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

Short title: Lung involvement in Rosai-Dorfman disease

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Contributions

Q.M., J.H., and F.C.A. designed the study.

Q.M., S.B., P.M., J.-F.E., Ph.G., N.A., G.P., J.D., J.H., and F.C.-A. collected the data.

J.F.E. and F.Ch. centrally reviewed the histological samples.

J.F.E. determined the *BRAF* status.

S.B. and Ph.G. reviewed the chest CT scans, and P.M. reviewed the 18FDG PET scans.

Q.M. and F.C.A. conducted the statistical analysis.

Q.M., S.B., Ph.G., J.H., and F.C.-A. analyzed and interpreted the data.

Q.M., S.B. and F.C.-A. wrote the manuscript.

All authors critically reviewed and approved the final version of the manuscript.

Q.M. and F.C.-A. take full responsibility for the integrity of the work.

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The authors declare that they have no conflicts of interest to report.

Abstract

Background: Destombes-Rosai-Dorfman disease (RDD) is a rare multisystemic histiocytosis. Pulmonary involvement during RDD is poorly described. Here, we aimed to examine the clinical features, radiological features, and outcomes of 15 patients with RDD with lung involvement.

Patients and Methods: The cases of RDD with lung involvement were extracted from the French National Histiocytosis registry. Efficacy of the MEK inhibitor cobimetinib in treating lung disease was evaluated with an ¹⁸fluorodeoxyglucose positron emission topography (¹⁸FDG PET) scanner and chest computed tomography (CT) scans.

Results: Fifteen patients (6 women; median age of 40 years at RDD diagnosis) were included. All patients had evidence of systemic disease with extra-pulmonary localizations of the disease (lymphadenopathy (n=12), skin (n=9), bones (n=6), retroperitoneal involvement (n=3), sinuses (n=3), parotid (n=2), sub mandibular gland (n=1) and breast (n=1)). Presenting symptoms were dominated by dyspnea and dry cough in 7 patients. Restrictive physiology was observed in 2 out of 5 patients.

Bronchoalveolar lavage demonstrated lymphocytosis in 1 out 5 cases. Eight patients

received corticosteroids, all but one with variable immunosuppressive or immunomodulatory therapies. Two patients received cobimetinib for severe lung disease with dramatic pulmonary metabolic and tumoral responses. Two patients died during follow-up: one due to hemoptysis and the other from an unrelated cerebral tumor.

Conclusions: Pulmonary involvement in RDD is rare, proteiform, and sometimes severe.

The MEK inhibitor cobimetinib can lead to dramatic responses.

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Introduction

Destombes-Rosai-Dorfman disease (RDD), first described by Paul Destombes in 1965 ¹, was recognized as a distinct clinicopathological entity by Rosai and Dorfman in 1969 ². RDD is a rare non-neoplastic disease, mainly occurring in children or young adults, and is characterized by the accumulation of large CD68⁺, PS100⁺, and CD1a⁻ histiocytes, with frequent histological finding of emperipolesis ³. RDD is now considered as an entity classified as a part of a distinct non-Langerhans cell histiocytosis group (R-group) ⁴ and frequently has a benign although protracted disease 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 ³, most frequently involving the sinuses, central nervous system, orbitals, skin, soft tissue, and bones ⁵. Intrathoracic involvement is exceptionally observed in RDD. The most frequent intrathoracic presentations of RDD are the mediastinal or hilar lymphadenopathies, sometimes mimicking sarcoidosis, as well as tracheal involvement. Interstitial lung disease has been rarely described ⁶. Radiographic features are non-specific, ranging from patchy ground-glass attenuation to cysts or nodular opacities ⁷⁻⁹. The outcomes of lung RDD are not well defined. We aimed to describe clinical and imaging presentations, response to treatments, and outcomes of intrathoracic RDD, focusing on the efficacy of the MEK inhibitor cobimetinib.

Patients and methods

Patient selection and inclusion criteria

We conducted a retrospective multicenter study from 2007 to 2018. Based on the French histiocytosis registry, we screened patients who received a diagnosis of RDD according to the 2018 consensus criteria³. Briefly, RDD diagnosis relied on compatible clinical and imaging features, histological documentation of RDD supported by 2 pathologists (J.-F.E. and F.Ch.), and exclusion of other diseases that can be associated with a reactive “RDD-like” process, including L-group histiocytosis. Other exclusion criteria were: data insufficiency in medical records, presence of a mutation in the *SLC29A3* gene, and the unavailability of chest thoracic computed tomography (CT) scans for review. The presence of *SLC29A3* mutations is responsible for a multi-systemic syndrome called “H syndrome”, that includes hyperpigmentation, hypertrichosis, short stature, insulin-dependent diabetes, arthritis and systemic inflammation, and features of immunodeficiency. They may have an infiltration of various organs by large histiocytes with emperipolesis mimicking RDD. However, the H syndrome is a distinct entity, and we decided to exclude these patients from the present analysis. 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 characteristics and classification of intrathoracic RDD

Clinical, biological, and imaging data were retrospectively collected by practitioners in charge of the patients and were centrally reviewed by Q.M. and F.C.-A. Pulmonary resting function tests were also noted when available. Chest high-resolution computed tomography (HRCT) scans were reviewed by 2 experienced radiologists (S.B. and Ph.G.). When several lung HRCT scans were available, the first one was arbitrarily chosen to perform the analysis. Intrathoracic RDD was considered probable in patients with extra-thoracic RDD and mediastinal or lung involvement observed on the HRCT scan, with the

exclusion of other possible diagnoses, such as lung cancer. Intrathoracic RDD was considered as the definitive diagnosis when histological documentation was obtained from intrathoracic samples. Intrathoracic involvement was divided into four categories according to its predominant localization to the pleura, lung, laryngo-tracheo-bronchial tree (airways), or mediastinum. The time of RDD diagnosis was arbitrarily considered as the date of pathological documentation. Follow-ups ended in November 2018. For treatment efficacy, the baseline evaluation was considered as the last evaluation before treatment initiation.

***BRAF* status and phosphoERK expression**

Histological samples were centrally reviewed by J.-F.E. or F.Ch.. *BRAF* mutation detection on codon V600 was performed by pyrosequencing and as previously described ¹⁰. Alternatively, detection was performed by multiplex picodroplet digital PCR when not detected by pyrosequencing ¹¹. Assessment of phosphorylated extracellular signal-regulated kinase (phosphoERK) expression was performed with the anti-phospho ERK 1/2 antibody for the patients treated by cobimetinib. The primary antibody against phosphoERK was Monoclonal Rabbit D13.14.4E (Cell Signaling, Leiden, The Netherlands), directed against phospho p44/42 (ERK1/2) Thr202/Thr204. Slides of 4 µm-thick of formalin-fixed tissue were incubated on automate BOND system (Leica). Detection of primary antibodies was performed with Bond Polymer Refine Detection kit (Leica), after heat induced epitope retrieval using BOND Epitope Retrieval Solution 2 for 20 minutes.

Literature review

We performed a search of PubMed and Web Of Science using the keywords “Rosai Dorfman” OR “sinus histiocytosis” AND “thorax”; “lung”; “mediastinal” OR “bronchic” to identify cases of intrathoracic RDD from 1978 through September 2018 published in English and French journals. We included observational studies and case reports, and excluded all abstracts, editorials, reviews, and commentaries. We screened the titles and abstracts from all sources. Subsequently, full-text articles of the selected studies were reviewed, and we also searched the references sections of these articles to identify additional studies. Data were extracted from included articles using a predefined data collection sheet that included demographic, clinical, histopathological, and radiological presentations, treatments, and outcomes, including deaths. Intrathoracic involvement of RDD was grouped in 4 categories (pleural, mediastinal, lung, and airways), as described above, with several categories of intrathoracic involvement possibly being present in the same patient.

Outcomes

As the data collection was retrospective, there were no uniform clinical and imaging evaluations. We assessed treatment response by reviewing medical documentation. Chest CT scans were reviewed by 2 independent radiologists (S.B. and P.G.) to evaluate tumoral responses when measurable. Complete and partial remissions were defined as either the complete or partial resolution of symptoms or imaging findings suspected to be due to RDD. Stability and progression were defined as either having no change or as worsening in symptoms or imaging findings, respectively.

For the patients treated with cobimetinib, baseline and in-treatment 18 fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET)/HRCT were performed with the same hybrid PET/CT scanner (Siemens Biograph mCT Flow, Siemens Medical

Solutions USA, Inc.) and according to the guidelines of the European Association of Nuclear Medicine, as previously described ¹². A quantitative analysis of uptake was performed using the standardized uptake value (**SUV**), defined as the ratio of the measured FDG activity to the injected activity, which was then normalized to body mass. To quantify ¹⁸F-FDG uptake, loosely fitting regions of interest covering pathologic uptake were placed manually over the axial image plane. Then, the SUV_{max} in this set of regions of interest was determined.

Conventional CT was performed with a slice thickness of 1 mm using a contiguous reconstruction algorithm with soft and lung filter reconstruction.

All CT images were retrieved on an image archiving and communication system (Picture Archive Communication System (PACS) 2.0; GE Medical Systems, Mt Prospect, IL, USA) and then analyzed using the mediastinal (window level, 50 Hounsfield units (HU) window (width), 400 HU) and lung window settings (width 1500 HU, level – 600 HU). MinIP, or the minimum intensity projection algorithm, and MIP, or maximal intensity projection, were applied to each set of CT scans. CT scans were used to measure target lesions selected for response assessment: 1 lesion in patient #2 and 4 measurable lesions in patient #5. One patient (#15) treated with cobimetinib for multi-systemic involvement did not have any measurable target lesion in the lung and was not eligible for the evaluation of cobimetinib efficacy for RDD lung disease.

A sum of the longest diameter for all target lesions was calculated and reported as the baseline sum of the longest diameter. The baseline sum of the longest diameter was used as a reference value by which to characterize the objective treatment response.

Statistical analyses

Data are presented as the median and range for continuous variables and as the number and percentage for categorical variables. No statistical test was used to compare SUVmax values before and after treatment, due to the small number of patients.

Results

Patients' characteristics

Eighty-one patients from the French RDD registry were screened. Ten had mutation in the *SLC29A3* gene. Among the remaining 71 patients, 34 had a chest CT scan available for review: chest CT scan was normal in 15 patients. Four patients had lung radiological abnormal findings that were explained by other disease (2 infectious pneumonia, 1 cardiogenic edema, and 1 patient with a long history of smoking presented with emphysema), and were thus excluded. Overall 15 patients were ultimately included in this analysis (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 the onset of symptoms and diagnosis was 24 months (range 1-111). The detailed characteristics of the patients are presented in **Table 1**. Seven patients had definite intrathoracic RDD, and 8 had probable intrathoracic RDD. Fourteen patients had lung involvement, 1 had mediastinal involvement, 1 had pleural involvement, and 1 had isolated tracheolaryngeal (airways) involvement. Two patients (#1 and 8) had RDD associated with systemic lupus erythematosus and immunodeficiency manifestations (recurrent warts and fungal and bacterial skin infections). One additional patient (#4) had antiphospholipid syndrome. All patients had at least one extra-thoracic organ involvement. Twelve patients (80%) had lymphadenopathy with a cervical localization in 3 cases (25%). Other organs and areas affected by RDD were the skin (n=9), bones (n=6), perirenal area (n=3), sinuses (n=3),

central nervous system (n=2), parotid (n=2) and submandibular glands (n=1), and breast (n=1). As required for diagnostic criteria, a pathological documentation of RDD was obtained in all patients in at least one organ, mainly the skin (n=6), lung (n=5), lymph nodes (n=4), perirenal tissue (n=2), submandibular gland (n=1), parotid gland (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 the pituitary mass (patient #2), lymph node (patient #13), skin (patient #14), or bone and breast (patient #15). *BRAF* status was determined in 6 patients (the material was not sufficient for the others). The *BRAF*^{V600E} mutation was not found in any patient. One patient (#13) had the c.1405G>A; p.Gly469Arg of the *BRAF* gene. Eleven patients had a phosphoERK assessment (insufficient material for the others), which was positive (significant expression in histiocytes detected by immunohistochemistry) in 7 (64%).

Clinical presentation

Seven patients (47%) experienced persistent pulmonary symptoms, with associated chronic dyspnea and dry cough. 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 been a smoker (n = 11) or having been a former smoker/are a current smoker (n = 4). No patient was known to have any specific occupational exposure.

Radiological presentation

The radiological presentation of patients is described in **Table 2**. The median time between RDD diagnosis and the first analyzed lung HRCT scan was 7 months (ranging 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 (**Figure 1 and S1**). Parenchymatous nodules were observed in 8 patients. Three patients had interlobular septal thickening, while 3 patients had thin-walled cysts, and 3 patients had ground-glass opacities. Four patients had peribronchovascular and perilobular consolidation. Air-filled bronchi within the consolidation were stretched and squeezed. Miliary presentations, mainly in superior territories, pleura effusion without pleural thickening and fibrosis with a pattern of usual interstitial pneumonia were each observed in one patient (**Figure 1**). The pulmonary veins were of normal caliber in all patients. Mediastinum infiltration was seen in 3 patients (#5, 11, and 15)

Pulmonary function tests

Five (#4, 5, 6, 9, and 12) out of 15 patients underwent resting pulmonary function tests (**Table 2**). One (#6) had normal pulmonary function test results. In 4 cases, pulmonary function testing revealed a decreased diffusing capacity of the lung for carbon monoxide (**DLCO**). A restrictive pattern was observed in 2 cases, and an obstructive pattern with a normal forced expiratory volume in one second (**FEV**) was observed 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 (#2, 3, 6, 9, and 12). No patient had an endo-bronchial biopsy. Two patients underwent transbronchial biopsies, and 1 (#9) had specific histological features of RDD. Examination of the BAL fluid

showed a predominantly macrophagic alveolitis in 4 cases and an increased lymphocyte percentage in 1 case (patient #2).

Outcomes, treatments, and survival

Median follow-up was 50 months (range 2-99). Five patients (33%) were not treated. Three of them did not have any symptoms, neither respiratory nor extra-respiratory. Two patients (#12 and 14) had mild dyspnea and declined any treatment. In the 10 remaining patients, therapeutic strategies were guided by multi-systemic involvements in 6 and by lung involvement in 4 (#2, 4, 5, and 9). 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, cyclophosphamide, infliximab, vinblastine, and cytarabine were each used in one case.

Metabolic follow-up was available in 7 patients who underwent at least 2 ¹⁸F-DG-PET scans. Improvement of lung involvement was observed with cladribine and steroids (n=1; patient #9), vinblastine, cytarabine, and steroids (n=1; patient #7). Three patients (#1, 6, and 8) treated by methotrexate and steroids had stable lesions. One patient (#4) had radiological and metabolic symptom worsening with pegylated interferon.

Additionally, 2 patients (#2 and 5) with measurable metabolic lung disease were treated with the MEK inhibitor cobimetinib: both had a somatic genotyping of the *BRAF* gene, without the presence of the activating V600E mutation. One of the patients (#2) was treated with cobimetinib 20 milligrams/day because of central nervous system infiltration when lung infiltration appeared, together with a relapse of nervous system involvement. Cobimetinib was increased to 40 milligrams/day with a good efficacy in neurological and lung infiltrations. Phospho-ERK expression could not be evaluated in

the lung biopsy specimens of the 2 patients, due to the small size of the samples. SUVmax values decreased in lung target lesions in both patients (**Figure 2**) when less than 40 milligrams/day of cobimetinib was administered. Radiological analysis with tumoral assessment of these two patients showed a 42% and 29% decrease in lung infiltration after cobimetinib therapy (**Figure 3**). Treatment was well tolerated. The only side effect was an acneic rash in 1 patient. Additionally, one patient (#15) was treated with cobimetinib because of neurological involvement. At this time, the lung consolidation had disappeared. Cobimetinib treatment led to partial metabolic and tumoral remission in central nervous system and intra-thoracic lymph nodes infiltration.

Two patients died during follow-up: one because of massive hemoptysis (#4), 2 weeks after CT-guided lung biopsy, and one because of an unrelated brain tumor (#7), 11 years after RDD diagnosis, without clinical or radiological signs of intrathoracic progression.

Literature review

Sixty-nine references from the literature were screened, and 47 patients (27 men and 20 women) from 38 references were included in the analysis (**Figure S2 and Tables S1 and S2**). The median age at diagnosis was 45 years (range 2-81 years). The predominant feature of thoracic RDD was mediastinal involvement (n=27, 57%), followed by lung disease (n=14, 30%), airways (n=13, 28%), and pleural (n=4, 9%) involvements. Fifteen patients (32%) did not have any symptom of intrathoracic involvement. In symptomatic patients, dyspnea (23 cases, 49%) was the most frequent clinical manifestation. The median follow-up duration was 12 months (range: 2 weeks-12 years). Treatments were variable. Eleven patients (23%) did not have any treatment. In treated patients, steroids were the most frequently used (23 cases; 49% of cases). Clearance with rigid

bronchoscopy was used in 6 patients (13%). Overall, prognosis was good: 24 patients improved (52%), and 5 (11%) had stable disease. Nevertheless, 2 patients relapsed during follow-up, 3 worsened, and 5 died from intrathoracic involvement of RDD.

Discussion

In the present study, we showed that thoracic involvement of RDD is rare and heterogeneous, ranging from non-symptomatic disease to severe dyspnea with a 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 a rare restrictive pattern. Two patients in our center experienced a dramatic response to cobimetinib, as measured with ¹⁸F¹⁸FDG PET and chest CT scans.

Consistent with previous studies ^{8,13-16}, intrathoracic RDD encompass heterogeneous manifestations that can be classified as having lung, mediastinal, pleural, and airway involvements. Both in our cases and those of the literature ¹⁶, 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 cases, where 6 patients presented with dyspnea and/or dry cough.

The typical radiographic presentation of RDD was presented with nodular and peribronchovascular consolidation in chest CT scans. These CT findings are usually observed diffusely in all lobes of the lungs ^{17,18}. The radiological spectrum of RDD is similar to that of pulmonary lymphoproliferative disease, in particular mucosa-associated lymphoid tissue lymphoma ¹⁹. Single or multiple nodules or consolidation associated with lymphadenopathy were commonly observed. The lesions tend to be

peribronchovascular, with a stretching bronchogram in the consolidation and with no cavitation. Histiocytic infiltrates extend into the alveolar septa in the periphery and along the adjacent bronchovascular bundles and interlobular septa. The presence of cysts in 3 patients (as depicted in the Figure S1), can raise the possibility of associated Langerhans-cell histiocytosis, as previously reported ²⁰.

In our study, only one patient had laryngotracheal involvement. Most of the patients described in the literature with laryngotracheal involvement came from isolated case reports published by thoracic surgeons or bronchoscopy specialists. This can explain the difference between the rates of laryngotracheal involvement in our patients (1/15) and in previously reported cases (13/47). The management of these patients was highly heterogeneous with endoscopic desobstruction in 5 cases, medical management in 3 cases, surgery in 3 cases, and therapeutic abstention in 2 cases.

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

Corticosteroids were used in 8 patients in our cases and were associated with various drugs: interferon-alpha, methotrexate, or azathioprine. Cladribine was used in 4 cases, including 3 cases for intrathoracic disease leading to progression in 2 cases (#5 and 9) and to complete remission of lung disease in 1. In the literature, half of the cases were treated with corticosteroids. Improvement of intrathoracic involvement was described in four patients with cladribine. Other treatments were methotrexate (n=5), chlorambucil (n=4), pegylated interferon (n=1), vinblastine (n=2), and 6-mercaptopurine (n=1). Surgery and endoscopic clearance were also used. Due to a high prevalence of airways and mediastinal involvement, patients underwent surgery and/or laser excision or clearing by rigid bronchoscopy in 8 cases. Adjuvant radiotherapy supplemented surgery in 2 cases ^{21,22}.

Two patients in our series experienced a major response to cobimetinib. Cobimetinib is a MEK 1/2 inhibitor that is largely used in malignant melanoma and, more recently, has been used for treating histiocytoses²³. The RAS/Raf/MEK/ERK signaling pathway controls gene expression leading to cellular proliferation, apoptosis, and inflammatory responses. Although L-group histiocytoses frequently harbor the V600E mutation of the *BRAF* gene, RDD seems to be less frequently associated with gain of function mutations of genes of the MAPK pathway³. MEK inhibition has shown preliminary results in an adult with *KRAS*-mutated RDD, and RDD without mutations in the MAPK pathway^{24,25}. Even if we were not able to demonstrate somatic mutations of the RAS/Raf/MEK/ERK pathway in our patients, cobimetinib was associated with dramatic improvement of the lung involvement in 2 patients.

The main limitation of this study is that 8 cases were only “probable” cases, defined as the absence of pathological documentation from lung biopsy specimens. However, all cases were documented by centrally reviewed pathological analyses, which confirmed the RDD diagnosis. Moreover, in all patients, radiological presentation, exclusion of differential diagnoses, and outcomes were always consistent with lung RDD involvement. Another difficulty was the retrospective evaluation of the response to treatments, which were heterogeneous, and often given in association. Except for cobimetinib responses in 2 patients, which were assessed with metabolic and radiological evaluations, corticosteroids were given in all but one patients with immunosuppressive or immunomodulatory drugs. The small number of patients, the retrospective design of the study, and the variable evaluations did not allow the drawing of generalizable conclusions about treatment efficacy. Finally, many patients among the whole cohort did not have any chest CT scan. We thus can suppose that patients who did not have any pulmonary symptoms did not have chest CT scan, and we may have missed

some thoracic involvements in non-symptomatic patients. As some of the patients of our series (8/15, 53%), and from the literature (15/47, 32%) had thoracic involvement without any symptom, we think that the current approach to RDD evaluation should include a thoracic imaging at baseline, even if the need for a systemic treatment in non symptomatic patients is not clear and cannot be driven from our results.

In conclusion, RDD lung involvement is an uncommon interstitial lung disease. In our cases, it was always associated with evidence of multi-systemic disease. Pathological documentation of the disease should be obtained, and lymph nodes constitute easier localization for obtaining biopsy samples. Although clinical stability is seen in most cases of RDD lung manifestations, cobimetinib may be useful in life threatening or progressive disease.

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Patient	Sex, age*, smoking status**	Extra-thoracic RDD involvements	Biopsy specimens	Type of thorax involvement	IgG4 overlap	Treatments and outcomes
#1	F, 24 Definite No	Skin, CLA, Sinuses	LN, larynx, skin	Laryngotracheal narrowing (airways)	No	CS alone: S Peg: P CS + RTX: P CS + AZA: S CS + MTX: PR
#2	M, 51 Definite C	LN, Skin, CNS	Pituitary mass, lung	Consolidation (lung)	Yes (pituitary mass)	Before lung disease: CS, CYC, IFX, RTX, 2CDA, Cobi After lung disease: Cobi: PR
#3	M, 40 Probable C	LN	LN	Nodules, Cysts (lung)	No	CS: PR
#4	M, 28 Definite No	Skin, Perirenal	Retroperitoneal, lung	Nodules, consolidation (lung)	No	Peg: P Death (massive hemoptysis)
#5	F, 74 Definite No	LN, skin, bones, salivary glands	Submaxillary, lung	Nodule, consolidation (lung)	No	Peg: S 2CDA: P Cobi: PR
#6	M, 57 Probable F	LN, Bones	LN	Cysts (lung)	No	CS: PR then relapse CS + AZA: side effects CS + MTX: PR
#7	F, 15	Skin, LN, CNS	Skin,	Nodules	No	CS + vinblastine + cytarabine: CR

	Probable No		cerebral tissue	(lung)		Death from unrelated brain tumor
#8	F, 31 Probable No	LN, Skin	Skin	Cysts (lung), pleura	No	CS + MTX: PR
#9	M, 27 Definite No	CLA, bones, gastric	LN, lung	Ground glass opacities (lung)	No	CS: P CS + MTX: P CS+ 2CDA: CR Peg: CR
#10	M, 43 Probable F	LN, Skin, Sinus, Bones	Parotid nodule, skin	Miliary (lung)	No	No treatment. Clinical stability, asymptomatic
#11	M, 16 Definite No	Bones, LN	Lung	Reticulation s, consolidati on (lung)	No	No treatment. Clinical stability, asymptomatic
#12	M, 83 Probable No	Kidney	Retroperito neal	Fibrosis (lung)	No	No treatment. Clinical stability, mild dyspnea
#13	M, 70 Definite No	CLA, skin, kidney	Skin, tracheal	Nodule (lung)	Yes (lymph node)	No treatment. Clinical stability, asymptomatic
#14	F, 46 Probable No	Skin	Skin	Ground glass opacities (lung)	Yes (skin)	No treatment. Clinical stability, no pulmonary symptoms.
#15	F, 29 Probable No	LN, sinuses, parotid, bones, breast	Bone, breast	Linear consolidati on (lung and mediastinal)	Yes (skin, bone)	CS+ MTX: PR 2CDA (for CNS): P Cobi: PR

Table 1. Clinical and demographic characteristics of patients with Destombes-Rosai-Dorfman disease (RDD) with lung involvement

* At RDD diagnosis

CLA: Cervical lymphadenopathy; CS: Corticosteroids; LN: lymph nodes; CNS Central Nervous System; Peg: Pegylated interferon alfa; 2CDA: Cladribine; MTX: Methotrexate; RTX: Rituximab; IFX: Infliximab; Cobi: Cobimetinib; AZA: Azathioprine; M: male; F: female.

PR: partial remission; CR: complete remission; S: stable; P: progression (see Methods section for definitions).

“Definite” refers to the presence of histological documentation of RDD in the lung.

“Probable” refers to patients with histological documentation of RDD in another site than lung (see the Methods section).

** No : no smoking; F: former smoker; C: current smoker

Patient	Peribronchovascular consolidations*	Ground glass attenuation*	Nodules*	Others*	FVC (%) TLC (%)	FEV1/ FVC	DLCO (%)
#1	No	No	No	Tracheal nodule	NA	NA	NA
#2	No	Yes	Yes	No	NA	NA	NA
#3	No	No	Yes	Cysts	NA	NA	NA
#4	Yes	No	Yes	Stretching bronchograms	51 56	0.89	60
#5	Yes	No	Yes	Stretching bronchograms	112 104	0.64	70
#6	No	No	No	Cysts	118 114	0.78	116
#7	No	No	Yes	No	NA	NA	NA
#8	No	No	No	Cysts	NA	NA	NA
#9	No	Yes	No	Reticulations Crazy paving	108 96	0.91	61
#10	No	No	No	Miliary, mainly in superior territories	NA	NA	NA
#11	Yes	No	Yes	Reticulations Stretching bronchograms	NA	NA	61
#12	No	No	No	Reticulations UIP-like	88 67	0.65	NA
#13	No	No	Yes	No	NA	NA	NA
#14	No	Yes (mainly in upper lobes)	Ground glass pseudo-nodules	No	NA	NA	NA
#15	Yes	No	No	No	NA	NA	NA

Table 2. Radiological characteristics and pulmonary function tests in patients with Destombes-Rosai-Dorfman disease with lung involvement

* Chest CT scan findings; UIP: usual interstitial pneumonia; NA: not available; FVC: forced vital capacity, TLC: total lung capacity, FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide.

Figure legends

Figure 1. Computed tomographic findings of interstitial lung disease associated with Destombes-Rosai-Dorfman disease. A. Diffuse pulmonary nodules in miliary pattern opacities representing hematogenous dissemination; B. patchy groundglass infiltrates; C. peribronchovascular and subpleural interlobular septal thickening; D: nodular ground-glass opacity with sub-pleural intralobular septal thickening; E. Nodular pattern associated with small nodules and masses with an air bronchogram; and F: peribronchovascular consolidation containing an air bronchogram with stretching and squeezing (arrows) in a coronal slice from a minimal intensity projection (MinMip).

Figure 2. ¹⁸F-Fluorodeoxyglucose positron emission tomography in 2 patients (#2 and 5) with Destombes-Rosai-Dorfman disease with lung involvement treated with the MEK inhibitor cobimetinib. A and B. Upper: baseline; Bottom: after cobimetinib treatment. C. Maximal standard uptake values (SUVs) of lung hypermetabolism at baseline, first evaluation after cobimetinib, and last visit.

Figure 3. Chest computed tomography of the lungs in 2 patients with Destombes-Rosai-Dorfman disease (RDD) with lung involvement, treated with the MEK inhibitor cobimetinib.

Upper part: Lung involvement of RDD in a 52-year-old man (#2) (computed tomography (CT) guided percutaneous lung biopsy demonstrated pathological RDD findings). (A) Axial, coronal and sagittal CT scans show an upper right lobe consolidation with a displacement of the adjacent fissure. (B) Axial, coronal and sagittal CT scans show a 42% decrease in consolidation 2 months after increasing cobimetinib therapy.

Lower part: Lung involvement of RDD in a 74-year-old woman (#5) (CT-guided percutaneous lung biopsy demonstrated typical pathological RDD findings). (C) Axial, coronal and sagittal CT scans show multiple masses and nodules with peribronchovascular consolidation. (D) Axial, coronal and sagittal CT scans 2 months after cobimetinib therapy show a partial regression of the lesion, and lack of a new lesion. Measurements of several target lesions show a 29% decrease after cobimetinib treatment.

Figure S1. Chest computed tomography-scan showing cysts in 2 patients with Rosai-Dorfman disease

Figure S2. Flow chart of the literature review





