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Rosai-Dorfman disease: a report of eight cases in a tertiary care center and a review of the literature

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Abstract

Rosai-Dorfman disease (RDD) is a nonmalignant histiocytic disorder of unknown origin that is extremely rare. By immunohistochemistry, the RDD cells are characteristically S-100 positive and CD1a negative. Emperipolesis is a common histopathological finding, although not specific for RDD. Lymph node and cutaneous manifestations are most frequent, but diverse organs can be affected. The clinical course is unpredictable regardless of treatment. Here, we present a series of 8 cases presenting lymph node and/or cutaneous lesions. Lymph node involvement was seen in diverse regions, including mediastinal and retroperitoneal. The treatment response to steroids was diversified, and the chemotherapy response was disappointing. Associated autoimmune diseases (Sjögren syndrome and antiphospholipid syndrome) were observed in 2 patients. Regardless of therapy modality, these patients exhibited a favorable prognosis in a follow-up duration that ranged from 15 to 80 months.

Key words: Rosai-Dorfman disease; Sinus histiocytosis with massive lymphadenopathy; Histiocytosis

Introduction

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a clinico-pathological entity described by Rosai and Dorfman (1) just over 40 years ago. Children, adolescents, and young adults are more frequently affected by this disorder, but it may also occur in older adults (2,3).

RDD is an idiopathic disease, but its occurrence has frequently been observed after infectious disease. Because of this, a possible viral etiology, such as Epstein-Barr virus, human herpes virus 6, parvovirus B19, and polyomavirus, has been suggested by several authors, based on immunohistochemistry, PCR, and *in situ* hybridization studies (4-6). Notwithstanding the immunohistochemical and molecular results obtained in those studies, the relation of a virus to the etiology of RDD remains undefined.

Lymphadenopathy is the main clinical manifestation. Lymph node enlargement occurs more frequently in cervical and submandibular regions (4), but enlarged lymph nodes in mediastinal and retroperitoneal regions have also been described (2,7). Extranodal involvement has been observed in diverse organs, with the skin being most affected. Cutaneous RDD is a distinct entity, which is confined to the skin without lymphadenopathy and with different demographic features ranging from single papules to multiple nodules and plaques (8).

The involvement of unusual regions, such as the breast, kidney, thyroid, testis, and central nervous system, has also been reported (9-13). Interestingly, in one recent study, extranodal RDD cases were reported to be more common than nodal cases (77 *vs* 8%, respectively) (14).

Because enlarged and massive unilateral or bilateral lymph nodes are a frequent manifestation, in isolated or multiple regions, lymphoma may be clinically suspected (15). Extranodal RDD can also mimic other diseases, such as meningioma (16).

The histological feature of RDD, independent of nodal or extranodal lesions, is the proliferation of histiocytes with abundant pale cytoplasm, pericapsular fibrosis, and dilated sinuses in the lymph nodes. RDD cells can express S-100 antigen and are also positive for CD68, CD163,

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α1-antitrypsin, α1-antichymotrypsin, fascin, and HAM-56, whereas they are negative for CD1a by immunohistochemistry (17). The hallmark of RDD is emperipolesis, an unknown significant biological phenomenon, in which different types of bone marrow cells, such as lymphocytes or neutrophils, exist in the cytoplasm of histiocytes with a background of mature lymphocytes and plasma cells. This finding is not specific to RDD and can also be found in hematological disorders like idiopathic myelofibrosis and tumor cells (18,19).

The clinical course of RDD is unpredictable, regardless of treatment. The evolution of the disease is slow and may regress spontaneously (20). However, although RDD has been considered a benign disease, the clinical manifestations evolve, and patients may become nonresponsive to various treatments. An unfavorable or fatal outcome is not a common event, but deaths have been described in a large cohort study (21).

Because RDD is a very rare disease and patients exhibit a wide range of clinical presentations, there is no specific medical center that attends patients affected by this disease. Patients are frequently attended by many different medical specialties and in general hospitals; consequently, most of the publications are unique case reports. Therefore, our aim was to describe 8 cases of RDD, with patients who exhibited lymphonodal and/or cutaneous involvement. We also present a concise overview of the clinical and therapeutic responses to current and unusual treatment modalities for RDD.

Patients and Methods

Patients

In this retrospective study, demographic and clinical data were obtained from medical records. In the present study, we enrolled 8 patients, comprising adults and children, diagnosed and treated at the Hematology Service, Instituto Nacional de Câncer, Brazil, between January 2000 and October 2012. The diagnosis of RDD was based on histopathological and clinical criteria. Clinical information from patients included clinical presentation, treatment, and outcome. Immunohistochemical stains were performed in all cases to exclude the diagnosis of other histiocytic diseases, such as Langerhans cell histiocytosis (LCH). The Institute's Ethics Committee approved this investigation, and the study was conducted in accordance with the recommendations of the Declaration of Helsinki.

Results

Demographic, histopathological, and clinical aspects

As reported in Table 1, in this cohort encompassing 8 patients, we found all age categories from 2 to 53 years of age. There was an almost equal proportion of male (n = 3) and female (n = 5) and white (n = 3) and nonwhite (n = 5) patients. The median time from first clinical manifestation until the RDD diagnosis was 3.5 months (range, 1 to 12 months).

CD1a was negative in all cases, unlike S-100 protein immunoreactivity. Emperipolesis, which is the engulfment of hematological cells, was observed in almost all cases.

Lymphadenopathy was a predominant clinical manifestation, and was observed in 7 of the 8 patients (Table 1). These lymph nodes were often large and painful, suggesting an inflammatory reaction. Unilateral or bilateral cervical (n = 6) and submandibular (n = 5) regions were the most often involved, followed by axillary (n = 3), inguinal (n = 2), mediastinal (n = 2), and retroperitoneal (n = 1). In 3 patients, infectious disease (otitis or tonsillitis) was present at the same time as enlargement of lymph nodes. At RDD presentation, fever was observed in these last 3 patients. Extranodal lesions were observed in 2 patients (Patients 1 and 7) and, in these cases, were localized only in the skin. In 1 patient (Patient 1), the only manifestation of RDD was in the skin (Table 1). In another patient (Patient 7), skin lesions occurred concomitant with lymph node enlargement. Skin lesions in both patients were characterized by an infiltrative brownish plaque with irregular borders, and

Table 1. Demographic, clinical characteristics, treatment, and outcome of Rosai-Dorfman patients.

No.	Age/gender/ race	Type of lesion (location)*	First treatment	Response	Second treatment	Response	Outcome
1	53/F/W	Cutaneous	Steroid	No	Rt	Complete	84 months, CCR
2	4/F/N-W	Lymph nodes	Resection	Complete	No	-	60 months, CCR
3	2/M/N-W	Lymph nodes	Steroid	Partial	Steroid	Complete	60 months, CCR
4	14/F/N-W	Lymph nodes	Steroid	No	Ct** Steroid	No Complete	12 months, CCR
5	40/F/N-W	Lymph nodes	Steroid	Complete	No	-	60 months, CCR
6	28/M/W	Lymph nodes	Steroid	Partial	Rt	Complete	36 months, CCR
7	23/F/W	Lymph nodes Cutaneous	Steroid	Partial	Ct*** Rt + steroid	Partial Complete	15 months, CCR
8	3/M/N-W	Lymph nodes	Steroid	Partial	No	Partial	24 months, PR

No.: number identification; M: male; F: female; W: white; N-W: non-white; CCR: complete continuous response; PR: partial response; Rt: radiotherapy. * At presentation; Ct**: chemotherapy (cyclophosphamide, adriamycin, vincristine, prednisone); Ct***: vinblastine, prednisone.

pain was experienced. These lesions measured approximately 10 cm and were on both legs. In this cohort, 2 patients developed an autoimmune disease. One of them (Patient 4) was diagnosed with antiphospholipid syndrome (APS) 1 month after RDD diagnosis, which was diagnosed during a hemorrhagic cerebral vascular accident because of severe prothrombin deficiency. The patient was treated with glucocorticoids and chemotherapy. She made good progress but remains with neurological sequelae. Another patient (Patient 5) developed dryness of the mouth and eyes and had Sjögren syndrome (SS) diagnosed 8 months after RDD. After glucocorticoid treatment, she remained asymptomatic during the 2-year follow-up.

Response to treatment and outcome

As reported in Table 1, in 1 patient (Patient 2), whose disease localized only in one submandibular lymph node, its complete excision resulted in resolution without return of RDD. Oral prednisone was the treatment modality most employed (in 7 of 8 patients). This type of treatment was initially employed with doses from 1.0 to 2.0 mg/kg, but during follow-up this dosage was modified several times. After prednisone therapy, only 1 patient (Patient 5) presented a complete response and good progress, and after an extensive follow-up period she experienced no episodes of recurrence (Table 1).

Despite increased prednisone dosage and several weeks of therapy, 4 of 7 patients exhibited a partial response. However, subsequent prednisone treatment resulted in complete resolution in 1 of 4 patients (Patient 3). Radiotherapy resulted in later complete responses in 2 patients (Patients 1 and 6), and one of them presented skin lesions associated with lymph node involvement. Chemotherapeutic drugs like vimblastine, used alone, or drugs in combination (CHOP protocol: cyclophosphamide, vincristine, adriamicin, and prednisone) did not result in good responses in 2 patients (Patients 4 and 7; Table 1).

Discussion

The review of the literature performed in the present work is limited by the small number of published articles and small number of RDD patients included in the investigatory trial of drug treatment. Also, there are no data available in the literature about case reports involving long follow-up periods off specific therapy and relapses. We used the search term ‘‘Rosai-Dorfman disease’’ in the PubMed database. Therefore, although the present study encompasses a small number of patients, its main strength lies in the fact that all 8 patients were followed up by the same group of physicians for a long period. In our series of cases, findings such as age and gender were similar to those described in the literature.

Emperipolesis can be found in several hematological diseases, such as myeloproliferative disorders and lymphoma (18) and also in nonmalignant disease (22). This phenomenon consists of the engulfment of cells (commonly lymphocytes) inside another cell (histiocyte). Despite not being a pathognomonic marker for RDD, it has been considered an important indicator of this disease, and it was a common finding in pathological lesions of our patients. The significance of emperipolesis is still not fully elucidated.

The rarity of RDD has limited our understanding of the choice of the best treatment; however, according to the literature, therapy intervention is not necessary in some patients. In fact, spontaneous resolution in 2 patients presenting massive lymphadenopathy was reported (23). Also, it was possible to observe spontaneous regression of a mediastinal lymph node involvement in a 64-year-old woman (20).

Surgical resection of the lesion should be considered in cases of cutaneous or subcutaneous involvement. However, this modality of treatment can be unfavorable, because regrowth of the skin lesion was previously observed in 1 patient who had undergone complete excision of the lesion (24). Surgical resection of the lymph node has also resulted in the complete disappearance of RDD. In fact, in our cohort, this was observed in 1 patient presenting unilateral lymphadenopathy. He had no recurrence after 5 years of follow-up.

Radiotherapy can provide good results with cutaneous RDD. Consistent with this, one of our patients, who exhibited a unique skin lesion, was treated only with radiotherapy and obtained complete resolution without recurrence in a follow-up of 7 years.

Treatment with chemotherapy agents has been disappointing, and it is possible that different patients with RDD may respond to different drugs. Some patients could benefit from a combination of methotrexate/6-mercaptopurine/vinblastine/6-thioguanine (25). Anthracyclines, alkylating agents, and vinca alkaloids had limited efficacy in 2 patients in our series.

In our cohort, prednisone, as first therapeutic modality, did not result in complete regression of skin lesions or lymph node enlargement in 6 of 7 patients. In 4 patients, there was a partial response, which required additional therapy. Nevertheless, radiotherapy was a good approach in 2 patients nonresponsive to steroids, resulting in regression of the lesions in both patients (Table 1). However, it is remarkable that even patients initially unresponsive to steroids and chemotherapy may provide a good response to steroid therapy later.

Therapy based on steroids has been widely used as one of the most important drug treatments for RDD. Oral prednisone can have a remarkably favorable response, mainly in patients with lymph node involvement (26,27). However, intralesional corticosteroid, as well as oral prednisone, does not always result in resolution of cutaneous lesions (8,28). According to those authors, only surgical resection resulted in the resolution of the disease in 1 patient, after an unfavorable response using corticosteroid and radiotherapy.

Diverse modalities of unusual treatments have recently been adopted in an effort to reduce the clinical manifestation of RDD after the failure of corticosteroids, radiotherapy, or chemotherapy, each in an isolated or association schema (Table 2). After an ineffective response with cyclosporine A and corticosteroid, imatinib mesylate (glivec), a tyrosine kinase inhibitor which targets BCR-ABL and is widely used to treat chronic myeloid leukemia, was given for the treatment of a 41-year-old man with RDD localized in the skin, bone marrow, liver, and spleen. Imatinib caused resolution of the lesions, and the patient was free of the disease for more than 7 months (29). On the other hand, imatinib was unable to benefit the cutaneous RDD in another patient who previously received various modalities of treatment, such as corticosteroids, dapsone thalidomide, methotrexate, and isotretinoin (30). The rationale for the use of imatinib is based on the fact that histiocytes present in RDD lesions can exhibit platelet-derived growth factor receptors (PDGFRα, PDGFRβ), and c-Kit, and are targets for drugs such as BCR-ABL (29). Dapsone and thalidomide have been associated with regression of cutaneous RDD in some patients (31,32). Interferon-α treatment was also limited to a small number of patients with contradictory results (33-36). Other new therapeutic approaches in RDD include 2-chlorodeoxyadenosine (2-CdA, cladribine), a purine analog that has also been used in LCH (37). The response of both histiocytic diseases to 2-CdA can be supported by the fact that this drug decreases cytokine production from monocyte/macrophage lineage. After 2-CdA treatment, a marked resolution and sustained response of massive lymphadenopathy was observed in an 8-year-old boy (38) and also in a 45-year-old woman (39). Clofarabine, a second-generation purine analog, was recently used as salvage therapy in a group of 18 patients presenting diverse refractory histiocytic disorders. Three of these patients with RDD received clofarabine as salvage therapy. One female patient had a very good response and remained disease free for 17 months from the start of clofarabine. In another female patient, the disease progressed 4 months after clofarabine was discontinued, and 1 male patient had RDD recurrence after presenting a good response to clofarabine after six cycles (40). However, the contribution of all these above-mentioned agents in the treatment of RDD is unclear.

RDD is related to the development of an abnormal immune response, which could mean a breakdown in the immune system (41). Despite the rarity of RDD, the co-occurrence with LCH, lymphomas, or autoimmune disorders has been reported (Table 3). The exact relation between these entities is not known, but the relatively frequent association among these rare diseases suggests that there may be a pathophysiological relationship among them and not only a simple coincidence. This is the case of the association between RDD and LCH, which suggests a common monocytic-macrophage lineage origin (42-45). RDD associated with different types of lymphoma can be simultaneously diagnosed and can occur in the same organ (46-48). Lymphoma can also be diagnosed many years before RDD, as has been shown by Di Tommaso et al. (49). In an analysis of 14 deaths occurring in RDD patients, Foucar et al. (21) found that approximately 70% of deaths occurred in patients presenting some evidence of immune dysfunction as opposed to 12% in surviving patients.

All of these cases reported in the literature (Table 3) contribute to our understanding about the simultaneous occurrence of RDD with autoimmune diseases, such as SS and APS in 2 of our analyzed patients. APS is mainly

Table 2. Responses for unusual treatment in Rosai-Dorfman disease patients.

Location of lesion	n	Treatment	Type of response	Reference
Cutaneous	1	Acetritin	Partial resolution of lesion. Treatment was discontinued due to collateral events.	(24)
Cutaneous and systemic	1	Imatinib	Complete resolution. Free of recurrence for more than 7 months.	(29)
Cutaneous	1	Imatinib	Failure after 2 weeks of treatment.	(30)
Cutaneous	1	Topical dapsone	Favorable response. No recurrence after 1-year follow-up.	(31)
Cutaneous	1	Thalidomide	After 5 months of treatment the lesions underwent regression.	(32)
Cutaneous	2	Combined intralesional betamethasone, interferon and acitretin	No recurrence over a 1-year follow-up period.	(34)
Massive cervical lymph nodes	1	Cladribine	Complete response and no recurrence after 2 years of follow-up.	(38)
Massive cervical lymph nodes	1	Cladribine	Complete clinical and biological response after 30 months follow-up off therapy.	(39)
Bone lesions	3	Clofarabine	One good response, one progression, and one recurrence.	(40)

n: number of cases.

Table 3. Association of Rosai-Dorfman disease with other entities.

Age/gender	Clinicopathological entity	Site of RDD	Entity clinical features	Time interval	Reference
3/M	LCH	Cervical lymph node	Preauricular lymph node	Concurrent	(42)
45/F	LCH	Skin	Skin	Concurrent	(43)
68/M	LCH and NHL (splenic marginal lymphoma)	Skin, liver	Skin, palate	LCH and RDD were concurrent. Liver NHL occurred a few years later	(45)
80/F	NHL (nodal marginal zone lymphoma)	Lymph node	Lymph node	Concurrent: Both diseases occurred in the same lymph node	(46)
33/F	NHL (diffuse large B-cell lymphoma)	Retroperitoneal lymphadenopathy	Retroperitoneal lymphadenopathy	Concurrent: Both diseases occurred in the same lymph node	(47)
50/M	Nodal marginal zone lymphoma and AIHA	Abdominal lymph nodes	Abdominal lymph nodes	Concurrent	(48)
65/F	NHL (follicular B cell lymphoma)	Liver	Lymph nodes	NHL occurred previously to RDD and during NHL relapsing	(49)
7/M	SLE	General lymphadenopathy	Pericardial effusion	SLE occurred in the course of RDD	(51)
68/F	Uveitis and hypothyroidism	Skin	Uveitis, bilateral	Uveitis preceded RDD	(52)
38/F	AIHA	Skin	Anemia	Concurrent	(53)
13/M	Sarcoma, histiocytic	Splenomegaly	Retroperitoneal adenopathy and splenomegaly	Sarcoma histiocytic arose in RDD	(54)
55/M	SS	Lymph nodes	Dry mouth, dry eyes and PGE	Concurrent	(55)

RDD: Rosai-Dorfman disease; LCH: Langerhans cell histiocytosis; M: male; F: female; NHL: non-Hodgkin lymphoma; SLE: systemic lupus erythematous; AIHA: autoimmune hemolytic anemia; SS: Sjögren syndrome; PGE: parotid gland enlargement.

characterized by disseminated vascular thrombosis, resulting in multiorgan failure. Although bleeding is uncommon in APS, this was the first clinical manifestation in our patient. RDD can occur in association with APS and systemic lupus erythematous (SLE) or SLE occurring in the course of RDD (50,51). Other associations of RDD and immune diseases are also described in Table 3 (52-54).

To our knowledge, the case in the present study is the second case showing the association of RDD and SS. The first published case presented generalized lymphadenopathy, splenomegaly, and simultaneous autoimmune exocrinopathy (55). The diagnosis interval between RDD and SS of our patient was a few months, and we cannot rule out the simultaneous occurrence of these diseases.

In our 8-case series, there were no deaths and no long-term morbidity related to RDD, except the cognitive deficit secondary to a hemorrhagic cerebral vascular accident in a female patient with APS.

In conclusion, at present, there is no ideal schema to treat in a similar manner the diverse types of RDD lesions. Because the disease is self-limited, therapy should be tailored to the individual lesion or patient. Chemotherapy does not result in a favorable response. Steroids can result in a plateau-lasting stability, and may even cause an unfavorable response during the first attempt. The literature and our cases illustrate the coexistence of RDD and immune deregulatory disorders by simultaneous onset or temporal decoupling.

Together, these findings suggest that RDD may consist of an immunological response to an unknown stimulus (40). Taken into account that RDD can mimic several diseases or can emerge prior, concurrently, or after immune deregulatory diseases, it is imperative that these patients be followed up for a long period.

In light of the rarity of RDD and the paucity of studies using new therapeutic approaches, it would be important to identify the centers of excellence for innovative therapy to be used in the context of clinical trials.

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