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# Cutaneous Rosai-Dorfman disease: a case report and literature review

Enfermedad de Rosai-Dorfman cutánea:  
reporte de un caso y revisión de la literatura

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## Key words:

Lymph nodes, extra nodal involvement, emperipolesis, immunohistochemistry, S-100 protein.

## Palabras clave:

Ganglios linfáticos, compromiso extraganglionar, emperipolesis, inmunohistoquímica, proteína S-100.

## ABSTRACT

This study reports a clinical case of cutaneous Rosai-Dorfman disease, its manifestation, and its evolution in 10 years, thus contributing to the limited bibliography about it and which review is also an important aim of this paper. This clinical study included a histopathological and immunohistochemical review of the lesions. Since this is a skin disease, not a life-threatening condition, and due to the lack of therapeutic resources and funds, only one excision surgery of a small lesion was performed without further therapeutic attempts. This article states the importance of distinguishing this disease from other malignant ones, because of the different prognosis made in each case. Treatment is necessary only for cosmetic purposes or in case of becoming a life-threatening condition. It is also suggested that Rosai-Dorfman disease and its cutaneous form could be two different entities.

## RESUMEN

Este trabajo reporta el caso clínico de una paciente con enfermedad de Rosai-Dorfman cutánea, su forma de manifestación y su evolución de 10 años, contribuyendo a la escasa bibliografía existente y cuyo estudio es también un importante objetivo de este artículo. Este estudio clínico incluyó los estudios histopatológico e inmunohistoquímico de las lesiones. Debido a la falta de recursos terapéuticos y económicos, y puesto que es una enfermedad confinada a la piel, sin peligro vital, se practicó sólo la extirpación quirúrgica de una pequeña lesión y no se hicieron otros intentos terapéuticos. Este artículo pone de manifiesto la importancia de distinguir esta enfermedad de otras entidades malignas y su pronóstico diferente en cada caso. El tratamiento se hace necesario sólo con fines estéticos o en caso de riesgo vital. Se sugiere que la enfermedad de Rosai-Dorfman y su forma puramente cutánea podrían ser dos entidades diferentes.

## Abbreviations and acronyms

SHML: Sinus histiocytosis with massive lymphadenopathy  
 RDD: Rosai-Dorfman disease  
 ESR: Elevated erythrocyte sedimentation rate  
 CRDD: Cutaneous form of Rosai-Dorfman disease  
 SRDD: Systemic form Rosai-Dorfman disease  
 EBV: Epstein-Barr virus  
 HHV-6: Human herpesvirus-6  
 α-IFN: α-Interferon

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**S**inus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease (RDD) is an unusual but distinct clinic-pathologic entity of unknown etiology,<sup>1</sup> histological characterized by a benign histiocytic proliferation.<sup>2</sup>

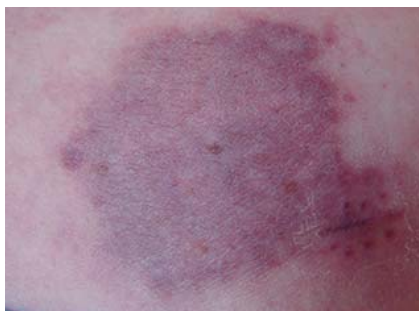
It was first described by Destombes in 1965,<sup>3</sup> by Azoury and Reed in 1966, and then recognized as a definite entity<sup>4</sup> in 1969 by Rosai and

Dorfman.<sup>5</sup> Herewith we report a new case of SHML with only cutaneous involvement.

## CASE REPORT

A 64-year-old woman presented with a one-year history of slowly growing papular lesion, which evolved into a well-defined and firm brownish of 1.2 x 1.2 cm-diameter nodule on her left arm. Lymphadenopathy or any other significant abnormality could not be clinically detected. The nodule was excised and the microscopic examination revealed a dense infiltration of normotypic lymphocytes and nests of histiocytes with intracytoplasmic intact lymphocytes (emperipolesis), surrounded by plasma cells.

The patient did not go back for any check-ups until seven years later, when she presented



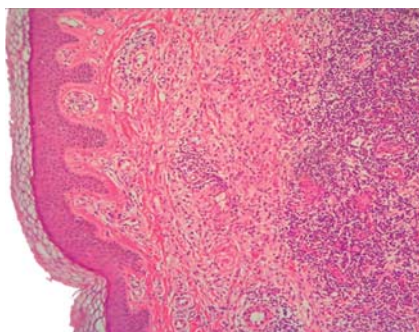
**Figure 1.**

Plaque in the left thigh.



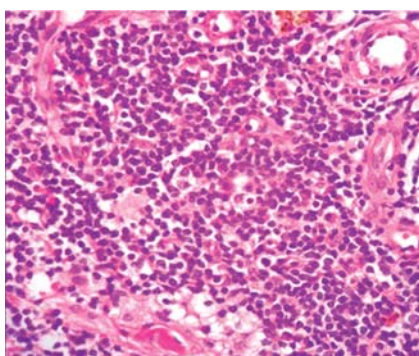
**Figure 2.**

Plaque in the right leg.



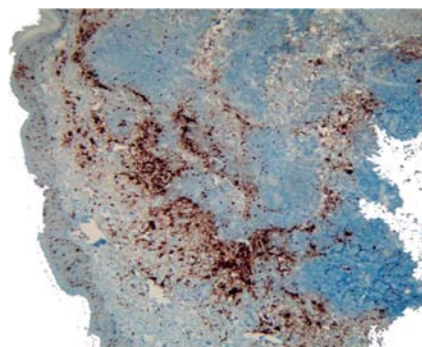
**Figure 3.**

Panoramic view of the skin biopsy showing nodular dermal lymphoid infiltrates with sparing of the epidermis. H&E, 40X.



**Figure 4.**

Lymphohistiocytic infiltrates with plasma cells and large macrophages showing emperipolesis. H&E, 200X.



**Figure 5.**

Immunohistochemical staining for protein S-100 showing positive reaction in numerous macrophages in the dermal infiltrate. S-ABC, hematoxylin counterstaining, X40.

with two large plaques of four to five years of evolution. Examination revealed a lilaceous, indurate, 7 x 5.5 cm-diameter plaque in her left thigh (*Figure 1*), and a similar one, of 5 x 2 cm diameter, on her right leg (*Figure 2*). Lymphadenopathy, hepatosplenomegaly, or any other associated abnormality could not be clinically detected. An incisional skin biopsy showed similar changes with orthokeratosis and slight acanthosis; the dermis presented a dense infiltration by lymphocytes, plasma cells, and histiocytes without prominent emperipolesis (*Figures 3 and 4*). The immunohistochemical laboratory study showed positive reactivity of the histiocytes with S-100 protein (*Figure 5*). The results of a complete blood test, liver function tests and immunologic studies were within normal limits. Serum protein electrophoresis was normal. A CAT scan of the chest and abdomen did not show lymphadenopathies.

These histopathological and immunohistochemical findings were considered to be in agreement with the diagnosis of Rosai-Dorfman disease.

## COMMENT

Any age group can be affected by SHML, but the majority of patients are teenagers and people in their 20's (mean age: 20.6 years). It presents as a febrile condition with expansive but painless, usually self-limited, lymphadenopathy, confined mostly to cervical (or other) lymph nodes, and often accompanied by anaemia, an elevated erythrocyte sedimentation rate (ESR), leukocytosis with neutrophilia, and polyclonal hypergammaglobulinemia.<sup>6-8</sup> Generally, anaemia is normochromic, normocytic, but, occasionally, it is hypochromic, microcytic.<sup>9</sup> It is more common in black and white population, whereas it is rarely reported in Asians. There is a mild predominance in men (1,4:1).<sup>1,6,10</sup>

Concomitant involvement of extra nodal sites is commonly noted in RDD (43%), like the nasal cavity (paranasal

sinuses, soft tissues, eyelid), orbit, bone, salivary glands, central nervous system, oral cavity, genitourinary system and the skin.<sup>1,2</sup> On the other hand, extra nodal disease without lymph node involvement is uncommon.<sup>10</sup>

Although cutaneous involvement in RDD is the most frequent extra nodal manifestation (11%), purely cutaneous disease is exceptional (3%) and not well documented.<sup>1,10</sup> Until 2008, there were approximately 80 cases reported.<sup>3</sup>

The cutaneous form of RDD (CRDD) was first described in 1978, by Thawarani et al.<sup>10</sup> Age distribution ranges from 15 to 68 years old,<sup>1</sup> with a mean age of 45 years<sup>11</sup> and a predominance in women (2:1).<sup>1</sup> Affected population is mainly Asian and white; this information contrasts with the one of patients with systemic RDD (SRDD) with lymph node involvement.<sup>1,6,10</sup>

Cutaneous lesions are characterized by yellow-brown papules<sup>7</sup> or red nodules that can be solitary, in groups or dispersed, often with purple-brown discoloration, erythema, or hyper pigmentation. They can occur in any part of the body, but limbs are the most frequently involved, followed by the trunk and face.<sup>3,4,11</sup> In most of the case studies, skin lesions were divided into three main types as follows: papulonodular (79.5%), indurated plaque (12.8%) and tumour (7.7%).<sup>3</sup>

In the last years, two cases of CRDD with bilateral eyelid swelling were reported: one, in a 19-year-old girl with bilateral upper eyelid swelling; and the other, in a 6-year-old girl with bilateral upper and lower eyelid swelling along with other cutaneous peculiarities. The latter is probably the youngest person affected by purely CRDD.<sup>12</sup>

Moreover, the diagnosis of coexisting CRDD and Morphea was confirmed; and recently, one case that actually presented both diseases has been reported. Probably that occurred due to an autoimmune and/or infectious aetiology for both diseases, although it could also be a simple coincidence, considering that coetaneous scleroderma (morphea) is a common dermatological condition.<sup>13</sup>

Clinical appearance of cutaneous lesions and histological features in CRDD are identical to those of cutaneous lesions in RDD with lymph node involvement.<sup>14</sup>

Compared to classic SHML, no significant laboratory abnormalities or systemic symptoms have been reported in patients with CRDD,<sup>3</sup> although there have been reports of a few patients that presented tiredness and weight loss.<sup>14</sup>

Approximately 13% of patients with RDD show immune disorders, such as bilateral uveitis, positive antinuclear antibody, lupus erythematosus, rheumatoid arthritis, hypothyroidism, and lymphoma.<sup>14</sup> Uveal damage is the most frequent association, which will not affect the prognosis but will increase morbidity.<sup>6</sup> Bilateral anterior uveitis has been

described in relation to CRDD, as well as to classic SHML, and it probably represents uveal involvement by RDD.<sup>1</sup>

The clinical course of RDD can vary: some lesions heal spontaneously over weeks or even months, and others persist for years or are recurring after excision.<sup>14</sup> However, in a small percentage of cases, the disease may progress, affecting kidneys, the lower respiratory tract or the liver. In those cases, autoimmune haemolytic anaemia, neutropenia, lymphocytopenia, and immunologic abnormalities, such as antinuclear antibody expression, are ominous findings.<sup>2</sup>

When RDD is limited to the skin, most reports indicate a favourable long-term prognosis with spontaneous regression.<sup>2,9</sup>

Reported cases show clinical follow-ups of patients with CRDD, from 6 months to 11 years (mean age = 17 months), that present lesion disappearance (non-dependant on the treatment), continuance or reappearance, similar to SRDD cases.<sup>1,3</sup> Further lymphadenopathy or lesions in other places of the body are not reported, and the disease remains localized in the skin. Nevertheless, longer follow-up periods are clearly recommended to avoid omitting the subsequent development of the systemic disease.<sup>1</sup>

It is possible that some patients with purely cutaneous symptoms may have clinically unrecognized systemic lesions. However, there have not been reported cases of cutaneous disease developing into a systemic disease.<sup>14</sup>

Origin and pathogenesis of SHML are still unknown.<sup>2</sup> Suggested causes include a definite infectious process leading to a histiocyte response by the body and, as a consequence of an immunologic failure resulting in an accumulation of histiocytic cells.<sup>15</sup> The related infection processes include Epstein-Barr virus (EBV),<sup>9,16</sup> human herpes virus-6 (HHV-6),<sup>16,17</sup> herpes simplex virus,<sup>6,16</sup> varicella, and herpes zoster.<sup>16</sup> It can be rarely associated to *Brucella*, *Klebsiella rhinoscleromatis* and *Nocardia*, although additional studies cannot confirm the connection.<sup>15</sup>

Serologic examinations have found antibodies to HHV-6 in patients with SHML; also, HHV-6 DNA and late-phase HHV-6 antigens have been detected in SRDD<sup>1</sup> lesions, but not in CRDD tissue samples, except in one case. However, HHV-6 has often been detected in a great amount of reactive and infectious disorders of lymphoid tissue, and, therefore, its presence is RDD non-specific.<sup>7</sup>

This information suggests a pathogenetic connection between SHML and HHV-6 infection. Likewise, HHV-6 infection could be a consequence in patients with SHML.<sup>1</sup> Similarly, EBV may play a role in the aetiology, because high EBV antibody titers were detected in one case.<sup>2</sup> Histologically, lesions are distinguished by a dense dermal infiltrate



proliferation of polygonal S-100 positive histiocytes, exhibiting emperipolesis and a mixed but mainly chronic inflammatory infiltrate.<sup>1</sup>

The difference between the histological findings of skin lesion biopsy in cutaneous manifestations of RDD with lymph nodes involvement and those found in RDD limited to the skin, is not only based on histological ground.<sup>1,6</sup> The main peculiarity of RDD is the existence of large histiocytes with abundant pale eosinophilic cytoplasm, indistinct cytoplasmic borders, vesicular nuclei and distinct nucleoli. These histiocytes exhibit the phenomenon of emperipolesis, where lymphocytes (and occasionally plasma cells or neutrophils and red blood cells) are found in the cytoplasm.<sup>2,7,14,16</sup> After a thorough inspection, emperipolesis has been found in 86% of histological studies.<sup>18</sup> There may be an accompanying inflammatory reaction consisting of lymphocytes, plasma cells, neutrophils or epithelioid cells, but distinctive histiocytes of RDD are positive for S-100, negative for CD1a, and variably positive for CD68.<sup>7,14</sup> There is an encircling inflammatory background of lymphocytes, plasma cells and some neutrophils. Foucar et al. believe that the presence of emperipolesis and S-100 protein expression by the histiocytes is diagnostic of RDD. Two other criteria emphasized by Chu and LeBoit are the presence of histiocytes in dilated lymphatic spaces and clustered lymph nodes at the periphery of the lesions. CRDD differs histologically from nodal disease in that there is a greater degree of fibrosis, fewer histiocytes and diminished emperipolesis.<sup>2</sup> The positivity of S-100 protein can discard the possibilities of inflammatory pseudotumor and other cutaneous histiocytosis. In addition, S-100 staining can facilitate the identification of emperipolesis and can be helpful to confirm the diagnosis.<sup>6</sup>

From a clinical point of view, the differential diagnosis suggests that CRDD should be distinguished from cutaneous lymphoma, histiocytosis, sarcoidosis, dermatofibrosarcoma protuberans, infectious processes and other infiltrating neoplasms.<sup>19</sup> Nevertheless, the diagnosis of CRDD is supported by histopathologic findings.

The histological differential diagnosis of CRDD is very important and includes malignant lesions, as well as a connection with histiocytosis of Langerhans cells, which is very rare and lethal.<sup>10</sup>

In the histological differential diagnosis with malignant histiocytosis (histiocytic lymphoma), the mitotic activity and atypia help to discard it. Emperipolesis is also absent.

In relation to the hemophagocytic syndrome associated with T-cell lymphoma, histiocytes are S-100 negative.

Distinguishing CRDD from reticulohistiocytoma cutis is difficult because histiocytes can rarely be S-100 posi-

tive, but the ground-glass appearance of the histiocytic cytoplasm is prominent, plasma cells are absent and emperipolesis is scattered and focal.

In contrast to CRDD, Langerhans cell histiocytes present positive histiocytes CD1a and Birbeck granules on electron microscopy, as well as absence of emperipolesis.

The differential diagnosis with eruptive xanthoma is given by the absence of plasma cells, histiocytes with negativity for S-100, and the presence of extra-cellular lipids.

Finally, in adult xantogranuloma the infiltrate is similar to the one of CRDD, but histiocytes are negative for S-100 and do not show emperipolesis.<sup>20</sup>

In general, treatment for CRDD is not necessary, but sometimes it may be required for aesthetic reasons or symptomatic mitigation.<sup>14</sup> Treatment is really necessary when lymph node or extra nodal tissue extension causes serious problems, such as vital organs constriction or other life threatening manifestations.<sup>15</sup>

Regardless of the relapse in a small number of patients, surgery is still the most effective treatment.<sup>3</sup> Other therapies, such as radiotherapy,<sup>3,7,14</sup> cryotherapy,<sup>3,14</sup> and chemotherapy<sup>3</sup> with Vinca-Alkaloid and Alkylating agents,<sup>7,21</sup> Isotretinoin,<sup>3</sup> systemic glucocorticoids,<sup>7,14,21,22</sup> anthracyclines, antimetabolites, as well as  $\alpha$ -interferon ( $\alpha$ -IFN),<sup>15</sup> can be used when the disease appears in a devastating or diffused way. Elevated 300 mg daily doses of thalidomide have been reported to keep expansive coetaneous disease<sup>3,14</sup> under control. The analysis of the real efficiency of any of these therapeutic methods is hard to confirm, due to the peculiarity of this disease.<sup>14</sup>

Between 1972 and 1996, Pulsoni et al. studied the cases of RDD therapy. Their results were the following: 50% of patients did not need treatment; 82% of them healed spontaneously; in 12% of the cases the disease remained; and the rest corresponds to two patients, one of them had a partial remission and the other one died of amyloidosis with renal collapse.<sup>15</sup> In this study, the use of antibiotics and/or antituberculous drugs had unfavourable results. Systemic steroids produced partial disappearance of fever and lymph node dimension or symptom reduction.

Those patients requiring a more aggressive therapy due to their vital organ involvement had to be treated with chemotherapy, radiotherapy, surgery or immunomodulators.

Surgery and radiotherapy show the best results, even resulting in a complete remission. Radiotherapy by itself has demonstrated to be efficient in few patients (near 33%), but chemotherapy has not had good results in most of the cases.

The importance of the antimetabolite and the  $\alpha$ -IFN treatment is not well defined yet.<sup>15</sup>

Regarding tyrosine kinase inhibitors therapy, Utikal et al. had a successful result in a patient with RDD treated with imatinib mesylate; however, Gebhardt et al. did not have any response.

Although there are many probable explanations for the failure of imatinib treatment, such as the dosage used or the development of the disease before beginning the therapy, Gebhardt et al. conclude that CRDD and SRDD could be two different entities. According to them, that

might explain the different responses of each one to tyrosine kinase inhibition with Imatinib.<sup>21</sup>

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