Unusual Presentation of Rosai-Dorfman Disease: Report of a Rare Case

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Study Design A
Data Collection B
Statistical Analysis C
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Patient: Male, 40
Final Diagnosis: Rosai-Dorfman disease
Symptoms: Dry cough • dry mouth • dry skin • general fatigue • itchy eyes • joint pain • neck swelling • shortness of breath
Medication: —
Clinical Procedure: Complete blood cell, C reactive protein, creatinine, antibody and rheumatological studies • histopathological and radiological study
Specialty: General and Internal Medicine

Objective: Unusual clinical course
Background: Rosai-Dorfman disease is a rare disorder that was previously described as sinus histiocytosis with massive lymphadenopathy. The disease is derived from overproduction of monocytes, which play an important role in immunity. The overproduction of macrophages will lead to accumulation of the cells in the affected tissue.

Case Report: A 40-year-old Saudi male presented with shortness of breath with joint pain starting 3 months prior. His main complaints were a dry cough, bilateral neck swelling, dry mouth, dry skin, itchy eyes, and general fatigability. Physical examination showed that the patient had prominent bilateral parotid swelling that measured roughly 5 by 3 cm, which was firm and tender, with a smooth surface and no local signs of inflammation. Joint examination revealed non-tender and non-swollen joints, with mild limitations of movement. Eye examination revealed dry eyes after having a positive Schirmer test. For diagnosis, the patient underwent complete blood count, autoantibody, histopathology, immunohistochemistry, and radiological assessment. The histopathological study confirmed Rosai-Dorfman disease. Rosai-Dorfman disease can involve various presentations, as in this patient, who exhibited a highly unusual presentation in association with autoimmune disease.

Conclusions: Rosai-Dorfman disease must be considered as differential diagnosis in patients who present with bilateral lymphadenopathy with multisystem complaints, as the disease can present with various characteristics.

MeSH Keywords: Autoimmune Diseases • Histiocytosis, Sinus • Sarcoidosis • Sjogren's Syndrome

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/912423>

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Background

Rosai-Dorfman disease (RDD) is a rare disorder that is also known as sinus histiocytosis with massive lymphadenopathy. The disease derives from overproduction of monocytes, which play an important role in immunity. Children, adolescents, and adults are all frequently affected by this disorder [1,2]. RDD affects the lymph nodes, and patients most commonly present with bilateral lymphadenopathy. Extranodal infiltration occurs in 40% of the patients; this is evident in the skin, soft tissues, eyes, bones, nasal sinuses, central nervous system, salivary glands, kidneys, respiratory tract, liver, breast, and gastrointestinal tract. The largest report of RDD (1969) involved 423 cases, with 182 patients having extranodal disease [1–4]. The patient may present with fever, weight loss, malaise, joint pain, shortness of breath, difficulty swallowing or speaking, night sweats, leukocytosis, elevated erythrocyte sedimentation rate, and polyclonal hypergammaglobulinemia [1–5]. Associations with autoimmune diseases (Sjogren's syndrome and antiphospholipid syndrome) have been observed in 2 patients with Rosai-Dorfman syndrome [6].

The pathologic findings that Rosai and Dorfman described became the basis for a new entity called 'sinus histiocytosis with massive lymphadenopathy'. These pathologic findings were:

- 1) emperipolesis: histiocytes with engulfed lymphocytes (most common), plasma cells and erythrocytes;
- 2) marked fibrosis of the lymph node capsule with lymphocyte and plasma cell infiltration;
- 3) dilation of subcapsular and medullary septate;
- 4) increased intra-sinusal histiocytosis with little atypia and few mitoses.

The classical findings of RDD include emperipolesis and histiocytes staining positive for S100 and CD68 and negative for CD1a.

Case Report

A 40-year-old Saudi male presented with shortness of breath (SOB) and joint pain that had started 3 months prior to admission. The SOB had a progressive course, and it was aggravated by moderate exertion and relieved by rest (grade 2 in severity). The joint pain was continuous and had a generalized involvement of all body joints, especially the large joints, which showed greater limitation of movement. His main complaints were dry cough, bilateral neck swelling, dry mouth, dry skin, itchy eyes, and general fatigability. There was no medical history of allergy, and there was no relevant family history. The patient smoked a packet of cigarettes daily. On examination, his general condition and vital signs were normal. The patient had prominent bilateral parotid swelling that measured

Table 1. Laboratory investigation.

Complete blood count	Result	Normal range
RBC	5.23 (H)	(3.60–4.69)×10 ¹² /L
WBC	5.40	(3.70–10.1)×10 ⁹ /L
HB	14.6	(11–15) g/dL
MCV	82	(75–84)
ALT	14	(<54)
AST	12	(<52)
Urine creatinine	0.6 (L)	0.72–1.25 mg/dl
Serum uric acid	6.7	3.4–7 mg/dl
C-reactive protein	19 (H)	< 5 mg/l
Erythrocyte sedimentation rate	5	0-15 mm/h
Autoantibody		
ANA	Negative	
Rheumatoid factor	Negative	
ANTI-RO SSA	Positive	
ANTI-LA SSB	Negative	

(H) – high; (L) – low.

roughly 5 by 3 cm, which was firm and tender, with a smooth surface and no local signs of inflammation. The joint examination revealed non-tender and non-swollen joints, with only mild limitations of movement. The eye examination revealed dry eyes after having a positive Schirmer test. The rest of the systemic examination was normal. To reach a diagnosis, the patient underwent complete blood count, as well as autoantibody (Table 1), histopathology, immunohistochemistry, and radiological assessment (Figures 1–3). The complete blood count showed high red blood cells and high C-reactive protein with low creatinine. Also, autoantibody assessment was positive for anti-RO SSA but negative for antinuclear antibody, rheumatoid factor, and anti-LA SSB. A specimen from the submandibular lymph node was taken for histopathological evaluation. Then, we performed a radiological chest x-ray (Figure 1), ultrasound for enlarged lymph nodes (Figure 2), and CT scan of the chest (Figure 3). The result of the radiological examination was suggestive of sarcoidosis stage III; therefore, the patient was prescribed prednisolone (5 mg) for 1 month. Subsequently, the histopathological result showed that the patient had Rosai-Dorfman disease associated with Sjogren's syndrome. There was no significant improvement, he was switched to azathioprine (50 mg) for 2 months. On follow-up, he showed improved symptoms.

Histopathology

An excisional biopsy from the right submandibular lymph nodes was done. The specimen was examined grossly and microscopically at multiple levels. The microscopic sections revealed an enlarged lymph node with preserved topography; however, there was architectural distortion, with marked expansion of the sinuses at the expense of the cortex and paracortex. The sinuses were obstructed by static lymph and contained a mixed population of cells, including lymphocytes, plasma cells, and histiocytes. The most characteristic cells in the sinuses were histiocytes with marked phagocytic properties. These cells were generally large and irregularly-shaped, with abundant, acidophilic, and sometimes vacuolated cytoplasm. Most had a single nucleus

Figure 1. Chest X-ray showing bilateral basal lung reticulation and non-homogenous opacity suggesting air space/interstitial disease; heart size is normal.

Figure 2. Neck ultrasound showing diffuse cystic changes in the parotid and submandibular glands.

Figure 3. Chest computed tomography (CT) showing bilateral basal pulmonary diffuse interstitial thickening and ground-glass appearance; lymph node is seen at the aortopulmonary window with no hilar lymphadenopathy.

and distinct, central nucleolus. Mitosis was rare. The intracytoplasmic vacuoles contained engulfed cells, mostly lymphocytes, but plasma cells and erythrocytes were also seen. Some of the engulfed cells, particularly lymphocytes in the vacuoles, were viable, reproducing the phenomenon of emperipolesis; others were degraded, with many forming nuclear fragments. These cells are clearly visible on the smear. Few lymphoid follicles were present in the relatively preserved areas. The medullary pulp included numerous plasma cells, some binucleated, and mature lymphocytes. Rare eosinophils were noted but there were no neutrophils. There was mild fibrosis of the capsule and pericapsular fibrofatty tissues. We also found a small amount of salivary gland tissue composed of serous acini, likely parotid in origin, and some salivary gland tissue was also found adherent to the lymph node, which is partially involved in the process. No granulomas and no microorganisms were seen. There was no evidence of malignancy. Excisional biopsy concluded the diagnosis as benign lymphadenopathy consistent with Rosai-Dorfman disease.

Immunohistochemistry

The following types of immunostaining were performed with external positive and negative controls:

- S100 (4C4.9): The characteristic histiocytes were highlighted;
- CD3 (2GV6): This stained the mature and reactive T cells in the background; and
- CD20 (L26): This stained the mature and reactive B lymphocytes in the background and highlighted the remnants of lymphoid follicles.

Discussion

Parenchymal involvement of the lung is relatively rare in RDD cases, in a series of 9 patients with intrathoracic manifestation [7]. RDD can infiltrate the skin and soft tissue (16%), nasal cavity (16%), eyes/eyelids (11%), bones (11%), central nervous system (7%), salivary glands (7%), kidney (3%), airway (respiratory tract; 3%), and liver (1%) [1]. In this case, the patient presented with shortness of breath, joint pain, dry cough, bilateral neck swelling, dry mouth, dry skin, itchy eyes, and general fatigability. The differential diagnosis of this case was sarcoidosis and Sjogren's syndrome. The laboratory test was normal, with elevated anti-RO SSA. After the radiological study, which was suggestive of sarcoidosis as the chest computed tomography (CT) showed bilateral basal pulmonary diffuse interstitial thickening and ground glass appearance, the lymph node was seen at the aortopulmonary window with no hilar lymphadenopathy (Figure 3). The diagnosis was thought to be sarcoidosis stage III, which involves parenchymal infiltrates without bilateral hilar lymphadenopathy associated with Sjogren's syndrome; however, the symptoms were not associated with sarcoidosis, which is

connected to Sjogren's syndrome; thus, immunohistochemistry and histopathological study was carried out, S100 (4C4.9) antigen were positive which is diagnostic for RDD. The final diagnosis was RDD associated with Sjogren's syndrome, depending on immunohistochemistry, and histopathology. As sarcoidosis shows non-caseating granulomas in histopathology, which is negative in our case. Finally, RDD and sarcoidosis could present with similar complaint of SOB in case of infiltration of respiratory tract in RDD patient. The patient started on prednisolone (5 mg) for 1 month after the diagnosis. One month after diagnosis follow up showed no improvement with prednisolone of the SOB or the joint pain. Patient shifted to azathioprine (50 mg) for 2 months. On second follow up 3 months after the diagnosis and after taking azathioprine for 2 months, the patient showed improvement. There was an appointment after 6 months, but the patient stopped coming to the hospital. Regarding treatment, some cases show no response to corticosteroids. In a case report for Edward Chen et al. [8], the patient presented with scattered nodules overlying indurated plaques within hyperpigmented patches on the medial right lower leg, biopsy revealed histiocytic proliferation, Immunohistochemical staining of the histiocytes showed positive stain for S100, the patient was diagnosed as RDD. The patient started on intralesional triamcinolone and fluocinonide 0.5% cream with no response, patient did not respond to radiotherapy nor methotrexate. The patient responded to thalidomide, with no activity of the disease after 9 months of thalidomide treatment on follow-ups. On the other hand, in a 14-month-old female presenting swelling of the right parotid for 1 month, an examination revealed a palpable, bilateral, painless cervical lymphadenopathy with a maximum diameter of approximately 2 cm. The lymphadenopathy was confirmed by ultrasound, ranging from 6.5 mm to 24.6 mm as cystic and solid nodular lesions. The patient was discharged on amoxicillin with clavulanic acid. The patient came back after 11 days, with more swelling and pain in the cervical area. The patient showed high ESR and CRP, and an MRI revealed a 43×28 mm diameter solid mass attributable to lymph nodes, entirely occupying the right parotid gland. Chest radiograph showed a right mediastinal enlargement. A cervical lymph node biopsy was then performed, and histopathologic examination showed the presence of emperipolesis, with notable sinus infiltration of large histiocytic cells with pale cytoplasm. Further immunohistochemistry assessment showed cells with a positive reaction to CD68 and S-100 protein, which changed the diagnosis to RDD. The patient was given prednisone 1.5 mg/kg/day continued for 40 days with tapering. At follow-up, the patient had reduction of the swelling in both parotid and cervical areas. ESR and CRP were normal 20 days after treatment. MRI and US of the parotid showed reduction of size 20 days after stopping the treatment. At 12-month follow-up, the patient was asymptomatic and there was only US evidence of minimal residual lymph nodes on both sides [9]. In another case, a patient presented with chronic cough and was found to have

Table 2. Articles review.

Author	Age/sex	Presentation	Onset of symptoms	Treatment	Follow up
Our case	40/Male	Shortness of breath, with joint pain, bilateral neck swelling	3 months from presenting complain	*NA	*NA
Mantilla J.G. et al.	65/Female	Chronic cough	*NA	*NA	*NA
Hasegawa M. et al.	64/Female	Asymptomatic/regular check-up	*NA	*NA	*NA
Jing X. et al.	51/Female	Back and hip pain/mass on her right clavicle	One month	*NA	*NA
Arilala Sendrasoa F. et al.	38/Female	Malaise, fever, anorexia, and weight loss. Bilateral painless cervical, axillary and inguinal lymphadenopathies	One year	Corticosteroids, antibiotics	The patient died 2 months after diagnosis
Li M. et al.	39/Male	slowly growing red and raised lesion below the left nostril and left preauricular region	9 months	Oral thalidomide, <i>in situ</i> photoimmunotherapy	The patient's condition only responded to photoimmunotherapy
Chen E. et al.	49/Female	Lower limbs eruption	6 years	Intralesional triamcinolone, fluocinonide cream, radiation, methotrexate, thalidomide	The patient condition only responded to thalidomide
Saleem S. et al.	16/Female	Gradual painless left upper eyelid drooping, lumps in her cervical region	6 months	Methylprednisolone injections, oral Prednisolone	4 weeks, there was improvement of her symptoms
di Dio F. et al.	14 months/ *NA	Swelling of the right parotid, palpable bilateral cervical lymphadenopathy	One month	Oral prednisone	20 days, 40 days, 4 months, 12 months, with gradual improvement and free of symptoms at 12 months
Penna Costa A.L. et al.	49/Female	Cough, dyspnea and chest pain	2 years	Surgical excision of para-aortic lymph node, with lymph nodes from the left hilum and pulmonary ligament	Monthly up to 12 months with minimal symptoms after the surgery

* NA – not available.

multiple pulmonary nodules in the right middle and lower lobes on chest CT, with associated right hilar lymphadenopathy, and the largest nodule measured 1.4 cm. The patient was managed by surgical excision of the lesions and associated lymph nodes. A histopathology report was positive for histiocytes with emperipolesis, and further immunohistochemical staining was positive for S-100 protein, which changed the diagnosis from suspected malignancy to RDD. At 6-month follow-up after surgery,

the patient was free of additional symptoms and there was no evidence of new chest lesions on imaging [10]. Case reports have many shown different results regarding treatment – some cases respond to corticosteroids or other immunosuppressive medication, and others show response to immunomodulatory agents, as in our case. Some cases show improvement and no recurrence of the disease after surgical removal of the affected lymph node in localized disease (Table 2).

Conclusions

RDD can exhibit various presentations, as in this case, where the patient's presentation was highly unusual and was associated with autoimmune disease. Incorporation of immunohistochemistry and histopathology is helpful in the diagnosis of RDD. In our case, there were many significant major findings highly suggestive of our final diagnosis. Starting with the presenting symptoms, joint pain was continuous and had a generalized involvement of all the joints, especially the large joints, which showed greater limitation of movement. His main complaints were associated with dry cough, bilateral neck swelling, dry mouth, dry skin, itchy eyes, and general fatigability. The patient had prominent bilateral parotid swelling, and the eye examination revealed dry eyes after a positive Schirmer test. Autoantibody was positive for anti-RO SSA, but negative for antinuclear antibody, rheumatoid factor, and anti-LA SSB. A specimen from the submandibular lymph node was taken for a histopathological evaluation. Then, we performed a radiological chest x-ray, ultrasound for enlarged lymph nodes, and CT scan of the chest. Also, the investigation results for this patient were highly remarkable and fully supported the diagnosis. Ultimately, immunohistochemistry and histopathological studies was carried out, showing positive for S100 (4C4.9) antigen, which is diagnostic for RDD. The final

diagnosis was RDD associated with Sjogren's syndrome, based on immunohistochemistry, and histopathology. Rosai-Dorfman disease must be kept in mind in the differential diagnosis of patients presenting with bilateral lymphadenopathy with multisystem complaints, as the disease can have various features. Most of the patients are in good health and have no significant symptoms relating to this disease, which complicates the diagnosis. We report an unusual location of Destombes-Rosai-Dorfman disease. Our patient lacked clear signs or symptoms, thus making the management much complicated, and he did not respond to the first approach of treatment. We initially suspected sarcoidosis based on the patient presenting symptoms, but subsequently diagnosed him as having RDD.

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Conflict of interests

None.

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