

Intrathoracic Rosai-Dorfman Disease with Spontaneous Remission: A Clinical Report and a Review of the Literature

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Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare non-neoplastic disease that is characterized by a proliferation of histiocytes mostly in lymph nodes. However, the etiological mechanism of RDD still remains unclear. Intrathoracic manifestations of RDD are only observed in 2% of patients with RDD. Spontaneous remission was reported in about 20% of patients with RDD; however, there are no reports of an intrathoracic manifestation of RDD that showed a spontaneous remission within a short period of time. A 64-year-old Japanese female with dry cough and left chest pain was introduced to our hospital, and computed tomography revealed a pulmonary nodular lesion and enlarged mediastinal lymph nodes. The bronchial specimen obtained from the abnormal mucosal lesion showed massive infiltration of histiocytes underneath the bronchial epithelium and emperipolesis, a typical pathological finding in RDD, which is characterized by the presence of histiocyte-like cells engulfing intact lymphocytes. These histiocytes were positive for S-100 (one of the known positive markers of RDD) and for CD68 (a marker for various cells of the macrophage lineage). All these findings are consistent with the diagnosis of RDD. These radiological and endoscopic findings spontaneously resolved within four months without any treatment. In conclusion, clinicians should be aware of this disease as one of differential diagnoses of pulmonary nodules in combination with mediastinal lymph node enlargements, especially in order to differentiate it from primary lung cancer.

Keywords: emperipolesis; localized intrathoracic lesions; Rosai-Dorfman disease; sinus histiocytosis with massive lymphadenopathy; spontaneous remission

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Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, was first described by two pathologists, Rosai and Dorfman (1969). It was reported that around 40% of RDD patients have lymph node disorders and extranodal involvement, but intrathoracic manifestations of RDD was reported in only 2% of patients with RDD (Foucar et al. 1990). Furthermore, there have been only 9 cases of RDD with localized intrathoracic lesions (Ohori et al. 2003; Shi et al. 2009; Ali and Mackay 2009; Hida et al. 2009; Zhou et al. 2010; Roberts and Attanoos 2010; Cartin-Ceba et al. 2010; Kaseda et al. 2011). No standard treatment for RDD has yet been established, but a good prognosis has been reported (Foucar et al. 1990), and another report (Gotou et al. 2008) noted that 20% of the cases showed spontaneous remission. We herein report a patient with localized intra-

thoracic RDD that showed spontaneous remission in a short period of time.

Clinical Report

A 64-year-old Japanese female developed dry cough and slight left chest pain in July of 2008. She was referred to our hospital for an evaluation of an abnormal chest X-ray film. She was a never-smoker and occasional alcoholic drinker, and she had never taken any supplements or Chinese medicines. She was an office worker and she had no history of inhalation of toxic materials. She had undergone surgical treatment of a left inguinal herniation when she was 63 years old. She had been treated essential hypertension and hyperlipidemia with telmisartan (40 mg/day), doxazosin mesilate (2 mg/day), amlodipine besilate (5 mg/day) since she was 58 years old. She did not have any fam-

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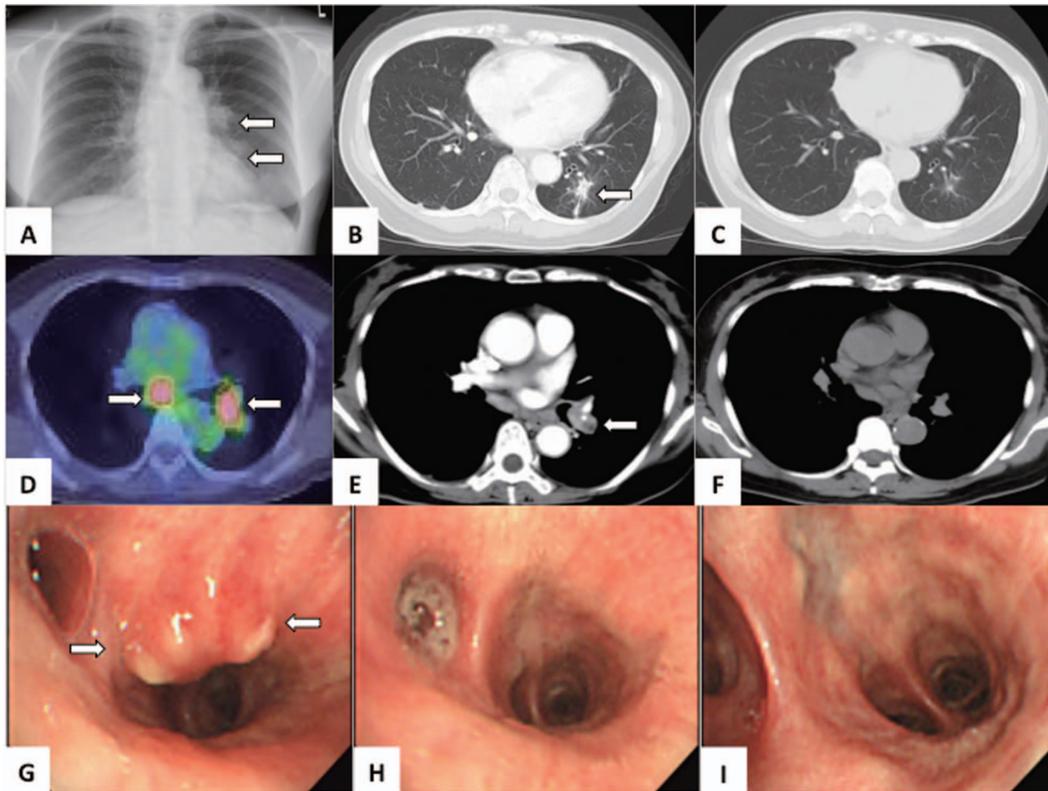


Fig. 1. Radiological and bronchoscopic findings of the present patient.

Chest radiograph on admission (A), showing a pulmonary nodule about 2 cm in diameter in the left middle lung field and an enlargement of left hilum. Lung window of chest computed tomography (CT) on admission (B), demonstrating an irregular pulmonary nodule 1.6 cm in diameter in the left lower lobe. Mediastinal window of chest CT on admission (E), representing subcarinal and left hilar lymph node swellings. The pulmonary nodule in the left lower lobe nearly disappeared (C), and mediastinal and hilar lymph nodes disappeared on mediastinal window (F) one month after admission. Fluorodeoxyglucose-positron emission tomography (FDG-PET) finding (D), showing high uptake of the left lung nodule (standard uptake values; SUV max 3.87) and enlarged mediastinal (SUV max 11.8) and left hilar (SUV max 8.46) lymph nodes. Bronchoscopic findings of the present case on admission (G), a protruded lesion with comparatively smooth surface on the bifurcation of the left lower lobe bronchus. One month and four months (I) after the admission, the abnormal bronchoscopic finding improved without any treatment.

ily history or allergic diseases. A physical examination on admission revealed that a height of 150.9 cm, weight of 46.6 kg, body temperature 35.5°C, pulse rate 55/min, blood pressure 120/80 mmHg, and SpO₂ 98% (room air), with no remarkable abnormal findings. Laboratory findings on admission demonstrated a slight elevation of the peripheral white blood cell count (9,800/ μ l) and serum C-reactive protein (2.6 mg/dl), and an increased erythrocyte sedimentation rate (58.0 mm/hour). Chest X-ray on admission (Fig. 1A) showed a nodular opacity in the left lower lung field and an enlargement of the left hilum. Chest computed tomography (CT) on admission (Fig. 1B and E) also revealed a pulmonary nodular lesion of 1.6 cm in size with spiculations in the left S⁹ with an enlargement of the subaortic and subcarinal lymph nodes. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) (Fig. 1D) marked high uptake of the left lung nodule (standard uptake values; SUV max 3.87) and mediastinal enlarged lymph nodes (SUV max 11.8). Magnetic resonance imaging of the brain, abdominal CT and bone scintigraphy showed no abnormal findings.

Bronchoscopic findings performed on the 6th day after admission proved a protruding lesion with a comparatively smooth surface on the bifurcation of the left lower lobe bronchus (Fig. 1G).

The specimen obtained from the bronchial mucosal lesion revealed massive histiocytic infiltration underneath the bronchial epithelium, with lymphocytes within the cytoplasm of the histiocyte-like cells, known as emperipolesis, which is the pathological findings of the presence of viable hematologic cells within the cytoplasm of histiocyte-like cells (Fig. 2A). These histiocyte-like cells were also positive immunostaining for S-100 (one of the known positive markers for RDD) and for CD68 (a marker for cells of monocyte/macrophage origin) (Fig. 2B and C). All these pathological findings were consistent with RDD. Additionally, an immunohistochemical analysis of the specimen did not show an increase of IgG4⁺ cells.

Her symptoms and abnormal findings of the chest X-ray, CT (Fig. 1A, B and E) and bronchoscopy (Fig. 1G) spontaneously recovered without any treatment one month

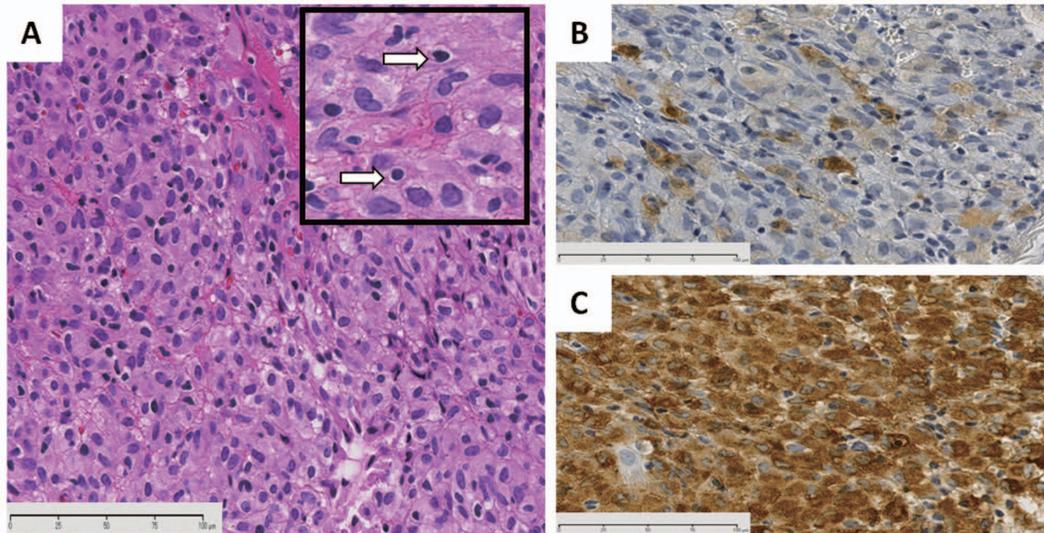


Fig. 2. Histopathological and immunohistochemical findings of the specimen obtained from a left bronchial biopsy specimen.

A: Hematoxylin-eosin staining showed dense infiltration of histiocytes and emperipolesis (closed window; the finding of the histiocytes engulfing intact lymphocyte.). B and C: Immunohistochemical analysis demonstrated that the histiocytes were positive for S-100 protein (B) and CD68 (C). Original magnification (600 ×).

Table 1. Reported cases of Rosai-Dorfman Disease with localized intrathoracic lesions.

Authors	Age	Sex	CT findings	Diagnostic procedure	Treatment	Outcome
Shi et al.	58	M	a mass in the left lower lobe	left lower lobectomy	surgery alone	no recurrence
Ali et al.	43	F	a mass in the right hilum	surgical biopsy	surgery alone	stable
Zhou et al.	39	F	a mass in the trachea and above the carina	surgery	surgery alone	stable
Ohori et al.	81	M	left sided pleural effusion	pleural biopsy	unknown	unknown
Roberts et al.	61	M	a nodule in the upper lobe	open lung biopsy	surgery alone	stable
Hida et al.	61	M	mediastinal mass	thoroscopic lung biopsy	surgery alone	stable
Cartin et al.	41	F	mediastinal lymphadenopathy	lung biopsy	surgery alone	stable
Cartin et al.	26	M	bilateral interstitial infiltrates	lung biopsy	corticosteroid	worsening
Kaseda et al.	66	F	enlargement of mediastinal and hilar lymph nodes	thoroscopic lung biopsy	surgery alone	stable

after admission, and disappeared after four months. No signs of recurrence were noted as of five years after the admission.

RDD, also known as sinus histiocytosis with massive lymphadenopathy, was first described by two pathologists (Rosai and Dorfman 1969). There have been more than 750 reported cases (Shi et al. 2009), mostly with disorders of the lymph nodes and extranodal involvements including skin, central nervous systems, soft tissues, upper airways, bone, salivary glands, and orbital cavity. Those are founded with accounting for 40% of RDD. On the other hand, intrathoracic manifestations of RDD are rare and represent only 2% of the cases with RDD (Foucar et al. 1990), and only 9 cases of RDD with localized intrathoracic lesions have been reported (Table 1) (Ohori et al. 2003; Shi et al. 2009; Ali and Mackay 2009; Hida et al. 2009; Zhou et al. 2010; Roberts and Attanoos 2010; Cartin-Ceba et al. 2010; Kaseda et al. 2011). The discriminative pathological findings of the present patient were diffuse bronchial prolifera-

tion of histiocytes with round or oval shaped nuclei and clear and weakly acidophilic cytoplasm (McClain et al. 2004). These histiocytes often engulf intact histiocytes and lymphocytes, and this phenomenon is called as emperipolesis. These histiocytes are immunohistochemically positive for S-100 protein and CD68, and negative for CD1a (McClain et al. 2004). Although it had not been examined in the present patient, CD163 of a specific marker of macrophages is useful to distinguish this disease between other benign and malignant lymphoproliferative disorders including Langerhans cell histiocytosis (Lau et al. 2004). Immunohistochemical and pathological findings in the present patient demonstrated histiocytosis underneath the bronchial epithelium, emperipolesis, and positive immunohistochemical findings for S-100 and CD68 and negative for CD1a, which is consistent with a diagnosis of RDD. Shrestha et al. (2009) proved the possible overlap of RDD with IgG4-related lung disease. Additionally, two out of 12 cases of autoimmune pancreatitis carried the diagnosis of

pulmonary involvement of RDD and 6 out of 8 cases admitting RDD showed increase of IgG4⁺ cells (Shretha et al. 2009). Our patient demonstrated no increase of IgG4⁺ cells.

Etiological mechanism of this disease is still unclear, but Epstein Barr virus (EBV) or human herpes virus (HHV)-6 may be involved (Rosai and Dorfman 1969). IgG antibody for Epstein-Barr virus (EBV)-viral capsid antigen and EBV-nuclear antigen, and IgM antibody for HHV-6 were negative and IgG antibody for HHV-6 was positive in the present case. In addition, HHV-6-specific DNA was detected within the histiocytes from RDD patients in 7 out of 9 cases by *in situ* DNA hybridization (Luppi et al. 1998). The current patient had a previous infection of HHV-6. Further examinations are therefore necessary to elucidate the pathological role of these viruses.

The pulmonary nodular lesion in the left S⁹ was not evaluated in the present patient; however, it seems that the lung nodular lesion had the same etiology as the bronchial and mediastinal abnormalities, according to the simultaneous spontaneous remission of the lung lesion with bronchial and mediastinal lesions on the chest CT findings.

Reported average age of patients with RDD is 20.6 (from infant to over 80 years) and they have a slightly male predominance with no correlation with a smoking habit (Cartin-Ceba et al. 2010). Bilateral neck lymph node enlargements without tenderness are seen in around 90% of all RDD patients (McClain et al. 2004). Sore throat, malaise, fatigue, night sweat, and body weight loss may be observed. Prolonged erythrocyte sedimentation rate, an elevation of peripheral white blood cell count, hypochromic normo- or microcytic anemia, and hyperglobulinemia are also observed (McClain et al. 2004).

The present patient showed a high uptake of FDG in the mediastinal and pulmonary lesions, as previously reported (Ali and Mackay 2009). Differential diagnoses of other malignant diseases including primary lung cancer and malignant lymphoma should be considered in relation to the findings with CT and FDG-PET.

RDD has a relatively good prognosis, and about 50% of the patients did not need any treatments due to a recent report (Pulsoni et al. 2002). Another report stated that 20% of the cases show spontaneous remission, and there are very few but fatal diseases (Goto et al. 2008). However, patients with lower respiratory tract manifestations have been reported to show poorer prognoses or even death (Goto et al. 2008). Foucar et al. (1990) reported that 45% of such cases either died directly because of the disease or died with some conditions in connection with this disease, while another 33% were alive with persistent or progressive disease (Foucar et al. 1990; Ohori et al. 2003). As shown in Table 1, however, all cases of RDD with localized intrathoracic lesions showed good prognoses except for one case. It is speculated that there were only one case with central airway involvement in these patients, and that might be the reason of relatively a better prognosis.

No treatment strategy has been established for RDD,

and the efficacy of oral administration of corticosteroid is recently reported (Oka et al. 2009). Pulsoni et al. (2002) proposed that corticosteroid treatment should be considered in febrile patients other than those with infectious diseases. Surgical treatment or radiotherapy should also be considered in life-threatening diseases with rapid progression in the lymph node or extranodal lesion enlargements and resistance to corticosteroids. Treatment with systemic chemotherapy and interferon- α showed unsatisfactory results (Löhr et al. 1995; Pulsoni et al. 2002). The current patient came out with only minor symptoms with dry cough and left chest pain that spontaneously disappeared. In contrast to other reported cases that showed spontaneous improvement or stable disease (Shi et al. 2009; Ali and Mackay 2009), the disappearance of intrathoracic lesions in only several months is a rare phenomenon. The five-year follow-up reached no relapse in this case; however, a re-exacerbation of RDD has been previously reported (de Silva and Joshi 2005) after a spontaneous remission, therefore, physicians should keep in mind of these characteristics of RDD.

In conclusion, this report presents a patient with localized intrathoracic RDD that showed spontaneous remission without any treatment. The radiological findings of CT and FDG-PET resemble common intrathoracic malignant diseases, including primary lung cancer and malignant lymphoma. The characteristic pathological findings of massive histiocytosis and the clinical course of spontaneous improvement are thus considered to be an important clue for making an accurate diagnosis of this disease.

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Conflict of Interest

The authors declare no conflict of interest.

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