CASE REPORT
https://doi.org/10.26432/1809-3019.2022.67.021

Rosai-Dorfman-Destombes disease: case series and literature review

Doença de Rosai-Dorfman-Destombes: série de casos e revisão de literatura

Júlia Isabel Richter Cicogna[1], Vitor de Lima Costa[1], Sérgio Augusto Buzian Brasil[2]

ABSTRACT

Introduction: Rosai-Dorfman-Destombes (RDD) disease is a rare histiocytic disorder with a prevalence of 1:200000 people in the United States. The characteristic clinical presentation is a large and painful bilateral cervical mass in young adults, but more than a quarter of cases show extranodal manifestations. Skin, paranasal sinuses, soft tissue, bone, salivary glands, oral cavity, and central nervous system can be affected, resulting in a very distinct constellation of symptoms in each patient. Systemic manifestations such as fever and leukocytosis are also frequent. The usual course is benign, with spontaneous regression in many cases. However, a minority of patients suffer from progressive disease, occasionally resulting in death, usually due to local infiltration of vital structures. **Objective:** This study aims to describe the clinical, radiological, and anatomopathological characteristics as well as individualized therapeutic procedures and outcomes of five cases of RDD disease that have been diagnosed in a reference hospital in São Paulo and compare these findings with recent bibliography on this rare disease. **Case reports:** Five cases are presented, of patients ranging from 24 to 61 years old. The clinical presentation of every case was very unique, varying from neurologic symptoms, mesenteric lymph nodes, development of masses in the thigh, in one case, and on the cheek presenting as sinusitis in another. Observation of these five cases demonstrates the uniqueness of every RDD disease case. Each one has a different clinical manifestation, impact on quality of life, and response to therapy. **Conclusion:** As a rare disorder, RDD already poses a diagnostic challenge, and the variety of signs and symptoms makes the investigation even more difficult since this disease can affect different tissues. Considering this, it is important that physicians are aware of clinical suspicion and promptly arrange a biopsy, which is fundamental for diagnosis.

Keywords: Destombes-Rosai-Dorfman syndrome, Histiocytosis, Lymphadenopathy, Emperipolesis

RESUMO

Introdução: A doença de Rosai-Dorfman-Destombes (RDD) é uma doença histiocítica rara que compreende cerca de 100 novos casos por ano nos Estados Unidos da América. A apresentação clínica característica é uma massa cervical bilateral grande e dolorosa em adultos jovens, porém mais de um quarto dos casos apresentam manifestações extranodais. Pele, seios paranasais, tecidos moles, ossos, glândulas salivares, cavidade oral e sistema nervoso central podem ser afetados, resultando em uma constelação de sintomas muito distinta em cada paciente. Manifestações sistêmicas como febre e leucocitose também são frequentes. O curso usual é benigno, com regressão espontânea em muitos casos, ou resposta à terapia. No entanto uma minoria de pacientes sofre de uma doença progressiva, ocasionalmente resultando em morte, geralmente devido à infiltração local de estruturas vitais. **Objetivo:** Este estudo tem como objetivo descrever as características clínicas, radiológicas e anatomopatológicas, os procedimentos terapêuticos instituídos e os resultados obtidos em cinco casos de RDD diagnosticados em um hospital de referência de São Paulo, bem como comparar esses achados com a bibliografia recente sobre essa rara doença. **Relatos dos casos:** São apresentados cinco casos, de pacientes com idade variando de 24 a 61 anos. A apresentação clínica varia entre sintomas neurológicos, desenvolvimento de linfonodos mesentéricos, crescimento de massas na perna, em um caso, e na face em outro, apresentando-se como sinusite. A análise da história clínica desses pacientes demonstra a singularidade de cada caso de RDD. Cada um apresenta uma diferente manifestação clínica, além de diferentes impactos na qualidade de vida e resposta à terapia. Conclusão: Por ser uma doença rara, a RDD já representa um desafio diagnóstico, e a variedade de sinais e sintomas dificulta ainda mais a investigação. Diante disso, é importante que os médicos estejam atentos à suspeita clínica e providenciem prontamente a biópsia, fundamental para o diagnóstico

Palavras-chave: Síndrome de Destombes-Rosai-Dorfman, Histiocitose, Linfadenopatia, Emperipolese

[1]Santa Casa de São Paulo, Departamento de Medicina Interna – São Paulo (SP), Brazil.
[2]Santa Casa de Sao Paulo, Departamento de Medicina Interna, Serviço de Hematologia – São Paulo (SP), Brazil.
Corresponding author: Júlia Isabel Richter Cicogna. Rua Martinico Prado, 241 – apto·54 – Vila Buarque, 01224-010 – São Paulo (SP), Brazil.
E-mail: jrichtercicogna@gmail.com
Article received: 08/15/2022. Article approved: 09/28/2022. Article published: 12/13/2022.
Responsible Editor: Prof. Dr. Eitan Naaman Berezin (Editor-in Chief).

INTRODUCTION

Rosai-Dorfman-Destombes (RDD) disease is a rare histiocytic disorder first described by Destombes in 1965 and later by Rosai and Dorfman in 1969[1]. Histiocytoses are rare disorders characterized by macrophage, dendritic cell, or monocyte-derived cell accumulation in various tissues. RDD is part of the "R group" of histiocytoses, which includes familial RDD, sporadic RDD, and other miscellaneous non-cutaneous, non-Langerhans cell histiocytoses[2].

RDD disease is a rare disorder with a prevalence of 1:200000 people and an estimated 100 new cases per year in the United States[3]. The characteristic clinical presentation is a large and painful bilateral cervical mass in young adults. Although initially described as a disease of the lymph nodes, more than a quarter of cases show extranodal manifestations, especially involving the skin, paranasal sinuses, soft tissue, bone, salivary glands, oral cavity, and craniospinal tissues[4]. Some studies suggest that extranodal involvement is even more frequent, affecting up to 43% of cases[5]. Patients also usually develop systemic symptoms, including fever, polyclonal hypergammaglobulinemia, neutrophilic leukocytosis, and show an increased erythrocyte sedimentation rate. Some cases show evidence of immune-mediated diseases, such as arthralgias, glomerulonephritis, or recurrent infections. The usual course is benign, with spontaneous regression or response to steroid therapy in many cases, but a minority of patients (<10%) suffer from a progressive disease, occasionally resulting in death, usually due to local infiltration of vital structures[4].

Histologic examination typically shows pericapsular fibrosis and dilated sinuses heavily infiltrated with large histiocytes, lymphocytes, and plasma cells. Emperipolesis, that is, the engulfment of lymphocytes and plasma cells by histiocytes that express S100, is considered typical of RDD. Immunohistochemical stains of RDD cells are also positive for CD68 and CD163, whereas CD1a is typically negative[6]. Historical studies found the RDD cells to be polyclonal in nature. However, there are recent reports of *MAP-ERK* pathway alterations in about a third of RDD patients, which suggests that at least a subset may be neoplastic in nature[7]. Recent studies have also raised the possibility of a clonal origin, owing to the presence of *KRAS*, *NRAS*, and *MAP2K1* genes[6].

OBJECTIVE

This study aims to describe the clinical, radiological, and anatomopathological characteristics as well as therapeutic procedures and outcomes of five cases of RDD disease that have been diagnosed in the reference hospital Irmandade Santa Casa de Misericórdia de São Paulo and compare these findings with recent bibliography on this rare disease.

CASE REPORTS

This study is a case series of five patients diagnosed with RDD disease at the reference hospital, Irmandade Santa Casa de Misericórdia de São Paulo. Data were collected from medical records after approval by the institutional review board (CAAE: 60648422.7.0000.5479). The study consists of an introduction to the disease and a description of each case, including symptoms, associated factors, radiological and anatomopathological features, therapeutic measures, and outcomes. Finally, a discussion was elaborated through a literature review based on articles from the past 10 years using electronic databases such as PubMed, SciELO, and Lilacs. The keywords "sinus histiocytosis", "Rosai-Dorfman Disease", "Destombes-Rosai-Dorfman Syndrome", ""Lymphadenopathy," and "Emperipolese" were used, as well as their Portuguese equivalents.

Case 1

A 28-year-old male presented with a mass in his right thigh in June 2015. Ultrasound showed an absence of tumor with skin and subcutaneous thickening. Surgical excision was diagnostic of cutaneous RDD disease. Investigation with cervical, thoracic, and abdominal computerized tomography (CT scan) revealed multiple lymph node enlargements up to 1.5 cm all over the neck, as well as pericaval, periaortic, iliac, and inguinal nodal disease, measuring up to 1.9 cm, associated with densification of the adjacent fat and cutaneous tissues. The patient went through six cycles of chemotherapy with cyclophosphamide, vincristine, and prednisone, with volumetric reduction of all nodules on follow-up imaging. Up to 2018, the patient remained asymptomatic when he discontinued follow-up.

Case 2

A 61-year-old male presented in December 2019 with a 6-month history of headaches, right facial palsy, and seizures. In physical examination, an allodynia of the right V2 dermatome topography (maxillary division of trigeminal nerve) was observed. Brain magnetic resonance imaging (MRI) showed a 4.3×3.8×3.0 cm mass in the trigeminal cave (Meckel cave), occupying the pontomesencephalic cistern. A biopsy was performed and a diagnosis of RDD disease was made after an immunohistochemical study (positive for S100 and CD68; negative for CD4, CD8, CD58, and granzyme). He underwent treatment with radiotherapy for a month and received 4 mg dexamethasone daily. MRI follow-up showed that the lesion remained stable. However, the patient developed panhypopituitarism

and he is currently under medical monitoring with endocrinology, hematology, and ophthalmology.

Case 3

A 24-year-old female presented with bilateral exophthalmos and blurred vision in May 2011. A biopsy and immunohistochemical study of orbit and neck tumor samples were diagnostic of RDD disease. She went through bilateral orbital tumor excision and six cycles of chemotherapy with cyclophosphamide, vincristine, and prednisone in 2011, as well as 10 sessions of local radiotherapy in the next year. The patient had total remission of the disease and has been asymptomatic ever since.

Case 4

A 42-year-old female presented with mesenteric lymph nodes discovered using abdominal ultrasonography performed because of abdominal pain in June 2012. RDD was diagnosed after a biopsy and immunohistochemical study. She underwent treatment with prednisone and had a complete remission. She remained asymptomatic up to 2021 and has been through annual follow-up consultations.

Case 5

A 33-year-old male presented symptoms compatible with sinusitis and developed a mass in his left cheek in 2019. He underwent a biopsy, which was diagnostic of RDD disease after an immunohistochemical study. In 2021, he noted a mass in his left eye, and an MRI showed an infiltrative mass in the paranasal cavities, pterygopalatine fossae, and orbit floors. Besides that, an abdominal CT showed a nodular formation at the right renal pelvis with a size of 8.8×7.0×5.0 cm. He has been under treatment with prednisone, 20 mg daily, with a small tumor reduction, but in a recent follow-up consultation, he remains asymptomatic.

CONCLUSION

Observation of these five cases demonstrates the uniqueness of every RDD disease case. Each one has a different clinical manifestation, impact on quality of life, and response to therapy. As a rare disorder, it already poses a diagnostic challenge, and the variety of signs and symptoms makes the investigation even more difficult since this disease can affect different tissues. Most of the cases presented as extranodal diseases, in accordance with some studies that demonstrated that even though RDD disease was first described as a disease of the lymph nodes, 25–43% of the cases presented as extranodal diseases[4,5]. Considering this, it is important that physicians are aware of clinical suspicion and promptly arrange a biopsy, which is fundamental for diagnosis.

The diagnostic and staging evaluation of newly diagnosed RDD patients should include an assessment of the extent of the disease as well as evaluation for conditions either known to be associated with RDD — particularly autoimmune disorders — or to contain an RDD-like reactive component secondary to malignancies[3]. An extensive medical history and physical and neurologic examination should be performed. In children, a chest x-ray and abdominal ultrasound are routinely performed initially. For older patients, a CT scan of the neck/chest/abdomen and pelvis is recommended. Fluorodeoxyglucose-positron emission tomography (FDG-PET)-CT is used by some investigators for initial staging when possible. However, there is no consensus among authors about the benefits of PET-CT in patients with RDD as compared to anatomic imaging. Laboratory evaluation should include a comprehensive metabolic panel, a complete blood count with leucocyte differential, C-reactive protein, and quantitative immunoglobulin levels. Bone marrow aspirate and biopsy are required only for patients with unexplained cytopenias or abnormal peripheral blood cells[3]. Serologies for HIV and hepatitis B and C are suggested to exclude these as associated diagnoses. Testing for antinuclear antibodies and rheumatoid factor is suggested, and further evaluation for evidence of autoimmunity should be carried out if other diagnoses are considered[3].

After RDD diagnosis and staging evaluation is established, observation is reasonable in many cases, because 20–50% of patients with nodal/cutaneous disease will have spontaneous remissions[3]. Surgery for RDD disease is usually limited to biopsy, but resection can be curative for unifocal disease. Besides that, surgery can help with disease debulking in cases of upper airway obstruction, spinal cord compression, or large lesions causing end-organ compromise[3]. Steroids are also usually helpful in reducing nodal size and symptoms, although responses have been variable. In one study, corticosteroids led to a response in 56% of the cases treated with prednisone at doses of 1 mg/kg with a prolonged but variably designed taper of 6–12 weeks. Of those treated initially, 15 (30%) patients developed recurrent disease[8]. That study also suggested that corticosteroids may be considered as a treatment option only for nodal disease or to relieve symptoms from the central nervous system or ocular involvement, even though the duration of response may be short-lived[8]. One case report demonstrated the first case of resolution of intracranial RDD disease following corticosteroid therapy[9]. In our case series, all patients received corticosteroids somewhere during their treatment, and case number 5 has been receiving them for a prolonged time. The optimal duration of therapy is unknown, and patients need

to be monitored for adverse effects[8]. Another drug treatment alternative, Sirolimus, led to complete remission in a child with resistant RDD disease and recurrent autoimmune cytopenias[10].

The treatment of RDD disease with chemotherapeutic agents has shown mixed results. Although chemotherapy is generally reserved for refractory or relapsed cases, sometimes it is used as initial therapy for disseminated or life-threatening diseases[3]. Anthracyclines and alkylating agents have little efficacy, whereas vinca alkaloids have shown variable responses[11]. Low-dose methotrexate (MTX) and d 6-mercaptopurine (6-MP) administered in combination were effective in a few patients[11,12]. Sustainable remissions after regimens containing vinblastine/MTX/6-MP and 6-thioguanine, vinblastine/prednisone/MTX/6-MP, or vinorelbine/MTX have been reported[13]. Furthermore, long-term remission of intracranial RDD has been reported after postsurgical maintenance with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like regimens[14].

New drugs under investigation may be useful in the treatment of RDD disease in the future. MAPK kinase (MEK) inhibitors may block the mitogen-activated protein kinase (MAPK) pathway and reduce KRAS-activating mutations, which are known to be involved in some RDD pathogenesis[15]. Besides that, a phase 2 trial of cobimetinib for patients with BRAF-wild type histiocytosis, including RDD, is ongoing (NCT02649972) with promising early results[16]. Since high levels of TNF-α and IL-6 are present in RDD, TNF-α inhibitors thalidomide and lenalidomide have shown promising results in some cases[3], and a review showed that low-dose thalidomide (100 mg per day) was effective in refractory cutaneous RDD[17].

Rituximab efficacy has been described, especially in autoimmune-related RDD cases[18]. The robust activity of targeted therapies in other histiocytosis raises interest in their potential for RDD, especially in cases with demonstrated somatic mutations; however, currently, the broad applicability of tumor sequencing and targeted treatments has not yet been established[3].

Radiotherapy has modest efficacy in RDD, although it can be beneficial in refractory soft tissue and orbital bone disease with visual compromise or resistant airway obstruction or to palliate local symptoms[3].

Data are insufficient to fully characterize the prognosis of RDD disease. Outcomes are usually favorable, particularly for cases of nodal and cutaneous disease, which are often self-limiting[3]. Similar to other studies[4], most of our cases had a benign course. Even though case number 2 suffered from a brain infiltration tumor, it had not progressively grown and had been stable. However, it must be stated that patients may have an unpredictable clinical course, with alternating periods of remission and reactivation that may last for years[3]. The role of tumor sequencing and targeted therapies, such as MEK inhibitors, is promising and requires further study.

RDD disease is a rare histiocytic disorder that was first described as a lymph node disease; however, more than a quarter of patients present extranodal involvement. The most affected sites are the skin, paranasal sinuses, soft tissue, bone, salivary glands, oral cavity, and craniospinal tissues. Due to this characteristic of involving various sites, the clinical manifestation of RDD can be unique in every patient. Furthermore, RDD most commonly develops as a benign disease, as up to half of the patients with nodal/cutaneous disease will have spontaneous remissions, but in about 10% of patients, it develops into a progressive disease, occasionally resulting in death. Regarding the variety of clinical manifestations and progression, every case is singular. In this study, five cases of patients of different ages, affected by RDD from diverse sites, presented with peculiar symptoms and evolved with distinct responses to therapy. Considering the rarity of this disorder, this description can contribute to the knowledge of this entity.

Funding: none.

Conflicts of interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Authors' contributions: JIRC: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **VLC:** Data curation, Formal analysis, Methodology, Writing – review & editing. **SABB:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing, Supervision.

REFERÊNCIAS

1. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. Arch Pathol. 1969;87(1):63-70. PMID: 5782438

2. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016;127(22):2672-81. https://doi.org/10.1182/blood-2016-01-690636

3. Abla O, Jacobsen E, Picarsic J, Krenova Z, Jaffe R, Emile JF, et al. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood. 2018;131(26):2877-90. https://doi.org/10.1182/blood-2018-03-839753

4. Piris MA, Aguirregoicoa E, Montes-Moreno S, Celeiro-Muñoz C. Castleman disease and Rosai-Dorfman disease. Semin Diagn Pathol. 2018;35(1):44-53. https://doi.org/10.1053/j.semdp.2017.11.014

5. Haroche J, Cohen-Aubart F, Rollins BJ, Donadieu J, Charlotte F, Idbaih A, et al. Histiocytoses: emerging neoplasia behind inflammation. Lancet Oncol. 2017;18(2):e113-25. https://doi.org/10.1016/S1470-2045(17)30031-1

6. Salama HA, Jazieh AR, Alhejazi AY, Absi A, Alshieban S, Alzahrani M, et al. Highlights of the management of adult histiocytic disorders: Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease, and hemophagocytic lymphohistiocytosis. Clin Lymphoma Myeloma Leuk. 2021;21(1):e66-e75. https://doi.org/10.1016/j.clml.2020.08.007

7. Bruce-Brand C, Schneider JW, Schubert P. Rosai-Dorfman disease: an overview. J Clin Pathol. 2020;73(11):697-705. https://doi.org/10.1136/jclinpath-2020-206733

8. Goyal G, Ravindran A, Young JR, Shah MV, Bennani NN, Patnaik MM, et al. Clinicopathological features, treatment approaches, and outcomes in Rosai-Dorfman disease. Haematologica. 2020;105(2):348-57. https://doi.org/10.3324/haematol.2019.219626

9. McPherson CM, Brown J, Kim AW, DeMonte F. Regression of intracranial Rosai-Dorfman disease following corticosteroid therapy. Case report. J Neurosurg. 2006;104(5):840-4. https://doi.org/10.3171/jns.2006.104.5.840

10. Cooper SL, Arceci RJ, Gamper CJ, Teachey DT, Schafer ES. Successful treatment of recurrent autoimmune cytopenias in the context of sinus histiocytosis with massive lymphadenopathy using sirolimus. Pediatr Blood Cancer. 2016;63(2):358-60. https://doi.org/10.1002/pbc.25770

11. Pulsoni A, Anghel G, Falcucci P, Matera R, Pescarmona E, Ribersani M, et al. Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): report of a case and literature review. Am J Hematol. 2002;69(1):67-71. https://doi.org/10.1002/ajh.10008

12. Averitt AW, Heym K, Akers L, Castro-Silva F, Ray A. Sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman Disease): diagnostic and treatment modalities for this rare entity revisited. J Pediatr Hematol Oncol 2018;40(4):e198-e202. https://doi.org/10.1097/MPH.0000000000001044

13. Jabali Y, Smrcka V, Pradna J. Rosai-Dorfman disease: successful long-term results by combination chemotherapy with prednisone, 6-mercaptopurine, methotrexate, and vinblastine: a case report. Int J Surg Pathol. 2005;13(3):285-9. https://doi.org/10.1177/106689690501300311

14. Rivera D, Pérez-Castillo M, Fernández B, Stoeter P. Long-term follow-up in two cases of intracranial Rosai-Dorfman Disease complicated by incomplete resection and recurrence. Surg Neurol Int. 2014;5:30. https://doi.org/10.4103/2152-7806.128003

15. Jacobsen E, Shanmugam V, Jagannathan J. Rosai-Dorfman disease with activating KRAS mutation – response to cobimetinib. N Engl J Med. 2017; 377(24):2398-9. https://doi.org/10.1056/NEJMc1713676

16. U.S. National Library of Medicine. ClinicalTrials.gov. Memorial Sloan Kettering Cancer Center. Single-agent cobimetinib for adults with histiocytic disorders. ClinicalTrials.gov Identifier: NCT02649972. [Internet]. Bethesta: National of Medicine; 2022. [cited 2022 Aug 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT02649972

17. Chen E, Pavlidakey P, Sami N. Rosai-Dorfman disease successfully treated with thalidomide. JAAD Case Rep. 2016;2(5):369-72. https://doi.org/10.1016/j.jdcr.2016.08.006

18. Petschner F, Walker UA, Schmitt-Gräff A, Uhl M, Peter HH. "Catastrophic systemic lupus erythematosus" with Rosai-Dorfman sinus histiocytosis. Successful treatment with anti-CD20/rutuximab. Dtsch Med Wochenschr. 2001;126(37):998-1001. https://doi.org/10.1055/s-2001-17109