung cysts. However, a biopsy was considered to be too invasive in this asymptomatic patient without functional or radiological worsening.

Or Kalchiem-Dekel (Reviewer 3)

We read with great interest the case report by Gianella 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-lobed 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-lobed 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.

We thank the reviewer for the helpful input and revised the discussion of the pulmonary manifestations of RDD and the differential diagnosis of pulmonary cysts accordingly. In addition, we found an additional publication (Umarai RAL et al, 2018) describing a RDD patient with lung cysts. References have been added.

Another interesting aspect of Rosai-Dorfman disease is the overlap with IgG4-related lung disease, mainly concerning 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).

We thank the reviewer for the helpful input and revised the discussion of the differential diagnosis and overlap between RDD and IgG4-related disease accordingly. References have been added.

1. 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.
As stated above in response to reviewer 2 we agree that the observed cystic lung lesions cannot be attributed to RDD with certainty without a lung biopsy. Therefore, we interpret our observation with more caution by stating that the cystic pulmonary lesions are possibly a lung manifestation of RDD in analogy to other histiocytic disorders.

2. Title: consider revising to: Inflammatory thyroid infiltration with emperipolesis.

We revised the title to emphasize the presence of multiple lung cysts and IgG-bearing plasma cells in a biopsy proven case of thyroid RDD: ‘Thyroid Rosai-Dorfman disease with infiltration of IgG4-bearing plasma cells associated with multiple small lung cysts’

3. 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 seemed to be engulfed by histiocytes in this case. This should also be mentioned in the legend of Figure 3A.

We revised the text and the figure legend accordingly.

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

5. P4, Line 16: please clarify the term severe sub-acute dyspnea.

The patient suffered from dyspnoea with inspiratory stridor and inspiratory-expiratory wheezing with insidious onset over a 3-month period. We revised the text accordingly.

6. 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.
Pulmonary function tests before surgery, and repeatedly after surgery were normal. Following surgery dyspnoea disappeared indicating that it was related to tracheal compression. We revised the text accordingly.

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

Histological examination of the tissue biopsies for the identification of infectious organisms using several stainings for pathogens were negative. This was added to the pathological description.

8. 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 histiocytic inflammation as well? Please clarify. Again, reconsider the phrase probably lung as the pathologic specimen obtained does not provide evidence of lung involvement.

Histological examination of several lymph nodes showed involvement of RDD with histiocytic inflammation. This notion was now added to the pathological description.

9. 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 histopathologic description can be provided with further clarification of the final diagnosis in the discussion.

The histopathological description and the discussion of the differential diagnosis and overlap between RDD and IgG4-related disease was revised and references added.

10. 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.

We agree with the reviewer that in the case series by Cartin-Ceba et al from the Mayo Clinic lung cysts were mentioned in 2 patients (#4 with lower lung predominance and #9, shown in Figure 2). We revised the discussion accordingly.
11. P5, lines 20-22: please provide reference to support this statement.

Minor comments:

We are grateful to the reviewer for helping us to improve the quality of our manuscript. All the minor comments were taken into consideration and the manuscript revised accordingly.

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

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

3. P4, line 42: provide normal range for VEGF-D

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

5. P6, line 26: this statement is redundant.

6. Figure 1A: the asterisk is not mentioned in the legend.

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

8. Figure 2: there is no “star” on the image.

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

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

1. P4, line 22: on room air

2. P4, line 28: walls instead of wall

3. P4, line 38 and P5, line 42: and instead of and/or?

4. P4, Line 46: 3,5 should be 3.5

5. P6, line 2: contain is not an appropriate word.
6. Figure 4 legend requires English editing.

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

1. P4, line 26: CT
2. P4, line 40: TSH, VEGF-D
3. P4, lines 42-43: ECG, FEV1, TLC