# Lung involvement in Destombes-Rosai-Dorfman disease: clinical and radiological features, and response to the MEK inhibitor cobimetinib

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Destombes-Rosai-Dorfman disease (RDD), first described by Paul Destombes in 1965, was recognized as a distinct clinicopathological entity by Rosai and Dorfman in 1969. RDD is now considered as a distinct non-Langerhans cell histiocytosis group, and frequently has a benign although protracted course. As observed in the first description by Destombes, the predominant clinical presentation is a massive, bilateral and painless cervical lymphadenopathy. Extra nodal localizations have been documented in 40% of patients, the most frequent being sinuses, central nervous system, orbital, skin, soft tissue, and bones involvements. Intrathoracic involvement is exceptionally observed in RDD. The most frequent intrathoracic presentations of RDD are mediastinal or hilar lymph nodes, sometimes mimicking sarcoidosis, and tracheal involvement. Interstitial lung disease has been rarely describe. The outcomes of lung RDD are not well defined. We aimed to describe clinical and imaging presentations.
Methods & Materials

Patient selection and inclusion criteria

We conducted a retrospective multicenter study from 2007 to 2018. Based on the French histiocytosis registry, patients who received a diagnosis of RDD according to the 2018 consensus criteria were screened. Other exclusion criteria were: data insufficiency in medical records, presence a mutation of the SLC29A3 gene, and the absence of chest thoracic computed tomography (CT)-scan available for review. The study was approved by the ethics committee Comité de Protection des Personnes Ile de France III (#2011-A00447-34) and was conducted in accordance with the Declaration of Helsinki.

Patient’s characteristics and classification of intrathoracic RDD

Clinical, biological, and imaging data were retrospectively collected by practitioners in charge of the patients and were centrally. Pulmonary resting function tests were also noted when available. When several lung HRCT scans were available, the first one was arbitrarily chosen to perform analysis. Intrathoracic RDD was considered probable in patients with extra-thoracic RDD and a mediastinal or lung involvement observed on HRCT scan, with the exclusion of other possible diagnoses such as lung cancer. Intrathoracic RDD was considered definite when histological documentation was obtained from intrathoracic samples. Intrathoracic involvement was divided into four categories according to the predominant localization to pleura, lung, laryngo-tracheo-bronchial tree or mediastinum. The time of RDD diagnosis was arbitrarily considered as the date of pathological documentation.

Outcomes

For the patients treated with cobimetinib, baseline and in-treatment 18 fluorodeoxyglucose positron emission tomography (\(^{18}\text{FDG-PET}\))/HRCT were performed with the same hybrid PET/CT scanner (Siemens Biograph mCT Flow, Siemens Medical Solutions USA, Inc.). A sum of the longest diameter for all target lesions was calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter was used as reference by which to characterize the objective treatment response.
Results

Patients’ characteristics

Eighty-one patients of the French RDD registry were screened, 34 had a chest CT scan available for review, and 15 were finally included (6 women and 9 men). The median age at disease onset was 40 years (range 14-74). The median age at RDD diagnosis was 40 years (range 15-83). The median time between symptoms onset and diagnosis was 24 months (range 1-111). The detailed characteristics of the patients are presented in this table (table 1).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age*</th>
<th>Extra-thoracic RDD involvements</th>
<th>Biopsy specimens</th>
<th>Type of thorax involvement</th>
<th>IgG4 overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>F, 24</td>
<td>Skin, CLA, Sinuses</td>
<td>LN, larynx, skin</td>
<td>Laryngotracheal narrowing (airways)</td>
<td>No</td>
</tr>
<tr>
<td>#2</td>
<td>M, 51</td>
<td>LN, Skin, CNS</td>
<td>Pituitary mass, lung</td>
<td>Consolidation (lung)</td>
<td>Yes (pituitary mass)</td>
</tr>
<tr>
<td>#3</td>
<td>M, 40</td>
<td>LN</td>
<td>LN</td>
<td>Nodules, Cysts (lung)</td>
<td>No</td>
</tr>
<tr>
<td>#4</td>
<td>M, 28</td>
<td>Skin, Perirenal</td>
<td>Retroperitoneal lung</td>
<td>Nodules, consolidation (lung)</td>
<td>No</td>
</tr>
<tr>
<td>#5</td>
<td>F, 74</td>
<td>Nodes, skin, bones, salivary glands</td>
<td>Sub maxillar, lung</td>
<td>Nodule, consolidation (lung)</td>
<td>No</td>
</tr>
<tr>
<td>#6</td>
<td>M, 57</td>
<td>LN, Bones</td>
<td>LN</td>
<td>Cysts (lung)</td>
<td>No</td>
</tr>
<tr>
<td>#7</td>
<td>F, 15</td>
<td>Probable</td>
<td>Skin, LN, CNS</td>
<td>Skin, cerebral tissue</td>
<td>Nodules (lung)</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>----------</td>
<td>---------------</td>
<td>----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>#8</td>
<td>F, 31</td>
<td>Probable</td>
<td>LN, Skin</td>
<td>Skin</td>
<td>Cysts (lung)</td>
</tr>
<tr>
<td>#9</td>
<td>M, 27</td>
<td>Definite</td>
<td>CLA, bones, gastric</td>
<td>LN, lung</td>
<td>Ground glass opacities (lung)</td>
</tr>
<tr>
<td>#10</td>
<td>M, 43</td>
<td>Probable</td>
<td>LN, Skin, Sinus, Bones</td>
<td>Parotid nodule, skin</td>
<td>Miliar (lung)</td>
</tr>
<tr>
<td>#11</td>
<td>M, 16</td>
<td>Definite</td>
<td>Bones, LN</td>
<td>Lung</td>
<td>Reticulations, consolidation (lung)</td>
</tr>
<tr>
<td>#12</td>
<td>M, 83</td>
<td>Probable</td>
<td>Kidney</td>
<td>Retroperitoneal Fibrosis (lung)</td>
<td>No</td>
</tr>
<tr>
<td>#13</td>
<td>M, 70</td>
<td>Definite</td>
<td>CLA, skin, kidney</td>
<td>Skin, tracheal</td>
<td>Nodule (lung)</td>
</tr>
<tr>
<td>#14</td>
<td>F, 46</td>
<td>Probable</td>
<td>Skin</td>
<td>Skin</td>
<td>Ground glass opacities (lung)</td>
</tr>
<tr>
<td>#15</td>
<td>F, 29</td>
<td>Probable</td>
<td>LN, sinuses, parotid, bones, breast</td>
<td>Bone, breast</td>
<td>Linear consolidation (lung and mediastinal)</td>
</tr>
</tbody>
</table>

Seven patients had definite intrathoracic RDD, and 8 had probable intrathoracic RDD. Fourteen patients had lung involvement, 3 had mediastinal involvement, 1 had pleural involvement, and 1 had an isolated tracheal laryngeal involvement. Two patients had RDD associated with systemic lupus erythematosus and immunodeficiency manifestations (recurrent warts, fungal and bacterial skin infections). One additional patient had antiphospholipid syndrome. All patients had at least one extra-thoracic organ involvement. Twelve patients (80%) had lymphadenopathy of cervical localization.
in 9 cases (60%). Other organs affected by RDD were the skin (n=8), bones (n=6), perirenal area (n=3), sinuses (n=4), central nervous system (n=2), parotid (n=2), submandibular gland (n=1) and breast (n=1). As required for diagnosis criteria, a pathological documentation of RDD was obtained in all patients in at least one organ, mainly in skin (n=6), lung (n=5), lymph nodes (n=4), perirenal tissue (n=2), submandibular gland (n=1), parotid (n=1), breast (n=1), larynx (n=1) and pituitary mass (n=1). Four patients exhibited histological features consistent with IgG4 related disease, together with histiocytic infiltration, in pituitary mass, lymph node, skin, or bone and breast.

**Clinical presentation**

Seven patients (47%) experienced persistent pulmonary symptoms, associating chronic dyspnea and dry cough in all of them. Physical examination revealed the presence of crackles in 2 patients. No patient had cyanosis, finger clubbing, or physical signs of pulmonary hypertension. None had episodes of acute pulmonary failure. Smoking status was defined as either never a smoker (n = 11) or a former or current smoker (n = 4). No patient was known to have any specific occupational exposure.

**Radiological presentation**

The radiological presentation of patients is described in this table (table 2).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Peribronchovascular consolidations</th>
<th>Ground glass attenuation*</th>
<th>Nodules*</th>
<th>Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Tracheal nodule</td>
</tr>
<tr>
<td>#2</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>#3</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Cysts</td>
</tr>
<tr>
<td>#4</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Stretching bronchograms</td>
</tr>
<tr>
<td>#5</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Stretching bronchograms</td>
</tr>
<tr>
<td>#6</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Cysts</td>
</tr>
<tr>
<td>#7</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>#8</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Cysts</td>
</tr>
<tr>
<td>#9</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Reticulations</td>
</tr>
<tr>
<td>#10</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Miliar, mainly in superior territories</td>
</tr>
<tr>
<td>#11</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Reticulations Stretching bronchograms</td>
</tr>
<tr>
<td>#12</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Reticulations UIP-like</td>
</tr>
<tr>
<td>#13</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>#14</td>
<td>No</td>
<td>Yes (mainly in upper lobes)</td>
<td>Ground glass pseudo-nodules</td>
<td>No</td>
</tr>
<tr>
<td>#15</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

The median time between RDD diagnosis and the first analyzed lung HRCT scan was 7 months (from 18 months before diagnosis to 42 months after RDD diagnosis). Globally, CT scans revealed involvement of the lung parenchyma in 14 out of 15 patients. Parenchymatous nodules were observed in 8 patients. Three patients had interlobular septal thickening, 3 patients had thin-walled cysts, and 3 patients had ground-glass opacities. Four patients had peribronchovascular and perilobular consolidation. Air-filled bronchi within consolidation were stretched and squeezed. Miliary, mainly in superior territories, pleura effusion without pleural thickening and fibrosis with a pattern of usual interstitial pneumonia were observed in one patient each. The pulmonary veins were of normal caliber in all patients. Mediastinum infiltration was seen in 3 patients.

**Pulmonary function tests**

Four out of 15 patients underwent resting pulmonary function tests. One had normal pulmonary function test results. In 3 cases, pulmonary function testing revealed a decreased diffusing capacity of the lung for carbon monoxide (DLCO). A restrictive pattern was observed in 2 cases, an obstructive pattern with a normal forced expiratory volume in one second (FEV) in 1 case. When performed (n=5), results of arterial blood gas analyses were always normal.
Bronchoscopy

Broncho-alveolar lavage (BAL) was performed in 5 patients. No patient had endobronchial biopsy. Two patients underwent transbronchial biopsies without any specific histological features. Examination of the BAL fluid showed a predominantly macrophagic alveolitis in 4 cases and an increased lymphocyte percentage in 1.

Outcomes, treatments, and survival

Five patients (33%) were not treated. Three of them did not have any symptom, neither respiratory nor extra respiratory. Two patients had mild dyspnea and declined any treatment. In the 10 remaining patients, therapeutic strategies were guided by multisystemic involvements in 6, and by lung involvement in 4. The 10 treated patients had a median of 3 lines (1-6) of pharmacological treatments. Overall, patients were treated with corticosteroids (n=8), methotrexate (n=5), cladribine (n=4), pegylated interferon-alpha (n=4), azathioprine (n=2), and rituximab (n=2).

Additionally, 2 patients with measurable metabolic lung disease were treated with the MEK inhibitor cobimetinib. SUVmax decreased in lung target lesions in both patients, under 40 milligrams/day of cobimetinib. Radiological analysis with tumoral assessment of these patients showed a 42% and 29% decrease of lung infiltration after cobimetinib therapy. Treatment was well tolerated.
Fig. 1: 74-year-old woman with nodes, skin, bones, salivary and lung involvement. The axial slide shows an important peribronchovascular thickening with nodules and mass.

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Fig. 3: 74-year-old woman with nodes, skin, bones, salivary and lung involvement. The coronal slide in MinMip shows an important peribronchovascular thickening with stretching bronchogram.
**Fig. 6:** 27-year-old man with cervical lymphadenopathy and pulmonary involvement as central bilateral ground glass.

**Fig. 5:** 30-year-old man with cutaneous, peritoneal, pericardial and pulmonary involvement. Coronal slide shows an important peribronchovascular thickening.
Fig. 4: 30-year-old man with cutaneous, peritoneal, pericardial and pulmonary involvement. Axial slide shows an important peribronchovascular thickening with pericardial effusion.

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Fig. 7: 57 year old man with random distribution cysts.

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**Fig. 8:** 42-year-old man with cutaneous, sinus, bone and pulmonary involvement. Lung involvement consists as diffuse nodules of hematogenous distribution (miliar).

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**Fig. 9:** 42-year-old man with cutaneous, sinus, bone and pulmonary involvement. Lung involvement consists as diffuse nodules of hematogenous distribution (miliar) in coronal and Maximal Intensity Projection (MIP).

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Fig. 10: Lung involvement in a 52 year old man. (a) Axial, coronal and sagittal CT show a upper right lobe consolidation with a displacement of the adjacent fissure. (b) Axial, coronal and sagittal CT shows a 42% decrease of the consolidation after cobimetinib therapy.

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Fig. 11: (a) Axial, coronal and sagittal CT show multiple mass and nodules with peribronchovascular consolidation. (b) Axial, coronal and sagittal CT after cobimetinib therapy shows a partial regression of the lesion without new lesion.

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Fig. 2: 74-year-old woman with nodes, skin, bones, salivary and lung involvement. The sagital slide in MinMip shows an important peribronchovascular thickening with stretching bronchogram.

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Conclusion

In the present study, we showed that thoracic involvement of RDD is rare and heterogeneous, ranging from non-symptomatic disease to severe dyspnea with restrictive pattern. In our cases and those of the literature, RDD lung involvement was characterized by male predominance, pulmonary symptoms in almost 50% of patients, frequent association with cervical lymphadenopathy, nodular and peribronchovascular consolidation presentation in chest CT scans, and rare restrictive pattern.

Consistent with previous studies, intrathoracic RDD encompass heterogenous manifestations that can be divided in lung, mediastinal, pleural, and airways involvements. Both in our cases and those of the literature, mediastinal and lung involvements were the most frequent presentations. Progressive dyspnea (n=18), cough (n=12), and stridor or hoarseness (n=6) were the main symptoms, as in our series, where 6 patients presented with dyspnea and/or dry cough.

Typical radiographic presentation of RDD was nodular and peribronchovascular consolidation presentation in chest CT scans. These CT findings are seen usually diffusely in all lobes of the lungs. The radiological spectrum of RDD are similar to those of pulmonary lymphoproliferative disease in particular those of lymphoma of mucosa-associated lymphoid tissue lymphoma. Single or multiple nodules or consolidation associated with lymphadenopathy were commonly observed. The lesions tend to be peribronchovascular, with stretching bronchogram in the consolidation and no cavitation. Histiocytic infiltrates extend into the alveolar septa in the periphery and along the adjacent bronchovascular bundles, and interlobular septa.

Treatments were highly variable, in our cases and those of the literature.

In conclusion, RDD lung involvement is an uncommon interstitial lung disease. In our cases, it was always associated with evidence of multi-systemic disease. A pathological documentation of the disease should be obtained, and lymph nodes constitute an easier localization for obtaining biopsy samples.
References


