CASE REPORT

Pulmonary IgG4+ Rosai-Dorfman disease

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SUMMARY

Rosai-Dorfman disease (RDD) is a rare non-malignant proliferation of histiocytes of unknown aetiology that mainly affects lymph nodes. Here we report a case of RDD that presented a diagnostic dilemma due to its atypical presentation and the overlap with IgG4 disease. Our case presented with interstitial lung involvement without lymphadenopathy. Open lung biopsy suggested the diagnosis of RDD. However, the predominant IgG4 positive plasma cells together with the absence of lymphadenopathy were not typical of RDD. Within 1 year, the patient developed diffuse lymphadenopathy and immunohistochemical staining of lymph node aspirates confirmed the diagnosis. Despite trials of corticosteroid therapy, the disease progressed.

BACKGROUND

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy (SHML), is a rare non-malignant proliferation of histiocytes of unknown aetiology that mainly affects lymph nodes and various extranodal sites. Pulmonary involvement is rare and occurs approximately in only 3% of cases with extranodal disease. Also, there has been a reported overlap between RDD and IgG4 disease. Here we report an atypical presentation of a case of RDD that presented initially with interstitial lung involvement without lymphadenopathy and within 1 year, developed the classic lymphadenopathy associated with RDD. Additionally, lung biopsy showed a significant proportion of plasma cells that were IgG4 positive indicating the overlap between RDD and IgG4 disease previously reported.

CASE PRESENTATION

A 76-year-old African-American man with a history of chronic pancreatitis, subtotal pancreatectomy for pancreatic pseudocyst and a smoking history of 1 pack per day for more than 50 years, presented with chronic dry cough and a 10 lb weight loss over 2 months duration with no associated fever or haemoptysis. He had no family history of lung disease and he used to work as a carpenter with no exposure to chemicals, birds or farming. His physical examination was normal with no palpable lymphadenopathy or clubbing.

INVESTIGATIONS

The investigations, including full blood count, renal function, liver function tests and serum calcium, were all within normal limits, but the erythrocyte sedimentation rate was elevated at 105 mm/h.

Chest high-resolution CT showed bilateral upper lobes coalescent air space opacities with spiculated

margins and architectural distortion, irregular subpleural nodular opacities scattered throughout both lungs bilaterally with an upper lobe predominance associated with bronchial wall thickening, calcified mediastinal lymphadenopathy consistent with a prior granulomatous infection and small bilateral pleural effusions. There was no evidence for significant air trapping, bronchiectasis or mucus plugging and no definite pulmonary fibrosis was identified (figure 1).

Other tests including sputum Gram stain and culture, acid-fast bacilli smear and culture, QuantiFERON-TB Gold test, fungal serologies, HIV test, antinuclear antibody, rheumatoid factor, cytoplasmic-antineutrophil cytoplasmic autoantibody and perinuclear-antineutrophil cytoplasmic autoantibody were all negative.

The patient underwent bronchoscopy with trans-bronchial biopsies showing marked chronic inflammation and palisading histiocytes bordering areas of necrosis. No microorganisms were identified.

Subsequently the patient underwent video-assisted thoracoscopy with right upper lobe wedge biopsy, which was negative for malignancy but showed extensive lymphoplasmacytic interstitial infiltrates accompanied by extensive fibrosis, destruction of pulmonary architecture, with focal vascular congestion, aggregates of alveolar macrophages and dilated lymphatics.

The peribronchiolar, the perivascular interstitium and the dilated lymphatics contained histiocytes demonstrating emperipolesis on H&E stain (figures 2 and 3). The pleura showed evidence of chronic inflammation and reactive mesothelial hyperplasia.

On immunohistochemical staining, histiocytes were S100, CD68 and CD163-positive but CD1a and Factor XIII-a negative. The lymphoid infiltrate was composed of a mixed population of CD3, CD20 small lymphocytes and plasma cells without evidence of monoclonality on kappa and lambda stained sections. Epstein-Barr virus latent

Figure 1 High-resolution CT of chest showing bilateral upper lobes coalescent air space opacities with spiculated margins, irregular subpleural nodular opacities scattered throughout both lungs bilaterally with an upper lobe predominance (mediastinal and lung windows).

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Figure 2 Extensive lymphoplasmacytic interstitial infiltrates accompanied by dense fibrosis and dilated lymphatics (H&E staining, original magnification $\times 40$).

membrane protein 1 was negative and no microorganisms were identified on Gomori Methenamine Silver and Ziehl-Nielsen stains. Notably, a significant proportion of plasma cells were IgG4 positive.

The patient underwent bone marrow biopsy as well which was negative for S100 and CD1a with no cytological evidence of lymphoma, leukaemia or metastatic tumour. MRI brain was normal.

DIFFERENTIAL DIAGNOSIS

The presence of emperipolesis together with positive immunohistochemical staining for S100 and CD68 supported the diagnosis of RDD but the lack of uncalcified enlarged lymph nodes in the neck and mediastinum militated against it. Also, the presence of a high proportion of IgG4 positive plasma cells in the lung biopsy together with a prior history of pancreatitis raised the possibility of IgG4 related disease with lung involvement. However, serum protein electrophoresis showed polyclonal gammopathy with normal serum IgG subclass 4 level at 26 mg/dl (range: 1–291 mg/dl). The pathology report from the prior pancreatic surgery did not include immunohistochemical staining for IgG4.

Negative immunohistochemical staining for both CD1a and Factor XIII-a helped to rule out pulmonary Langerhan's cell histiocytosis (PLCH) and Erdheim-Chester disease, respectively, while the absence of granulomas and negative stains ruled out granulomatous inflammation such as sarcoidosis and infectious processes such as mycobacterial and fungal infections.¹

Figure 3 Histiocyte demonstrating emperipolesis (lymphophagocytosis; arrow) (H&E staining, original magnification $\times 100$)

Within 1 year the patient developed generalised lymphadenopathy and fine-needle aspiration of the right groin lymph node was performed which showed groups of mononuclear and multinuclear histiocytes with emperipolesis. Immunohistochemical staining showed immunoreactivity for both S-100 protein and CD-68, which confirmed the diagnosis of RDD.

TREATMENT

Corticosteroid therapy was tried but with no response.

OUTCOME AND FOLLOW-UP

The patient's symptoms progressed within a few months with more pleural and parenchymal lung involvement (figure 4). The patient elected to go under hospice care where he passed away.

DISCUSSION

RDD, also known as SHML was first described in 1969 by Rosai and Dorfman.² It is a rare non-malignant proliferation of histiocytes of unknown aetiology that mainly affects lymph nodes and various extranodal sites as well.³ Extranodal involvement has been reported in approximately 43% of patients in one registry of RDD and 23% of cases had extranodal involvement only. Pulmonary involvement is rare and occurs approximately in only 3% of cases with extranodal disease.⁴

In contrast with nodal RDD, lower respiratory tract involvement carries a poor prognosis, almost one-third die of the disease and more than one-third have a progressive course.⁵

Cartin-Ceba *et al* reported mediastinal lymphadenopathy as the most common intrathoracic manifestation of RDD. Other intrathoracic manifestations included airway disease, pleural effusion, cystic and interstitial lung disease.⁶ Foucar *et al*⁷ found that all RDD patients with lower respiratory tract involvement had evidence of nodal disease. The initial presentation of our case with interstitial lung involvement in the absence of nodal disease was a unique feature which is very atypical for RDD.

The hallmark of the histiocytes in RDD is the presence of variable numbers of intact lymphocytes within their cytoplasm, a phenomenon referred to as *lymphophagocytosis* or *emperipolesis*.⁷

The most useful immunomarker for RDD is S100. The histiocytes also typically show immunopositivity with CD68, CD15, CD14, CD163 and α -1-antichymotrypsin and immunonegativity with CD1a and factor XIIIa.^{3 8}

In PLCH the Langerhans cell histiocytes are immunopositive with CD1a, S100, Langerin and E-cadherin, and show cytoplasmic Birbeck granules.⁹

Figure 4 Chest x-ray showing progression of the disease over a period of 2 years.

The histiocytes in Erdheim-Chester disease exhibit immunopositivity for CD68 and factor XIIIa with CD1a immunonegativity and variable S100 positivity plus the presence of symmetric osteosclerosis of long bones.^{10 11}

Another unique feature in our case was the significant proportion of IgG4 positive plasma cells on lung biopsy. Shrestha *et al*¹² reported an overlap in the histopathological appearance and IgG4 status of RDD and IgG4-related disease; they found that six of eight nodal (cervical, mediastinal) and extranodal (abdominal wall, thigh, hip and orbit) RDD cases showed increased IgG4+ cells.

Furthermore, a case of IgG4+ RDD of the lung was previously reported in which the patient presented with a lung nodule that was resected and the patient remained asymptomatic following the surgery.¹³

The overlap between RDD and IgG4 disease is further suggested by recent case reports that showed both pathologies in a subcutaneous lymph node that responded to steroid treatment and in the breast tissue in another case that was treated with surgical excision.^{14 15}

There is no ideal treatment for RDD; generally the management ranges from just observation to radiotherapy or surgical debulking depending on the organ involved and severity of the disease. Multiple chemotherapeutic agents have been tried with variable degrees of success and there has been some reported benefit from the use of corticosteroids.^{16 17}

Learning points

- ▶ Rosai-Dorfman disease (RDD) is a rare non-malignant proliferation of histiocytes of unknown aetiology that mainly affects lymph nodes and various extranodal sites as well.
- ▶ RDD should be considered in the differential diagnosis of interstitial lung disease even in the absence of lymphadenopathy.
- ▶ There is an overlap between RDD and IgG4 disease.
- ▶ Emperipolesis is a distinctive feature of RDD.

Patient consent Obtained.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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