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Spinal Rosai-Dorfman Disease with Isolated Severe Neuropathic Pain: A Case Report

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ABSTRACT

Introduction

Rosia-Dorfman disease (RDD) is a rare histiocytic disorder that presents as generalized lymphadenopathy. Rarely, patients experience atypical extra-nodal manifestations which can mimic other diseases.

Case Presentation

We report a challenging diagnosis of Rosai-Dorfman disease in a 52-year-old female presenting with isolated symptomatic neuropathic pain. After excluding common diseases, a challenging diagnosis was made based on imaging, CSF studies and clinical progression that showed thoracic spine involvement and emperipolesis confirming RDD diagnosis and with a great clinical response to corticosteroids.

Discussion

Clinical, laboratory and radiologic manifestations of the disease can vary a lot depending on the areas involved and patient progression. This can lead to challenges in establishing the diagnosis and deciding on treatment. Then unusual, first reported manifestations in our patient made the diagnosis exceptionally challenging, highlighting the importance of this report.

Conclusion

This disease can have an atypical presentation that should be detected early to avoid any delay in diagnosis or treatment. Our patient did well on corticosteroids and remained symptom free afterwards. Such unusual cases must be reported to aid in such a difficult diagnosis in future similar cases.

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INTRODUCTION

Rosai-Dorfman disease (RDD) is a rare non-neoplastic histiocytic disorder, also known as sinus histiocytosis with massive lymphadenopathy. Histopathologically, RDD emperipolesis is seen as the phagocytosis of erythrocytes and lymphocytes without their destruction [1]. Usually, this disease presents as painless lymphadenopathy affecting cervical nodes. However, extra-nodal involvement is seen in more than 40% of the cases [2]. Such presentations are challenging to diagnose because they have a plethora of symptoms and mimic many multisystemic illnesses and malignancies such as lymphomas, tuberculosis and other granulomatous diseases [3]. In addition, multi-site involvement is a common manifestation, affecting up to 73% of cases in some studies [4]. Involvement of the central nervous system (CNS) is rare with only 210 reported cases [5]. Due to this lack of literature, and in the absence of a consensus diagnostic and treatment approach, management of such patients is difficult [4]. Here, we present a patient with a progressive lymphadenopathy with thoracic spinal cord involvement, which is, to our knowledge, among the first reported cases of RDD with such a presentation.

CASE REPORT

We describe a case of Mrs. X, a 52-year-old female who presented to us on the 30th of January, of 2023 for lower back pain radiating to the thighs bilaterally. Two months ago, she received a lumbar spine corticosteroid injection for radiculopathy. Four weeks later she started having headaches and low-grade fevers of 38.5C. She presented to another institution where a head scan revealed chronic sinusitis, and she was then discharged on antibiotics. The symptoms continued, and on 13th of January 2023 she was admitted in another institution, and a repeat head scan was also normal and a urinalysis, troponin, Brucella serology, Borrelia serology, gamma-glutamyl transferase, alkaline phosphatase, bilirubin, Aspartate transaminase, and Alkaline Transaminase were insignificant. She was discharged on symptomatic treatment. Two weeks later she started having progressively worsening abdominal pain with back tenderness radiating to the thighs, where she was readmitted, and a plain brain and spine Magnetic Resonance Imaging (MRI) showed mild degenerative spondylosis. An electromyogram (EMG) which was normal, and she was diagnosed with fibromyalgia. The symptoms persisted until the patient presented to our institution on January 30th, 2023.

She is a non-smoker, occasional alcohol drinker without drug use history. She does not have previous medical or surgical history. She has no known allergies. There is no recent travel and no animal exposure. She lives in central Lebanon. Family history is significant for psoriasis, sarcoidosis, and breast cancer.

Upon admission, physical exam was only significant for lower back, lower abdominal, and anterior and posterior thigh tenderness. Neurological exam was normal.

Laboratory workup was unrevealing, provided in **Table 1**. X-ray of the lumbosacral spine showed mild disc narrowing L5-S1. Enhanced brain and spine MRI showed a linear leptomeningeal enhancement of the mid-thoracic vertebra with intramedullary cord edema and patchy intramedullary and diffuse circumferential intradural extramedullary enhancement at the conus medullaris at L5-S1. This was suggestive of infection or inflammation. Lymphoma was ruled out by enhanced whole body Computed Tomography (CT). Blood flow cytometry excluded leukemia. Positron Emission Topography (PET) CT scan was negative for any nodal involvement or uptake.

Upon further history, she mentioned that she had contact with refugees residing in Lebanon. This exposure, with the Lumbar Puncture (LP) and imaging results, raised the possibility of tuberculosis (TB) and she was started empirically on isoniazid, rifampin, pyranzimide, ethambutol with dexamethasone. The symptoms completely resolved after the first dose of dexamethasone.

Cerebrospinal fluid (CSF) examination **(Table 2)** showed monocytic cells and basophilic monocytoid cells with a high nucleus-to-cytoplasm ratio, occasional plasma cells, and images of emperipolesis, a proliferation of histiocytic cells with phagocytosed lymphoid cells that are not fragmented, with a collection of lymphocytic cells around them **(Figure 1)**. CSF cytology showed reactive neutrophils and macrophages without malignant cells. CSF cultures showed no growth and negative brucella antibodies. Acid-fast stain, and PCR for Tuberculosis were also negative. Peripheral blood smear showed no morphological abnormalities and a complete rheumatological workup was normal.

TB treatment was stopped as the emperipolesis and histiocytosis were suggestive of Rosai-Dorfman Disease. The slides then underwent S-100 staining, which was strongly positive, further confirming the diagnosis.

The patient was kept on dexamethasone, and her condition improved. She was discharged on prednisone 80 mg once daily. After 2 weeks, another LP showed decreasing protein concentration and leukocyte count **(Table 2)**. Follow up MRI showed findings consistent with ongoing epiduritis and resolving myelitis.

The patient remained on prednisone, with no recurrence. Follow-up MRI showed improving T2 signal involving the central aspect of the spinal cord, decrease in intradural enhancement and loss of enhancement in the conus medullaris. On August 23, 2023, she was successfully tapered off steroids with no recurrence of

symptoms. She is still symptom free today and has not had recurrence of symptoms. Follow-up has stopped and she was instructed to return to the clinic in case she has any new findings.

DISCUSSION

This case illustrates an unusual presentation of RDD manifesting as cervical lymphadenopathy. The diagnosis could not be easily established due to the rarity of this disease and the unusual manifestations. Since first described in 1969, around 210 cases of RDD were reported, out of which 174 cases had CNS involvement [6]. The pathogenesis of RDD is not well understood, believed to be a reactive non-neoplastic histiocytic disorder that lacks clonality. Several mutations are linked to RDD including ARAF, MAP2K1, NRAS, KRAS, and CSF1R as well as multiple gene alterations in intracellular trafficking, transcription, cell cycle regulation, Deoxyribonucleic acid (DNA) mismatch, and ubiquitin-proteasome pathway [7]. However, some presentations are linked to infectious etiologies such as EBV, CMV, HIV, and Herpes virus-6 [2]. The prevalence of RDD is about 1:200 000, most common in young adult males of African descent [8].

RDD is classified as sporadic, cutaneous, and familial. The sporadic form classically presents as painless bilateral cervical lymphadenopathy mostly in the head and neck. It can also present as an extra-nodal disease in 40% of cases [8]. The median age is 50 years and it seems to have a slight female predominance of 1.5:1 [4]. The gender and age distribution go with our patient demographics but she did not seem to have a family history of such a presentation.

Skin involvement is seen in 10% of extra-nodal RDD cases, but isolated cutaneous manifestations are rare. Usually, this presents as skin-painless nodules, papules, or plaques affecting the head, neck, and upper trunk areas. These lesions can vary in size, shape, and color. The main diagnostic method is a histopathological picture of large histiocytes with abundant cytoplasm and emperipolesis showing phagocytosis of intact lymphocytic cells [9]. Intrathoracic involvement is not common, only seen in 2% of patients with RDD. The symptoms can mimic other diseases presenting as cough or even respiratory failure, it can appear as lung nodules, intrathoracic lymphadenopathy, pleural effusions, or interstitial lung disease. Cardiac involvement is extremely rare, described in less than 0.2% of patients [8]. Renal involvement is usually associated with poor prognosis. Symptoms can vary from flank pan and hematuria to severe renal failure which makes the diagnosis much more complicated [1]. Testicular involvement in men, bone, gastric and hematological manifestations of RDD have been described in the literature [10]. However, our case had isolated CNS affection which made the diagnosis rather challenging. She had none of these described systemic findings. The lack of such systemic symptoms in our patient made the diagnosis more challenging.

Involvement of the CNS is described in about 5 % of cases [6]. Moreover, Only 25% of the lesions reported are spinal, where it is mostly a manifestation of systemic disease [6]. In contrast to systemic RDD, isolated CNS manifestations lack constitutional symptoms and are usually unilateral. Symptoms may vary from headaches to seizures, motor and sensory abnormalities, and focal deficits [6]. Our patient's symptoms included lower back pain, non-specific abdominal pain, and thigh pain, which was unusual as per the literature. In a similar case reported by Huang et al., the patient experienced sciatica-like symptoms caused by RDD of the sacral bone, which is a very rare presentation seen with our patient.

Ophthalmic manifestations are described in 10% of CNS cases, where sinus and ophthalmic involvement is seen due to the close anatomical area. This can lead to vision impairment, with nasal obstruction, epistaxis and facial deformity [1]. Our patient did not have any ophthalmic symptoms.

Goyal et al. reported 60 cases of RDD followed-up from 1994 to 2017. They found that only 8% had nodal disease and above 90% had extra-nodal manifestations. 52% had skin and subcutaneous masses, 21% had bone or muscle involvement and 4 cases (6.2%) had CNS frontal lesions. Interestingly, the median time from initial presentation to diagnosis was around 7 months, which highlights how challenging the diagnosis of RDD is [4]. This was one of the largest studies of RDD reported. While a lot of the mentioned presentations were not seen with our patient, the article highlights the long median periods to establish the diagnosis in the presence of some suggestive findings. In our case, and with the lack of the already rare disease manifestations, the diagnosis remained challenging to establish.

In another case series, 3 middle-aged patients with multiple subcutaneous and intra-abdominal masses were found to have RDD after excisional biopsy [11]. According to the authors, extra-nodal disease can mimic malignancy and other viral illnesses, and that in most cases immunohistochemistry (IHC) is the main tool for diagnosis, especially that it excludes other diseases.11 In our case, IHC and pathologic examination of the CSF is what helped most in establishing the diagnosis, which goes with what this case series concludes.

According to Mar et al, computed tomography (CT), MRI, and Positron Emission Tomography (PET) are important tools to suspect RDD [12]. However, the diagnosis can overlap with other conditions like lymphoma, infection, and granulomatous disease. There are a variety of appearances on radiology for different RDD involvement [12]. For instance, cardiothoracic involvement can manifest as lymphadenopathy, tracheobronchial or lung nodules, pleural effusions, or cardiac masses [12]. Abdominal involvement

can affect any organ system, often presenting as masses or lymphadenopathy. Pelvic involvement can involve pelvic lymph nodes, and reproductive systems, and musculoskeletal involvement can manifest as subcutaneous masses or lytic bone lesions. Nevertheless, definitive diagnosis requires a multidisciplinary approach [12].

Rosai Dorfman Disease involving the CNS has a wide array of radiological findings. While intracranial lesions mostly consist of extra-axial masses mimicking a meningioma or diffuse pachymeningitis, spinal or epidural lesions are most common in the cervical and thoracic areas which are usually enhancing on MRI T2 [8]. A case report in 2019 describes significant edema on T1 and T2 and thickened meninges [13]. Another one describes a large enhancing soft-tissue mass at L5-S1, with histopathological findings of Rosai-Dorfman disease and complete resolution on steroids [14]. Furthermore, a case series of 11 patients with isolated CNS RDD reported the possible involvement of the spinal canal, skull dura and different cerebral lobes [15]. Isolated thoracic spine findings were, to our knowledge, never described before, which presented a radiological picture that is not very familiar, which posed further difficulty in reaching a diagnosis with our patient.

CSF and histopathological studies usually offer the definitive diagnosis. They show elevated proteins, low glucose, leukocytosis with lymphocytic predominance and emperipolesis as seen in our case. The histiocytes involved are usually positive for S100+, CD68+, and CD1a− (CD: Cluster of Differentiation) [8]. In our case they were positive for S100. On cytology, we hypercellularity with predominance of lymphocytes and histiocytes with emperipolesis is what is usually seen [16]. These findings were seen on CSF examination and IHC with our patient, and they were what confirmed our diagnosis.

Although there are no clear guidelines for the treatment of Rosai Dorfman disease, a consensus management was established by Abla et. Al. Although observation might be suitable for patients with uncomplicated lymphadenopathy, cutaneous RDD, or post-operatively for unifocal disease, treatment with prednisone (40-70 mg per day) or dexamethasone (8-20 mg per day) is recommended [8]. Surgical resection can also be an option for unifocal extra-nodal disease, or symptomatic cranial, spinal, sinus or airway disease. Neurosurgical evaluation in our patient deemed the lesions unresectable for no discrete masses could be found and due to the diffuse spread of enhancement involving different parts of the spinal cord and vertebrae. Sometimes, cladribine or methotrexate can be considered for in refractive diseases, however the exact duration of the therapy is unknown. Our patient was not offered any treatment other than steroids. Clofarabine is currently under study for CNS involvement but the myelosuppressive effects and the high cost of this medication are of concern [8]. In our case, the patient had an excellent response to prednisone and entered long-term remission, without any relapses even after steroids were tapered and stopped. She enjoys a healthy life with no residual symptoms.

Other treatments are also available, such as cladribine, methotrexate, vincristine and mercaptopurine [8]. However, such treatments have undesirable side effects such as immunosuppression, and the data regarding their effect on RDD is less conclusive. Up until this time, they are considered in cases refractory to corticosteroids or when corticosteroids are contraindicated [8]. Some case reports also consider sirolimus, but its use in this context is very limited, described more in the pediatric population. Besides, sirolimus availability and price can be limitations to its usage [8].

With regards to our patient, the initial non-specific symptoms of lower back pain and systemic symptoms of fever and headaches led to multiple inconclusive investigations. Initial differential diagnosis included infectious and rheumatologic causes, including degenerative disc diseases and discitis and ankylosing spondylitis. Upon imaging, MRI findings suggested inflammatory or infectious origins of the pain, excluding solid malignancies and discitis but keeping inflammatory and infectious etiology. Moreover, conditions such as sarcoidosis or granulomatous disease could be excluded by MRI. among the differentials. CSF analysis with emperipolesis is what shifted the diagnosis to RDD, confirmed by S-100 staining, which is very sensitive but not specific for RDD [12]. Emperipolesis and S100 staining together is what establishes the diagnosis. This case is a very good example of the diagnostic journey it takes to detect RDD, which involves a multi-disciplinary approach of neurology, rheumatology, infectious diseases, radiology and pathology.

CONCLUSION

RDD is a benign disease of histiocytes manifesting as a resistant refractory generalized lymphadenopathy sometimes with systemic manifestations that can be quite variant. Due to the wide array of reported sites of involvement, the clinical presentation as well as laboratory and radiologic findings can be diverse, posing a diagnostic challenge. While there are many cases describing RDD with CNS involvement, none has mentioned thoracic meningeal inflammation. To date, only CSF histopathological studies and microscopic evaluation aid in a definitive diagnosis. This is why reporting all new presentations of this disease is important, as they can aid in establishing an identifiable plethora of findings that help in establishing a timely diagnosis and a more cost-effective approach to this already rare disease.

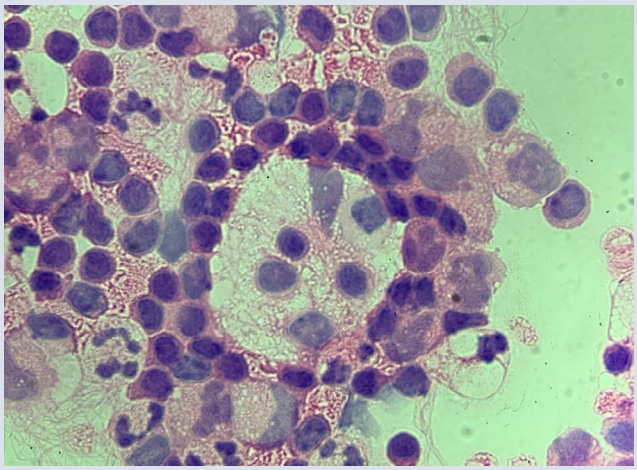

FIGURE 1 - Histiocytic cell proliferation with emperipolesis seen on CSF microscopy.

TABLE 1 - Patient's blood laboratory results

Lab Test	Reference Range	Units	Result
White Blood cells	4-10	*10^3/uL	7.49
Hemoglobin	12-16	g/dL	12.7
Mean corpuscular volume	81-99	fL	84
Platelets	150-400	*10^3/uL	248
HbA1c	4.8-5.9	%	5.8
Fasting Blood Sugar	74-106	Mg/dL	92
Creatine Kinase	26-140	U/L	171
ESR	5-20	mm	10
Sodium	136-145	mEq/L	138
Potassium	3.5-5.1	mEq/L	4
Chloride	98-107	mEq/L	103
Bicarbonate	22-29	mEq/L	26
Urea	<50	mg/dL	84
Creatinine	0.51-0.95	mg/dL	0.77
Serum Glutamic-Pyruvic Transaminase (SGPT)	<34	U/L	20
Serum Glutamic-Oxaloacetic Transaminase (SGOT)	<33	U/L	19
Lactate Dehydrogenase	135-214	U/L	180
C reactive Protein	<0.5	mg/dL	0.4
Total Cholesterol	<200	mg/dL	290
High Density Lipoprotein	>65	mg/dL	71
Low Density Lipoprotein	<130	mg/dL	208
Triglycerides	<200	mg/dL	128
Lab Test	Reference Range	Units	Result
Thyroid stimulating Hormone	0.35-4.94	mIU/mL	1.03
Free T3	1.7-3.71	pg/mL	3.28
Free T4	0.71-1.85	Ng/dL	0.91
Parathyroid Hormone	15-65	Pg/mL	41

TABLE 2 - Patient's CSF findings			
Lab Test	Unit	Upon admission	2 weeks after discharge
Volume	mL	1	1
Appearance		Slightly turbid	turbid
Color		Yellow	Off-white
Red blood cells	/mm^3	2.5	150
White blood cells	/mm^3	1880	960
Polymorphic Neutrophils	%	36	40
Lymphocytes	%	51	55
Monocytes	%	10	5
Atypical Lymphocytes	%	3	1
Glucose	mg/dL	33	55
Proteins	mg/dL	2155	363
LDH	U/L	318	

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Author contributions
All authors contributed equally and validated the final version of record.

Declarations

Conflicts Of Interests
The Authors declare that there is no conflict of interest.

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Registration
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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval
Written patient informed consent was taken.

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