Rosai-Dorfman disease of the cauda equina: illustrative case

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BACKGROUND Rosai-Dorfman disease (RDD) is a rare, nonmalignant histiocytosis. It typically occurs in lymph nodes, skin, and soft tissues, but numerous reports of central nervous system involvement exist in the literature. The peripheral nervous system has rarely been involved. In this study, the authors present a case of RDD isolated to the cauda equina. The presentation, management, surgical technique, and adjunctive treatment strategy are described.

OBSERVATIONS A 31-year-old female presented with 6 months of progressive left lower-extremity numbness involving the lateral aspect of the foot and weakness of the left toes. Magnetic resonance imaging of the lumbar spine demonstrated a homogeneously enhancing intradural lesion involving the cauda equina at the L2–3 levels. Histopathology after resection revealed a histiocytic infiltrate, positive for CD68 and S100, and emperipolesis consistent with RDD. No adjuvant therapy was administered, and the patient had full remission at the 1-year follow-up. Only five other cases of intradural RDD lesions of the cauda equina have been reported in the literature.

LESSONS RDD of the cauda equina is an especially rare and challenging diagnosis that can mimic other dura-based lesions, such as meningiomas. A definitive diagnosis of RDD relies on pathognomonic histopathological and immunohistochemical findings.

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KEYWORDS Rosai-Dorfman disease; histiocytosis; cauda equina; spinal oncology

Rosai-Dorfman disease (RDD) is a benign histiocytic disorder first reported by Destombes1 in 1965 and later distinguished as a unique disease separate from Langerhan’s disease by Rosai and Dorfman2 in 1969. Commonly characterized by profound lymphadenopathy, RDD has an overall prevalence of 1 case in 200,000 persons.3 Although the exact etiology of RDD is mostly unknown, viral infections, autoimmune components, or genetic alterations have been proposed as potential causes.4–10 RDD is subcategorized into nodal and extranodal types, the latter of which is less common.11 Extranodal RDD most commonly affects the skin, soft tissue, nasal and paranasal sinuses, and rarely the central nervous system (CNS) or peripheral nervous system.12,13 Isolated RDD of the CNS is observed in only ≈5% of cases.14 Even rarer is isolated spinal involvement, occurring in 20% to 25% of RDD cases with nervous system disease.15 Spinal RDD primarily affects the cervical and thoracic regions and presents with symptoms related to mass effect, such as myelopathy or radiculopathy, with sensory and/or motor impairment in the limbs.15,16 Radiologically, spinal RDD is homogeneously enhancing and has an affinity for the meninges, appearing and presenting like a meningioma.17–19 Herein, we present a rare variant of RDD of the cauda equina.

Illustrative Case

History and Examination

A 31-year-old female presented with 6 months of progressive left lower-extremity numbness involving the lateral aspect of the foot. She also noted weakness in her left toes, which caused difficulty with walking, but she did not have any loss of bowel and bladder control.
She denied any fevers, chills, night sweats, palpable lymphadenopathy, or unexplained weight loss, and laboratory findings were unremarkable. Magnetic resonance imaging (MRI) of the lumbar spine with contrast revealed an intradural lesion involving the cauda equina, centered at the L2 and L3 levels, as demonstrated in Fig. 1. Although there was concern that this lesion was a glioma drop metastasis, complete MRI of the neuraxis and computed tomography (CT) of the chest, abdomen, and pelvis did not reveal other lesions. Her past medical history was remarkable for a subcutaneous left flank cribriform carcinoma, which had been resected 10 years earlier. Because of her progressive symptoms and unclear diagnosis, the decision was made to perform a resection to relieve the patient’s radicular symptoms and obtain a tissue diagnosis.

Surgical Management and Postoperative Course

The patient underwent resection of the lesion with motor evoked potential (MEP) and somatosensory evoked potential (SSEP) neuro-monitoring through a L2–3 laminectomy. The intradural lesion was visible through the dura, and ultrasound was used for further confirmation of the lesion location prior to opening the dura. Upon dural opening, a tan mass was noted to be adherent to a nerve rootlet and had several finger-like projections onto adjacent rootlets in an en plaque manner, as illustrated in Fig. 2A. A nerve stimulator confirmed that the largest mass was not adherent to a motor root, which was then removed by circumferential microdissection followed by coagulating and sharply cutting the involved root proximally and distally. The mass was then rotated, and its en plaque attachment to adjacent roots was sharply divided. Similarly, a second lesion was removed after stimulation did not provoke a motor response. There were several other nerve rootlets with an en plaque appearance that were not directly connected to the main lesion. The stimulator was then used adjacent to the other remaining lesions, which were found to produce a motor response. Therefore, the remaining small lesions were left in place with the plan to defer further management decisions while awaiting pathology. MEP and SSEP recordings remained stable throughout the case, and the patient’s neurological function was stable postoperatively.

The patient had an uneventful postoperative course. At her 2-month follow up, she remained intact neurologically, free of the preoperative radicular symptoms, and free of systemic symptoms, such as palpable lymphadenopathy, skin lesions, or unexplained weight loss. Therefore, no further adjuvant therapy was prescribed. At the 6-month follow-up, the patient remained stable neurologically with no evidence of disease progression. Postoperative MRI of the lumbar spine at the 1-year follow-up showed near-total resection of the lesion with some mild, contrast-enhanced speckling along the nerve roots consistent with RDD, stable to immediate postoperative imaging (Fig. 3). The patient will undergo continued surveillance with imaging.

Pathology

Histopathological evaluation of the lesion revealed emperipolesis, a diffuse histiocytic infiltrate positive for CD68 and S100, as well as small lymphocytes positive for LCA, CD3 T cells, and CD20 B cells. Furthermore, CD138 and MUM-1 highlighted rare plasma cells, GAFP and EMA were negative, and Ki-67 was not increased (Fig. 2B-E). Taken together, these findings were consistent with a final diagnosis of RDD.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Histiocytoses are a heterogeneous group of rare disorders marked by abnormal growth of histiocytes that can infiltrate any tissue but have a predilection for skin, bone, lung, lymph nodes, and the CNS. Symptoms from histiocytoses are usually caused by mass effect of the histiocyte tumor mass toward adjacent tissue, as well as a chronic inflammatory response. Historically, histiocytoses have been classified as Langerhans cell histiocytosis (LCH) or non-LCH. However, the development of recent molecular techniques have paved the way for a more recent classification of histiocytoses, which includes five groups (L, R, C, M, and H) based on the clinical, histological, and molecular properties of each condition. RDD, also known as “sinus histiocytosis with massive lymphadenopathy,” is self-limited and benign. Commonly affecting children and young adults at a mean age of 39 years old and a male to female ratio of 1.8:1.0, RDD is typically marked by painless, bilateral cervical lymphadenopathy or myelopathy related to the mass effect; however, other systemic symptoms can include fever, weight loss, anemia, neutrophilia, and an increased erythrocyte sedimentation rate. Numerous reports in the literature have discussed CNS involvement of RDD. Intracranially, the lesions can present like space-occupying meningiomas with intradural, extra-axial involvement. In the spine, presentation within the lumbar region only occurs in 6% of patients according to a recent review, with the majority of cases presenting in the cervical and thoracic regions.
regions. Interestingly, although most cases of spinal RDD are intradural, the disease can also be intramedullary in 10% of patients. In our case, the lesion had encased several rootlets of the cauda equina. Although the mechanism of RDD, especially its dissemination into the CNS and spine, remains largely unclear, its presentation makes it challenging to diagnose the lesion based solely on imaging findings. Thus, resection is necessary to make a diagnosis, relieve mass effect, and prevent neurological deterioration.

Observations
In the present case, the patient presented with radicular symptoms and was found to have intradural RDD lesions situated on the nerve roots of the cauda equina without any other systemic manifestations. A literature review showed that this is the sixth reported intradural RDD lesion involving the cauda equina (Table 1). Eighty-three percent of the cases were female and showed symptoms of myelopathy/radiculopathy, and 67% of cases involved the lumbar levels and 33% the sacral levels. Fifty percent of patients presented with lower back pain or anal pain, and 33% had bowel or bladder incontinence. Only one patient had lymph node involvement or other hallmark RDD features.

Radiological Findings
Spinal RDD is challenging to differentiate from other dura-based lesions, such as meningiomas, lymphomas, metastases, and plasma cell granulomas, based on radiological imaging alone (Table 2). However, a dural tail and calcification favor meningioma. Of the RDD cauda equina cases from our literature review that commented on MRI contrast of the lesion, all showed contrast enhancement (Table 1). However, Ma et al. demonstrated an RDD lesion with T1 hypointensity, whereas Chhabria et al. and Bahauddin et al. demonstrated RDD lesions with iso- and hyperintensity on T2-weighted imaging, respectively. Nevertheless, it is important to note that RDD tends to invade multiple organs, with a higher recurrence rate of 22.2% and 6.7% in multiorgan and isolated spinal lesions, respectively. Therefore, positron emission tomography or CT scans are strongly recommended to rule out systemic lesions.

Histopathological Findings
In a recent systematic review of 47 RDD cases involving the spine, 93.6% were misdiagnosed preoperatively. Classic histopathological findings of RDD include infiltrates of lymphocytes, plasma cells, and large, pale histiocytes. Emperipolosis, or lymphophagocytosis, is frequently seen and pathognomonic for RDD. Furthermore, RDD histiocytes are immunoreactive for CD68 and S100 and negative for CD1a.
<table>
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<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Clinical Presentation</th>
<th>Lymph Node Involvement</th>
<th>Other RDD Features</th>
<th>MRI Findings</th>
<th>Spinal Levels</th>
<th>Pathology</th>
<th>Treatment</th>
<th>Disease/Clinical Status at Last FU</th>
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<tr>
<td>Ma et al., 2008&lt;sup&gt;25&lt;/sup&gt;</td>
<td>44, M</td>
<td>LBP, progressive numbness/weakness of LEs for 6 mos, bowel &amp; bladder incontinence for 3 mos</td>
<td>No</td>
<td>No</td>
<td>Intradural &amp; extramedullary; T1 &amp; T2 hypointense w/ homogeneous enhancement</td>
<td>T12–L4</td>
<td>Large lymphoplasmacytic areas infiltrated w/ large histiocytic cells, CD68/ S100+, CD1−, w/ emperipolesis</td>
<td>Resection</td>
<td>Improved numbness &amp; motor strength, resolved LBP, no recurrence</td>
</tr>
<tr>
<td>de Oliveira et al., 2016&lt;sup&gt;26&lt;/sup&gt;</td>
<td>50, F</td>
<td>Progressive spastic lower-limb paraparesis for 20 days</td>
<td>No</td>
<td>No</td>
<td>Intradural; homogeneous enhancement; adherent to conus medullaris &amp; cauda equina</td>
<td>L1</td>
<td>RDD</td>
<td>Resection</td>
<td>Improved: ambulatory w/ a cane w/o sphincter dysfunction; disease progression</td>
</tr>
<tr>
<td>Tripathi et al., 2017&lt;sup&gt;27&lt;/sup&gt;</td>
<td>7, F</td>
<td>Bilat LE pain, 0/5 strength in proximal bilat LEs</td>
<td>Yes</td>
<td>No</td>
<td>Contrast enhancement of cauda equina nerve roots &amp; pial enhancement surrounding conus</td>
<td>L4</td>
<td>S100+, CD1a−, emperipolesis</td>
<td>Steroids &amp; IVIG</td>
<td>Complete symptom resolution; no recurrence</td>
</tr>
<tr>
<td>Chhabria et al., 2018&lt;sup&gt;28&lt;/sup&gt;</td>
<td>19, F</td>
<td>Severe LBP, proximal Lt LE weakness, asymmetrical LE sensory loss, bladder bowel incontinence, saddle anesthesia</td>
<td>No</td>
<td>Anemia, elevated ESR</td>
<td>T2 isointense to hyperintense; involving the cauda equina nerve roots extending up to sacral level w/ spinal canal</td>
<td>Sacral</td>
<td>Lymphoplasmacytic infiltrate rich in histiocytes, CD68/ S100+, CD1−, w/ emperipolesis</td>
<td>Resection</td>
<td>Complete remission at FU</td>
</tr>
<tr>
<td>Bahauddin et al., 2022&lt;sup&gt;29&lt;/sup&gt;</td>
<td>52, F</td>
<td>Anal &amp; sacral pain</td>
<td>No</td>
<td>No</td>
<td>Intradural &amp; extramedullary; T1 isointense; STIR hyperintense; contrast enhancing; extrinsic bony erosions in pst vertebral bodies</td>
<td>S1–2</td>
<td>RDD</td>
<td>Resection &amp; steroids</td>
<td>Complete remission at 4-mo FU</td>
</tr>
<tr>
<td>Present case</td>
<td>31, F</td>
<td>Lt LE numbness, Lt EHL weakness</td>
<td>No</td>
<td>No</td>
<td>Intradural, homogeneously enhancing, involving cauda equina</td>
<td>L2–3</td>
<td>Diffuse histiocytic infiltrate, CD68/S100+ w/ emperipolesis; LCA/CD3 T-cell/CD20 B-cell+; GAFP/EMA−</td>
<td>Resection</td>
<td>Complete remission at 1-yr FU</td>
</tr>
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EHL = extensor hallucis longus; ESR = erythrocyte sedimentation rate; FU = follow-up; IVIG = intravenous immunoglobulin; LBP = low-back pain; LE = lower extremity; pst = posterior; STIR = short tau inversion recovery.
EMA and CD1a.36 Immunoreactivity for S100 differentiates RDD from granulomatous diseases, whereas negative expression of CD1a removes LCH from the differential diagnosis.37

Clinical Management

There is no standard approach to treating RDD; thus, treatment decisions should consider clinical features such as the distribution of lesions and symptoms.4–37 Frequently, if the patient is asymptomatic and there is little risk of end-organ damage, observation is appropriate, as many cases will resolve spontaneously. In one series, 40 of 80 patients with RDD did not require treatment, and 33 of those patients had spontaneous complete remission of the disease.38 Resection is the preferred option for interventional treatment and is appropriate when there is a unifocal extranodal disease for the debulking of cranial, spinal, sinus, or airway disease or other lesions that can compromise organ function.39,40 Total resection is preferred over subtotal resection because of a lower likelihood of recurrence.34 In our literature review of cases with RDD involving the cauda equina, for instance, resection was performed in 83% of patients. Disease progression was noted in only one patient post-surgically.

Adjuvant therapies, including radiation, corticosteroids, and chemotherapy, should be considered for unresectable, recurrent, or systemic RDD.3 Radiation therapy is particularly useful in progressive or recurrent disease.24 Chemotherapy is typically reserved for multifocal, refractory, or life-threatening systemic disease; thus, it was not a suitable option for the present case of unifocal disease with no systemic manifestations. Moreover, since the present case did not show signs of systemic or recurrent disease, a watchful waiting strategy was appropriate over adjuvant therapy. If the lesion enlarges on surveillance MRI or if the patient develops recurrent symptoms, radiation therapy can be considered next. There is no standard recommendation for radiation therapy, although typically, doses between 20 and 30 Gy are used. However, some authors recommend doses higher than 50 Gy; at least one report showed complete relief of symptoms with as little as 10 Gy.12

Systemic therapy options include corticosteroids, cytotoxic chemotherapy, immunomodulatory agents, and MEK inhibitors. Given the rarity of RDD, experience with systemic therapy comes from case reports and retrospective series. Steroids have been shown to induce responses when used both as a single agent and in combination with chemotherapy, although responses are variable and may not be durable.41 In our review, one patient underwent treatment with intravenous immunoglobulin, and one patient was placed on steroids postoperatively.

Response rates to cytotoxic chemotherapy are overall low; however, durable responses to combination regimens containing vinca alkaloids, such as prednisone, 6-mercaptopurine, methotrexate, and vinblastine, have been observed.41,42 Purine analogs are efficacious in other histiocytic disorders and effective in RDD. In a case series from MD Anderson, five patients with RDD were treated with cladribine, with two complete and two partial responses. The fifth patient had stable disease after two cycles of cladribine and then had a prolonged partial response to clofarabine. An additional patient, who had progression after an initial response to cladribine, also had a prolonged response to clofarabine.43 Purine analogs can cause significant myelosuppression, suggesting that they be reserved for severe or refractory cases.4 The immunomodulatory drugs lenalidomide and thalidomide have also been reported to induce responses in RDD. Lenalidomide, with or without steroids, has been shown to induce durable responses with a better side-effect profile than thalidomide.44 Seven patients were treated with rituximab, and 64% remained progression free after 24 months.

Unlike in Erdheim-Chester disease and LCH, BRAF V600E mutations are not frequently found in RDD.45 However, mutations in the MAPK pathway, mainly in the KRAS and MEK genes, were found in 36% to 40% of patients with RDD. In a retrospective review of patients treated at the Mayo Clinic and the University of Alabama, 16 patients with extranodal RDD were treated with the MEK inhibitor cobimetinib.44 Among these 16 patients, the response rate was 63%, with 5 complete responses and 5 partial responses. Responses were durable, with a progression-free survival rate of 65%. Mutations in the KRAS or MEK genes were associated with a higher response rate (88% vs 38%; p = 0.03) and 1-year progression-free survival (100% vs 29%; p < 0.001).

Last, there are no studies evaluating the role of adjuvant therapy following resection. Given that some lesions will not progress, some may eventually spontaneously regress. In our case, the patient's symptoms improved with surgery; therefore, we believed that observation after surgery was appropriate. If the lesion had progressed, the first step would be restaging studies. If the progression had localized to the spine only, radiation would be our treatment option. In the case of systemic progression, our first option would be systemic therapy with an MEK inhibitor.

Lessons

RDD of the cauda equina is a rare and challenging diagnosis that can mimic other dura-based lesions, such as meningiomas. Although both RDD and meningiomas can appear iso- or hypointense on T1-weighted imaging and demonstrate homogeneous contrast enhancement, only meningiomas have a characteristic dural tail or signs of calcification. A definitive diagnosis of RDD depends on histopathological and immunohistochemical confirmation. Resection is the preferred interventional approach to unifocal RDD and leads to symptom improvement and disease control in cases involving the cauda equina. Radiation therapy is appropriate for unresectable or recurrent lesions, and chemotherapy for multisystemic variants.


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Lesha, Mangham, Weaver. Acquisition of data: Lesha, Mangham, Nico, Portnoy, Weaver. Analysis and interpretation of data: Lesha, Nico, Portnoy. Drafting the article: Lesha, Mangham, Nico, Golembeski, Portnoy. Critically revising the article: Lesha, Mangham, Nico, Yagmurlu, Weaver. Reviewed submitted version of manuscript: Lesha, Mangham, Nico, Yagmurlu, Weaver. Approved the final version of the manuscript on behalf of all authors: Lesha. Statistical analysis: Lesha. Administrative/technical/material support: Mangham, Yagmurlu. Study supervision: Lesha, Mangham, Yagmurlu, Weaver. Photomicrographs: Golembeski.

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