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Rosai-Dorfman Disease Presenting as Massive Mediastinal Lymphadenopathy in an Elderly Man

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Abstract

We present a patient case of a 73-year-old man with new-onset substernal chest pain and B symptoms, found on computed tomography imaging to have massive mediastinal lymphadenopathy of more than 6 cm. Positron emission tomography imaging revealed fluorodeoxyglucose-avid nodes further extending to the axillary, abdominal, and inguinal regions. After a broad patient work-up for infectious, malignant, and rheumatic causes, he was ultimately diagnosed with Rosai-Dorfman disease, a rare histiocytic neoplasm, by excisional lymph node biopsy.

Keywords

Lymph nodes; Hospital medicine; Biopsy; Diagnostic medicine; Plasma cells; Histiocytes; Rosai Dorfman Disease

Background

Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytic disorder characterized by histiocytic infiltration into tissues, often manifesting with massive

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lymphadenopathy and B symptoms. Diagnostic delay is common because of under-recognition of this disorder.

Objective

To increase recognition of RDD on the differential of lymphadenopathy by reviewing the clinical presentation, diagnostic approach, and treatment strategies for this histiocytic neoplasm.

Case Report

A 73-year-old male Army veteran presented with 3 months of progressive substernal chest discomfort without features of angina, pleurisy, positional change, or gastrointestinal symptoms. His medical history was significant for tobacco use in sustained remission, pericarditis 1 decade prior, and a remote melanoma that was excised.

The patient was seen by his primary care physician, where he received ibuprofen for concern for a recurrence of pericarditis and was referred for a coronary computed tomography angiogram. Symptoms did not improve, and coronary imaging subsequently incidentally revealed bulky mediastinal lymphadenopathy, with the largest lymph node measuring more than 6 cm. Subsequent computed tomography scans of the chest, abdomen, and pelvis noted large lymphadenopathy extending to the hilar, axillary, abdominal, and pelvic regions (Figure 1).

On further querying, the patient reported progressive fatigue and an unintentional weight loss of 30 pounds, followed by onset of drenching night sweats and generalized weakness. A review of systems was otherwise negative. Social history was notable for prior extensive worldwide travel as part of his job in the military. He was in a monogamous relationship of more than 40 years. His family history was without known malignancies or autoimmune diseases. He was referred to admission for further work-up.

On presentation, he had normal vital signs with a body mass index of 22.7 kg/m^2. Physical examination revealed multiple mobile, palpable, nontender inguinal and axillary lymph nodes bilaterally. No organomegaly, synovitis, or rashes were noted. Initial laboratory data (Table 1) noted a leukocyte count of 8.50×10^3 cells/mL, a normocytic anemia with a hemoglobin level of 11.2 g/dL, and elevated inflammatory markers with an erythrocyte sedimentation rate of 102 mm/h and a C-reactive protein level of 3.8 mg/dL.

A wide differential diagnosis was considered for progressive B symptoms and widespread massive lymphadenopathy in this elderly patient who had an extensive travel history including infectious etiologies (syphilis, HIV, tuberculosis, herpes viruses, endemic mycoses), benign and malignant neoplasms (lymphoma, autoimmune lymphoproliferative processes, Castleman disease, histiocytic disorders), and noninfectious inflammatory disease (sarcoidosis, Still disease, hemophagocytic lymphohistiocytosis, IgG4-related disease).

Transbronchial fine-needle aspiration of the mediastinal lymph nodes was pursued and read as nondiagnostic with granulomatous inflammation and histiocytes. Staining and

cultures for fungal and mycobacterial diseases were negative. Because the patient preferred avoiding further invasive procedures, a broad serologic work-up was pursued with negative initial studies, including an antinuclear antibody, HIV antigen and antibody, rapid plasma reagin, hepatitis serologies, beta-D-glucan, antibody testing for endemic mycoses, and QuantiFERON gold. Serum electrophoresis did not show a monoclonal gammopathy. IgG4 subclass was elevated at 1202 mg/dL. A whole-body PET scan showed extensive fluorodeoxyglucose-avid lymphadenopathy without other avid sites (Figure 2).

Elevated IgG4 subclasses raised the question of an atypical presentation of IgG4-related disease, although the patient was without more typical retroperitoneal, pancreaticobiliary, or salivary gland involvement. Sarcoidosis manifesting with widespread lymphadenopathy was considered, but he lacked characteristic extranodal disease. Additionally, sarcoidosis as the cause of granulomatous inflammation is a diagnosis of exclusion in the absence of characteristic clinical features such as Lofgren syndrome. Because the serologic work-up and fine-need aspiration were not definitive, the patient ultimately agreed to pursuing an excisional inguinal lymph node biopsy.

Histomorphological examination of the excised inguinal lymph node showed markedly expanded sinuses filled with large histiocytes with round nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm (Figure 3, A-B). On immunohistochemistry, these histiocytes were positive for S100, CD68, cyclinD1, and OCT-2 (Figure 3, C). Between the sinuses, there were large numbers of polytypic plasma cells, with more than 40% expressing IgG4. Overall, the findings were consistent with a diagnosis of RDD with increased IgG4 plasma cells. Next-generation sequencing subsequently identified the presence of a KRAS mutation.

Discussion

RDD is a rare non-Langerhans cell histiocytic disorder characterized by histiocytic infiltration into tissues often manifesting with massive lymphadenopathy and B symptoms. The disease is rare, affecting only 1 in 200 000 people, and most commonly presents in children and young adults with cervical lymphadenopathy (1). RDD can occur sporadically or can be in association with various familial (H syndrome, autoimmune lymphoproliferative syndrome), malignant (leukemia, lymphoma, cutaneous clear-cell sarcoma), and autoimmune disorders (systemic lupus erythematosus, idiopathic juvenile arthritis, autoimmune hemolytic anemia) (1, 2). Although nodal involvement is the most common, extranodal sites can be involved in a minority of cases including skin, bone, central nervous system, and orbital tissues (1). Diagnostic delay is frequent, with a median time to diagnosis from symptom onset of 7 months and an average of 2 biopsies required (3).

The pathogenesis of RDD is poorly understood. Although it was previously favored to be a nonneoplastic histiocytic disorder without clonality, recent evidence suggests that at least a subset of RDD is clonal with several mutations identified including in KRAS, MAP2K1, NRAS, and ARAF. Diagnosis is secured by a compatible clinical syndrome, with pathology noting extensive sinusoidal expansion with large histiocytic cells with ill-defined, pale,

wispy cytoplasms, often with S100, CD68, and CD163 positivity (1, 2). Cyclin D1 and OCT-2 expression has also been described (4, 5). An increase in IgG4-positive plasma cells may be seen in RDD, although its significance remains ill-defined (1, 6).

Therapeutic approaches to RDD vary greatly. Sporadic RDD has a good outcome, with spontaneous remission reported in up to 50% of cases (7). Observation alone may be pursued for disease-limited nodal disease or surgical resection pursued for symptomatic cranial, spinal, or airway disease (2). Refractory disease or nonresectable extranodal disease has historically been treated with various therapeutic approaches, including corticosteroids, chemotherapy, and immunomodulatory therapy, though with response remaining highly variable and no clearly established standard of care in treatment (2).

With the identification of mutations associated with RDD, targeted therapies have now become a new hope for the treatment of RDD and other histiocytic disorders. For example, BRAF inhibitors, such as vemurafenib, have been recently shown to be highly efficacious in treatment of Erdheim-Chester disease, of which more than half of patients carry a BRAFV600E-activating mutation (8, 9). The MEK inhibitor, cobimetinib, has been observed to be effective in treating histiocytic neoplasms including RDD with NRAS, KRAS, and MEK1/2, among other mutations resulting from dependence on MAPK signaling (10, 11).

The patient was treated with systemic corticosteroids but did not have an improvement in his symptom burden or lymphadenopathy. After a *KRAS* mutation was identified, he received cobimetinib with symptom improvement. He is awaiting a repeat positron emission tomography scan to fully assess treatment response.

Overall, this case highlights that RDD and the spectrum of histiocytic disorders should be considered on the differential diagnosis for widespread lymphadenopathy and B symptoms, particularly if more typical investigations are not fruitful. Our patient was an elderly man with prominent mediastinal lymphadenopathy, although RDD more commonly presents with massive cervical node involvement in children and young adults. The treatment of these disorders continues to rapidly evolve as novel targeted therapies emerge. Last, this patient case underscores the increased yield of excisional lymph node biopsies compared with fine-needle aspirations or core biopsies in identifying the cause of lymphadenopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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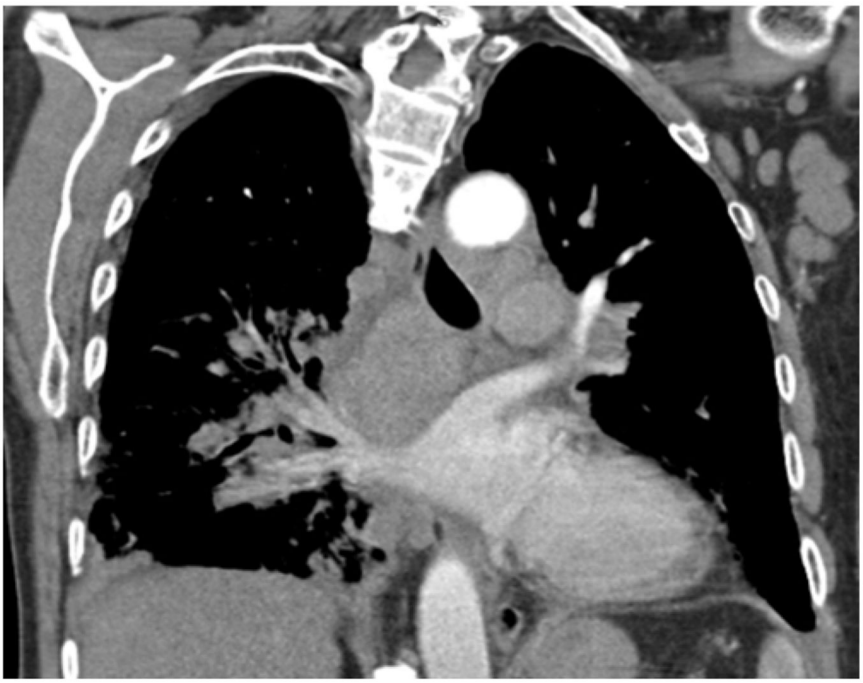

Figure 1.
Large mediastinal lymphadenopathy visualized on arterial phase computed tomography scan of the chest.

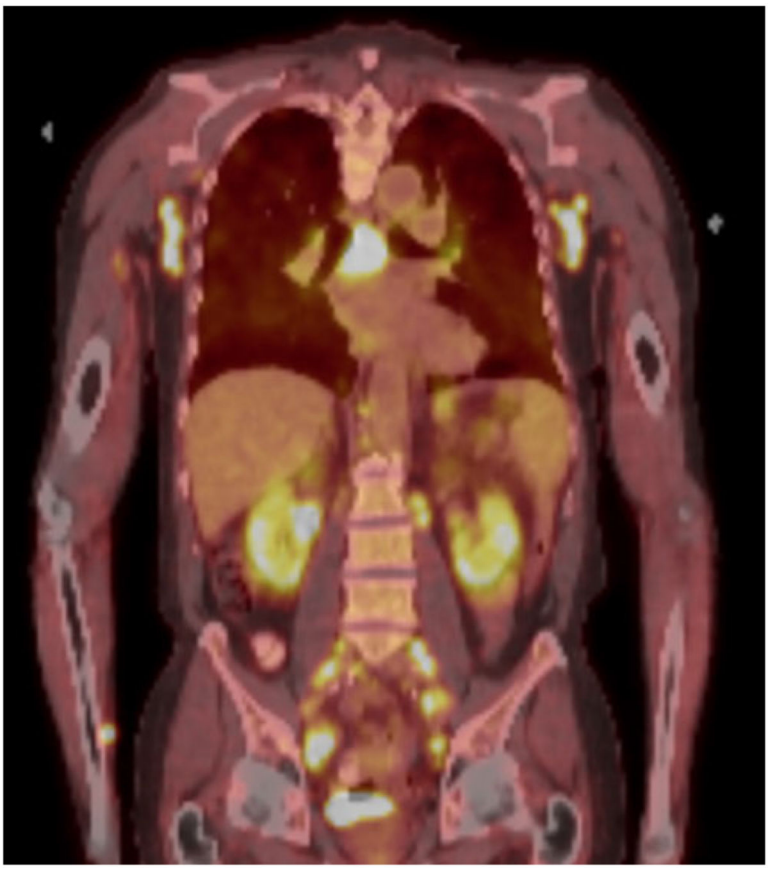

Figure 2.
Widespread fluorodeoxyglucose-avid lymphadenopathy in the axillary, mediastinal, retroperitoneal, and inguinal regions.

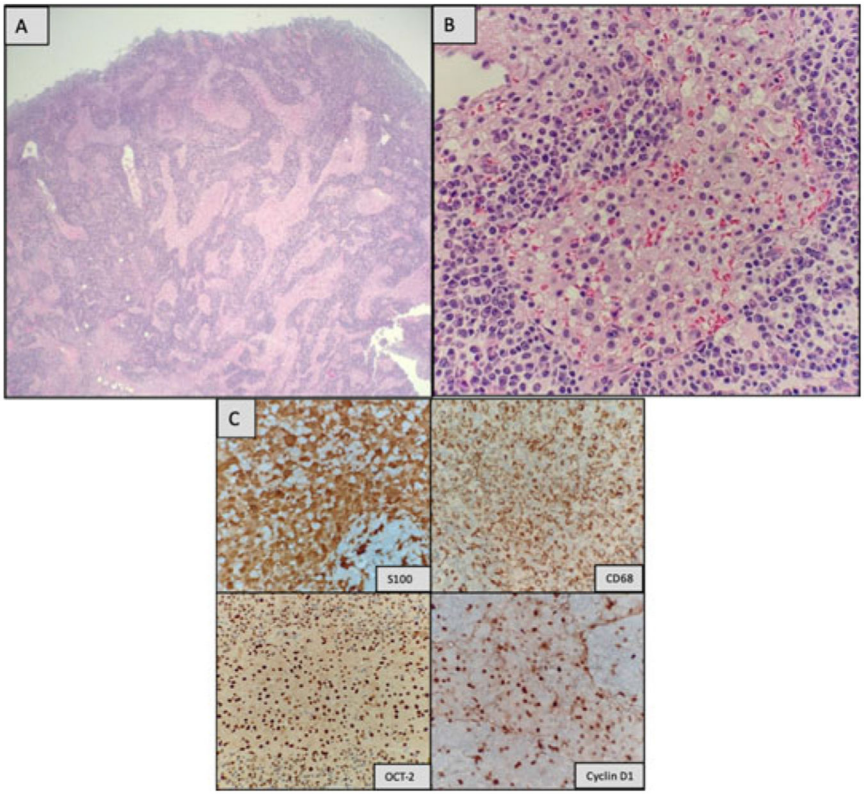

Figure 3.

Histomorphological findings of Rosai-Dorfman disease on the excisional biopsy. (A) Enlarged lymph node with markedly expanded sinuses (hematoxylin–eosin stain; original magnification, ×2). (B) Sinus histiocytosis surrounded by numerous plasma cells. The histiocytes comprise large cells with round nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm (H&E stain; original magnification, ×20). (C) Immunohistochemical stains with histiocytes positive for S100, CD68, cyclin D1, and OCT-2.

Table 1.

Laboratory and Microbiologic Findings on Inpatient Evaluation

Laboratory Values		**Microbiology Results**	
White blood cell count, *10^3/mL*	8.5	Blood cultures	No growth
Hemoglobin, *g/dL*	11.2	Urine culture	No growth
Platelet count, *10^3/mL*	244	HIV antigen/antibody	Negative
Blood urea nitrogen, *mg/dL*	19	Hepatitis B surface antigen	Negative
Creatinine, *mg/dL*	1.1	Hepatitis B core antibody	Negative
Erythrocyte sedimentation rate, *mm/h*	102	Hepatitis C antibody	Negative
C-reactive protein, *mg/dL*	3.8	Treponema pallidum antibody	Negative
Ferritin, *ng/mL*	447	QuantiFERON Gold	Negative
Antinuclear antibody	Negative	Beta-D-glucan	Negative
Serum protein electrophoresis	No monoclonal gammopathy	Urine histoplasma antigen	Negative
IgG4, *mg/dL*	1202	Serum histoplasma antibody	Negative
Beta-2 microglobulin, *mg/L*	8.4	Serum Blastomyces antibody	Negative
Angiotensin-converting enzyme, *U/L*	45	Brucella antibody	Negative

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