Surgical Neurology International

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Editor: **James I. Ausman**, MD, PhD University of California, Los Angeles, CA, USA

Case Report

A new case of cervical intramedullary sinus histiocytosis causing paraplegia and review of the literature

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Received: 08 July 15 Accepted: 20 October 15 Published: 28 January 16

Abstract

Background: Rosai–Dorfman disease (RDD) is an uncommon, benign histiocytic proliferative disorder of unknown origin. It predominantly affects the lymph nodes, but can also be found extranodal in different organs. Nervous system involvement is rare, and the most cases are intracranial. Surgical treatment is indicated when the central nervous system (CNS) in compromised.

Case Description: We herein describe the management of a 27-year-old woman who presented progressive spinal cord symptoms, secondary to an isolated intramedullary lesion, which had a histological confirmation of RDD. To our knowledge, this is the 6th case reported in English written manuscripts. We review these cases and analyze some of the literature concerning the disease.

Conclusions: RDD shows some variability in the involvement of the entire neuraxis, and because its ability to mimic meningeal and primary brain tumors, it is essential to be aware of this entity and consider RDD in the differential diagnosis of various lesions of the CNS. The conclusive diagnosis must be obtained by histological methods, so surgical approaches have to be discussed. Although it is not considered as a malignancy, options for postoperative medical treatment are variable and include radiation, chemotherapy or maybe monoclonal antibodies for refractory or recurrent cases.

Key Words: Cervical, Rosai–Dorfman disease, sinus histiocytosis, spinal cord

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.175070

Quick Response Code:

INTRODUCTION

Sinus histiocytosis with massive lymphadenopathy (SHML), initially described in 1969 by Rosai and Dorfman,[22] is a rare, nonneoplastic lymphoproliferative disorder that is characterized by its histological features. Clinically, It predominantly affects the lymph nodes but can also be found extranodally in different organs and usually presents with other constitutional symptoms such as fever, malaise, weight loss, and raised inflammatory markers.[1-7] Central nervous system (CNS) involvement as a site of extranodal disease is uncommon and the majority of cases present with epidural or subdural disease involving the spine or skull base[2-5,9,11,16,24] Intra-

How to cite this article: Rocha-Maguey J, Felix-Torrontegui JA, Cabrera-López M, Gutiérrez-Castro M, Montante-Montes de Oca D. A new case of cervical intramedullary sinus histiocytosis causing paraplegia and review of the literature. Surg Neurol Int 2016;7:9.
http://surgicalneurologyint.com/A-new-case-of-cervical-intramedullary-sinus-histiocytosis-causing-paraplegia-and-review-of-the-literature/

parenchymal involvement is specially rare. We describe the management of a 27-year-old woman who presented with progressive spinal cord symptoms secondary to an isolated intramedullary lesion which had a histological confirmation to be Rosai-Dorfman disease. To our knowledge, this represents the sixth case of parenchymal spinal cord involvement reported in English literature.

CASE PRESENTATION

This 27-year-old woman was in good health until 2 months before the discovery of her disease. On May 2014, she felt down spontaneously while walking. After this incident, she noticed certain difficulties in controlling her legs. Two days later, a progressive strength loss was developed on both legs, leaving her in a wheelchair 1 week later. Sphincters were intact at this time.

She consulted a general physician, who prescribed corticoid medication, obtaining some relief of her symptoms but never a complete recovery. After 6 weeks, she developed a complete and symmetrical spinal cord syndrome, referring an important weakness and numbness of the fingers on both hands and extending to the rest of her body. At this point, she developed urinary incontinence and severe constipation.

During the general examination, the patient was alert and cooperative. No fever present and we did not discover any important information on the pulmonary nor cardiovascular condition, no lymph nodes were palpated, the skin showed normal characteristics. The neurological exam demonstrated complete motor loss of both legs, with a partial sensory level of hypesthesia and hypalgesia at C6–C7. Reflexes were all hyperactive, with a positive bilateral Hoffman reflex and bilateral extensor plantar response. Laboratory data were entirely normal. A moderate increase on the erythrocyte sedimentation rate of 25 mm/h (normal: 15 mm/h) was detected. The cerebrospinal fluid analysis was within limits, with negative cultures. Magnetic resonance images (MRIs) of the cervical spine [Figure 1], demonstrated a well-defined oval intramedullary lesion expanding the spinal cord at the C7-Th1 level, with a clear hypointense signal on T2-weighted images, and showed homogeneous enhancement after gadolinium application, suggesting an intramedullary solid, and well-defined tumor.

The patient was taken into surgery, where we performed a C6–Th1 laminoplasty. The lesion was identified using transoperative ultrasonogram. After opening the dura, we observed a severely expanded spinal cord, but with a normal superficial appearance. A midline myelotomy disclosed a well-defined brownish soft mass that was progressively dissected from the spinal cord parenchyma and achieving an in bloc resection with the aid of bipolar forceps and microscissors.

The patient had an uncomplicated postoperative evolution. The histology of the lesion [Figure 2], characterized an important proliferation of large histiocytes with foamy cytoplasm, pale irregular nucleus and small vesicular nuclei, some of them with the appearance of engulfed intact lymphocites. Plasma cells, lymphocytes, and eosinophils were within the stroma of the lesion. The immunohistochemistry confirmation [Figure 3] reported mature lymphocytes that were positive to CD45/CD68 antibodies and positive CD20 and CD3 in mature B lymphocytes that were within larger histiocytes (emperipolesis); positive CD60 in histiocytes; positive CD30 in immuneblasts; positive CD15 in leucocytes and negative to the latent membrane protein-1 antibody. After defining the lesion, she underwent a complete evaluation including computerized tomography (CT) of the chest, abdomen, and pelvis, as well as a bone scan designed to locate extranodal sites of disease, however, none was identified. No order for adjunctive radiation or chemotherapy was considered at the time. By the 3rd week after surgery, she referred to increase in superficial and deep sensitive perception, when she began to identify pressure, light pain and was able to pinpoint stimulation in both legs. The patient was discharged to a spinal cord rehabilitation unit, and over the next 6 months, she was able to move some proximal muscles in the lower extremities, and she re-educated her sphincters.

DISCUSSION

The non-Langerhans cells histiocytosis are thought to arise from either a dendritic cell or a macrophage cell line, and can be clinically divided into three major groups – those that primarily affect the skin, such as the juvenile xantogranuloma (JXG) family, and reticulohistiocytoma; those that affect the skin, but have a major systemic component such as xanthoma disseminatum and multicentric reticulohistiocytosis; and those that predominantly involve systemic sites, although skin may also be affected, such as systemic JXG and sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai–Dorfman disease (RDD).[27]

The first report of SHML was described in 1965, by Destombes, as a lipid storage disorder developing after inflammation.[5] SHML, consisting of a nonmalignant proliferation of histiocytes and characterized by phagocytosis of intact lymphocytes by macrophages (emperipolesis),[2] and cervical lymph node enlargement was first described by Rosai and Dorfman in 1969.[22] It may affect many diverse sites with or without nodal involvement; the estimated incidence of classic nodal presentation of RDD is approximately

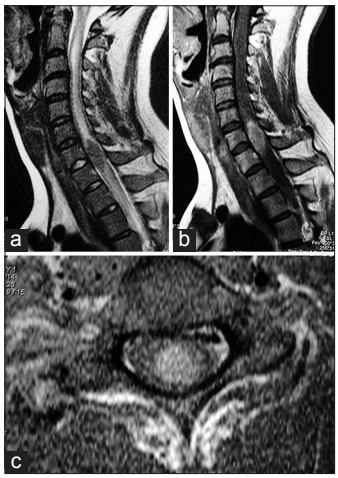

Figure 1: Magnetic resonance images of the cervical spine demonstrating a well-defined oval intramedullary lesion expanding the spinal cord at C7–Th1. (a) Sagittal T2-weighted-images demonstrating a well-defined hypointense mass causing an important edema above and under it. (b) Homogenous gadolinium enhancement is evident. (c) A predominant anterior location within the spinal cord is observed on axial images after the application of gadolinium

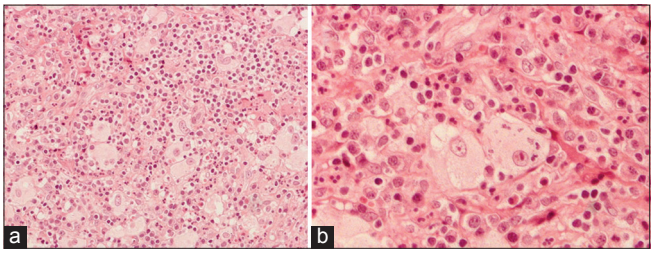

Figure 2: (a) Histopathology: Proliferation of large foamy histiocytes with abundant cytoplasm accompanied by plasma cells, lymphocytes, polymorphonuclear cells and eosinophils (H and E, ×10). (b) Intact inflammatory cells inside the cytoplasm of some histiocytes (emperipolesis)

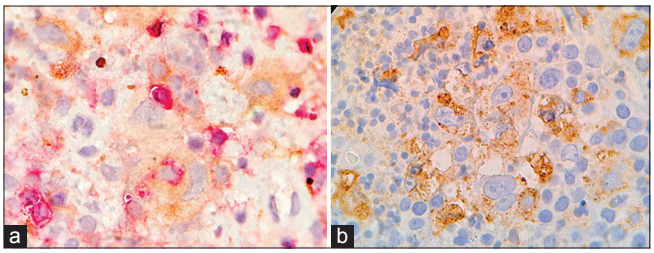

Figure 3: (a) Immunohistochemistry: Double immunohistochemical staining revealing histiocytes enhanced by CD68 (brown). Lymphocytes enhanced by CD45 antibodies (in red) confirming emperipolesis. (b) CD68 immunohistochemical staining enhancing the histiocyte population

100 cases/year. Reviewing different reports, the average age prevalence at the moment of discovery is around 22.5 years. Extranodal disease is apparent in about 40% of all cases, and most commonly involves the orbit, skin, respiratory tract, bone, kidneys, heart, and head and neck region.

RDD of the nervous system has also been reported in <5% of all cases and most of them in the brain.[17] Involvement of the spine has been described in only 20–25% of those with central nervous system (CNS) involvement[21] and can be intradural, extradural, or even rarer intramedullary (5%) in origin.[1,10,14] When affecting the CNS, it tends to occur at later ages (fourth and fifth decades), contrary to the classic form with cervical lymph node involvement that usually affects children and adolescents, although cases have been reported in infancy. Some authors raise the possibility that these are two different clinical entities, although the lesions are histologically identical. A predilection for males (66%) is notable with no ethnic distinction.[25]

Rosai and Dorfman[22] suggested that the disease is caused by an abnormal immunologic response or infectious factor. Becroft[3] demonstrated the importance between cellular immunity defect and histiocytic reaction. Epstein–Barr virus, Parvo B19 and herpes simplex virus 6 were implied to be the causative agents or opportunistic infections for patients to develop RDD in a few studies.[15] Although the exact mechanism leading to RDD has not been determined, much progress has been made in recent years through the study of familial RDD and other rare inherited syndromes, such as autoimmune lymphoproliferative syndrome and Faisalabad histiocytosis.[4]

The current hypothesis is that RDD is a subtle, yet undefined immunological defect, which promotes monocyte recruitment from the circulation into the nodal or extranodal sites, followed by transformation into the immunophenotypically distinct RDD histiocytes, demonstrating emperipolesis with functional uniqueness in terms of the cytokine expression profile.[16] Based on some isolated familial cases reported, it is suggested that RDD may result from an abnormal apoptotic defect leading to a progressive histiocytic accumulation; but as in the majority of sporadic cases reported in the literature, more studies are needed to determine these specific mutations. Some biological and ultrastructural studies propose that an important local polyclonal infiltration can be responsible, and conclude that it may be a reactive response rather than neoplasic.[19] In these situations, if well-defined and specific genetic defects are found, an increase in the therapy options can be developed to treat RDD in those patients with systemic involvement or symptomatic lesions. Despite all these assumptions, the exact pathogenesis of the disease still remains unknown.

However, evidence of RDD exclusive to the spine is increasing in the literature, with symptoms typical to the affected level, including weakness and sensory changes; most of them have been reported with an

Table 1: Relation of intramedullary snus histiocytosis cases reported in English written literature

Author/Year	Age	Race	Sex	Location	Clinical Presentation	Treatment
Osenbach/1996[18]	35	Afro-american	Male	Th5	Progressive numbness and paraplegia	Laminectomy and total excision
Jones/1997[11]	34	Afro-american	Male	Th5	Progressive numbness and paraplegia	Laminectomy and total excision
Yao/2013[29]	12	Asian	Fem	C4-C5	Right sided numbness and weakness	Laminectomy and total excision
El Molla/2014[6]	76	N/A	Male	C2-C4	Right sided hemiparesis	Laminectomy and total excision
Sandoval/2014[23]	53	White	Male	C5-C6	Multiple CNS lesions. Recurrent paraparesis intraxial C5-C6 and extraaxial T1-T2 and T5-T6	Intracranial biopsy, systemic steroids, radiotherapy, no benefit and not concluded
Rocha	27	White-Hispanic	Fem	C7-Th1	Symmetrical weakness of legs, body numbness and sphincter alterations	Laminoplasty and total excision

epidural or subdural location. Table 1 summarizes the reported cases with intramedullary involvement. In 1996 Osenbach,[18] published the first case who developed and exclusive intramedullary histiocytosis, in a middle-aged African American male with a single thoracic spinal cord lesion. Since then, another 4 cases have been reported with pathological histiocytic accumulation within the spinal cord. Recently, Sandoval-Sus *et al*. in 2014,[23] in a beautiful report of 6 cases with multiple CNS affections, where they present a recurrent case in which various intracranial lesions and multiple sites of spinal affection were detected, including an intramedullary C5–C6 nodule. The youngest case with intramedullary spinal cord involvement was reported a few months ago, by Yao in a 12-year-old Asian girl.[29] As in the present case, isolated RDD of the spinal cord, notably without lymph node involvement, systemic features, moderately raised serum inflammatory markers, or indeed extranodal disease elsewhere is very unusual.[9] To our knowledge, this is the 6th case that presents an isolated intramedullary mass without any systemic manifestation that is documented and published in English literature. To date, there is no particular relation for this kind of presentation between ethnic groups, age range, or gender.

Over 90% of the CNS Rosai–Dorfman involve the leptomeninges and are observed on neuroimaging as a dural-based, contrast-enhancing lesion, and mimicking a meningioma.[2,9,14,24,28] Although to be benign of the etiology, reversal of neurological deficits is mostly incomplete, and deaths have been reported due to the infiltration of vital organs.[7] Radiological features are often nonspecific, and a definitive preoperative diagnosis is often difficult. On CT, the lesion may appear as a homogenous, lobulated hyperattenuating mass with marked contrast enhancement. There may be moderate to severe perilesional edema causing certain mass effect; associated bone erosion may occur, but calcification is not likely. On MRI, the lesions are well-defined, lobulated, isointense on T1-weighted images, with homogenous intense enhancement on gadolinium injection. On T2-weighted images, the lesions appear hypo- to iso-intense. In our case, the characteristics previously described were very clear within the spinal cord, and were surrounded by an important vasogenic edema. MR spectroscopy with elevated choline levels may improve the specificity of preoperative diagnosis, and help in the differential diagnosis from meningioma. Because of the image characteristics, all RDD cases that have been reported with isolated involvement of CNS required an adequate diagnosis and definite confirmation by histopathology and immunohistochemistry techniques. In the absence of systemic manifestations, a preoperative diagnosis in these cases is often very difficult.

We elected to perform a three-level laminoplasty because no spinal instability was identified; the excision of the lesion was controlled under the sonographic image, assuming that the lesion was a primary ependymal tumor. Contrary to other authors, we detected a very well-defined plane of cleavage between the lesion and the spinal cord, making a complete excision very suitable, although the consistency of the lesion was very similar to that of a neurinoma. Besides of the preoperative clinical manifestations, there were non-neurologic complications and a progressive improvement was evident. Whatever the approach, surgical removal has been considered to be as the primary mode of treatment of CNS RDD in most of the reported cases, where cerebral or spinal decompression is the gold standard. Irradiation and/or steroid treatment have been tried in several cases with variable results. In one instance of RDD with spinal involvement, dramatic remission between prednisolone and vinblastine, without surgery, was mentioned.[8] However, the follow-up interval of this case and many others were not long enough to evaluate the effect of the regimen. So far, it is still unclear whether these adjunctive treatments are beneficial.

Since results with chemotherapy for RDD have not been encouraging, the use of chemotherapy is restricted to patients with the life-threatening disease or multiple relapses. Imatinib, a platelet-derived growth factor receptor B-inhibitor, demonstrated acceptable results in a recent case with RDD.[26] Some efficacy has been reported with the use of cytotoxic agents such as cladribine (2-chlorodeoxyadenosine) and clofarabine, especially in recurrent, refractory or severe cases.[12] Petschner *el al*.[20] reported some benefit with rituximab, an anti-CD20 monoclonal antibody, and azathioprine, which has been recommended for those cases with the refractory cerebral disease.[13] The emergence of different therapeutic options opens a new window on the early treatment of this disease; however, these require the accomplishment of well-supported studies.

CONCLUSIONS

The CNS involvement in RDD in various presentations is considered to be rare though there is an increase in the number of cases that have been documented of CNS-RDD. However, because of the variability of the involvement of the entire neuraxis, and its ability to mimic meningeal and primary brain tumors, it is essential to be aware of this entity and consider RDD in the differential diagnosis of various lesions of the CNS. The conclusive diagnosis must be obtained by histological methods. Since RDD was first described over 60 years ago, the mechanism behind this disease has not been discovered. Since it cannot be associated with a direct monoclonal cell population abnormality, RDD should not be considered as a malignancy, and it is also uncertain that an infectious or immunologic process may be responsible. Isolated molecular studies have suggested that RDD can be a polyclonal disorder. Intraxial presentation of RDD should be considered when a well-defined nodule surrounded by vasogenic edema is identified via radiologic examination. And finally, laminoplasty is a very well-developed procedure all around the world that we recommend for similar cases, because spinal stability is preserved, and with the aid of complementary ultrasonic aspiration, better chances to preserve neurological function will exist. The outcome is generally good, and the disease is usually self-limited; however, approximately 5–11% of patients die from this disease. Patients with combined immunologic abnormalities have a less favorable outcome and a higher fatality rate.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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