

# Combined Cutaneous Rosai-Dorfman Disease and Localized Cutaneous Langerhans Cell Histiocytosis Within a Single Subcutaneous Nodule

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**Abstract:** Rosai-Dorfman disease (RDD) is a reactive multisystem histiocytosis that typically presents with cervical lymphadenopathy and systemic symptoms. Cutaneous involvement occurs in approximately 10% of cases, and 3% of cases are limited to the skin without nodal or other extranodal involvement. Langerhans cell histiocytosis (LCH) is a clonal histiocytosis with a wide spectrum of presentations ranging from isolated skin or bone disease to multisystem involvement. Rare case reports have identified concomitant presentation of RDD and LCH; however, most of these reports have involved LCH and RDD occurring concurrently but at separate sites. We present a rare case of concurrent RDD and LCH presenting within a single skin nodule. The patient did not have any evidence of systemic involvement and has remained stable without additional treatment. We also review the literature on this unusual co-presentation and suggest possible underlying mechanisms. Finally, we recommend baseline laboratory and imaging studies and discuss treatment options based on the available evidence.

**Key Words:** Rosai-Dorfman disease, Langerhans cell histiocytosis, histiocytosis

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## INTRODUCTION

Rosai-Dorfman disease (RDD) is a multisystem macrophage-related disorder that classically presents with cervical lymphadenopathy.<sup>1</sup> Extranodal involvement is present in 43% of cases and may involve the upper respiratory tract, oral cavity, liver, spleen, testes, gastrointestinal tract, genitourinary system, and skin, among others.<sup>2</sup> Of these, the skin is the most commonly involved organ with 10% of cases having skin involvement and 3% of cases limited to the skin without nodal or other extranodal involvement.<sup>3,4</sup> Cutaneous manifestations are varied and include: yellow patches, skin-colored papules, red to brown papules, and subcutaneous nodules.<sup>2</sup> Patients often have systemic symptoms (fever, weight loss, and night sweats) and abnormal laboratory values

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The authors declare no conflicts of interest.

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(leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate, and polyclonal hypergammaglobulinemia).<sup>5</sup>

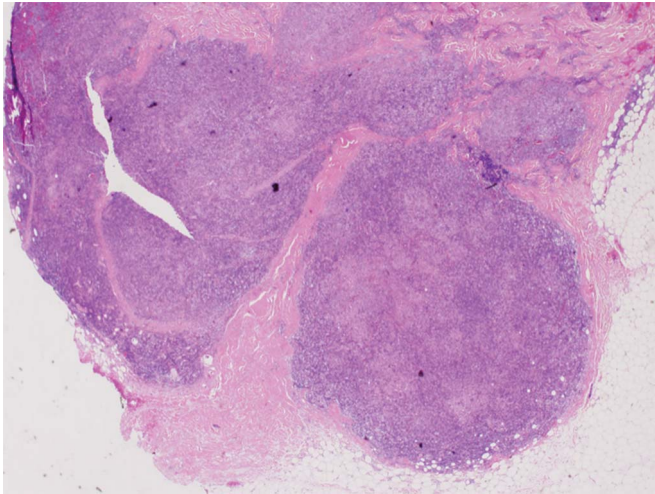
Langerhans cell histiocytosis (LCH) is a dendritic cell histiocytosis, which has a wide spectrum of clinical presentations ranging from localized cutaneous or bone disease to multiorgan involvement affecting the neurohypophysis, lungs, liver, spleen, and lymph nodes.<sup>6</sup> It is a clonal proliferation of Langerhans cells. LCH has recently been associated with BRAF<sup>V600E</sup> mutations, which lends some support to the idea that LCH is a neoplasm and not a reactive process.<sup>7</sup>

The co-occurrence of LCH and RDD is rare, and the first case was reported by Wang et al.<sup>8</sup> Only a handful of cases have been subsequently reported.<sup>9–13</sup> The majority of cases report concurrent LCH and RDD occurring simultaneously, but at distinct sites. We present a case of localized LCH and cutaneous-only RDD occurring within a single subcutaneous nodule. We also review the literature to discuss possible mechanisms leading to the concurrent expression of these 2 histiocytoses, recommend baseline laboratory and imaging studies, and discuss potential treatment options.

## CASE REPORT

A 48-year-old previously healthy woman presented to her dermatologist with an asymptomatic subcutaneous nodule on the left upper back that had been present for several months. The lesion was located adjacent to a scar from a previous excision of a basal cell carcinoma. The patient did not have any lymphadenopathy, fever, polydipsia, or other systemic complaints. On clinical examination, there was a freely mobile, 2 by 1 centimeter, skin-colored, dermal, and subcutaneous nodule without a punctum adjacent to a scar. The clinical differential diagnosis initially included cyst and recurrent basal cell carcinoma.

The excisional biopsy revealed a dense, diffuse, nodular, and interstitial infiltrate of histiocytes, lymphocytes, eosinophils, and plasma cells that had a “marbled” appearance with lightly and darkly stained areas at low power (Fig. 1). The infiltrate involved the middle and deep dermis and extended into the subcutaneous tissue. A few lymphoid follicles with germinal centers exhibiting reactive features, including well-spaced distribution, variable size, preserved mantle zone, and tingible-body macrophages, were identified. Examination on higher power revealed the presence of scattered large histiocytic cells with several foci of emperipolesis. The histiocytic cells were positive with S-100 immunostaining that also highlighted the emperipolesis (Fig. 2B). Closer inspection also revealed scattered loosely arranged aggregates of histiocytic cells with grooved reniform and/or “coffee bean”-shaped nuclei (Fig. 3A). CD1a immunostaining highlighted these focal aggregates and scattered cells in the infiltrate (Fig. 3B). Scattered plasma cells were highlighted with CD79a.



**FIGURE 1.** Subcutaneous nodule, hematoxylin and eosin stain ( $\times 20$ ), showing a “marbled” appearance at low power magnification.

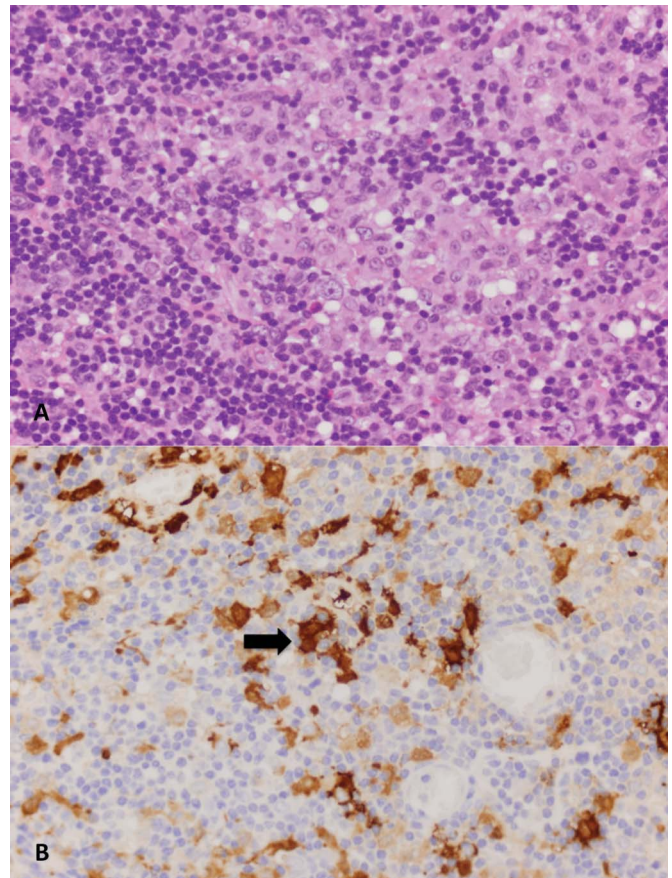
The plasma cells exhibited a polytypic pattern of kappa/lambda expression. A few scattered small clusters of CD123 positive cells, consistent with a small component of reactive mature plasmacytoid dendritic cells, were also present. A diagnosis of RDD and LCH was rendered.

In follow-up, the patient has not developed any additional cutaneous lesions or systemic symptoms. Additional staging workup was negative and included complete blood count, comprehensive metabolic profile, erythrocyte sedimentation rate, urinalysis, serum protein electrophoresis, and skeletal survey. She continues to have a small subcutaneous nodule immediately beneath her excisional biopsy scar that has been stable in size. She has declined any treatment at this time and has elected to continue with close clinical monitoring of her residual nodule.

## DISCUSSION

The first concurrent case of RDD and LCH was reported by Wang et al.<sup>8</sup> Their patient had multiple facial nodules with histopathological findings consistent with RDD. Within the largest lesion, they identified a small well-circumscribed aggregate of Langerhans cells consistent with LCH within the upper dermis. The patient did not have any systemic involvement and was treated successfully with cryotherapy.

The second reported case from Sachdev and Shyama<sup>10</sup> involved a 3-year-old boy with 2 separate enlarged lymph nodes. Biopsy revealed RDD of 1 node and LCH of the other. He was treated with low-dose oral steroids with complete resolution of the lesions in 3 weeks. The next case was reported as part of a larger series of RDD cases from China.<sup>12</sup> The patient presented with a red/brown plaque on the left arm and was successfully treated with surgical excision. O’Malley et al<sup>13</sup> presented a series of 9 cases with concurrent RDD and LCH. All except one of these cases involved lymph nodes only. The authors performed comparative genomic hybridization on 6 of the cases. They were able to identify either gains or losses in 4 of the 6 cases; however, they did not identify a consistent genetic abnormality and were not able to correlate the gains/losses to specific clinical or histopathological



**FIGURE 2.** A, Hematoxylin and eosin stain ( $\times 400$ ), showing large histiocytes with abundant cytoplasm containing viable lymphocytes. B, S-100 immunohistochemical stain ( $\times 400$ ), highlighting emperipolesis (arrow).

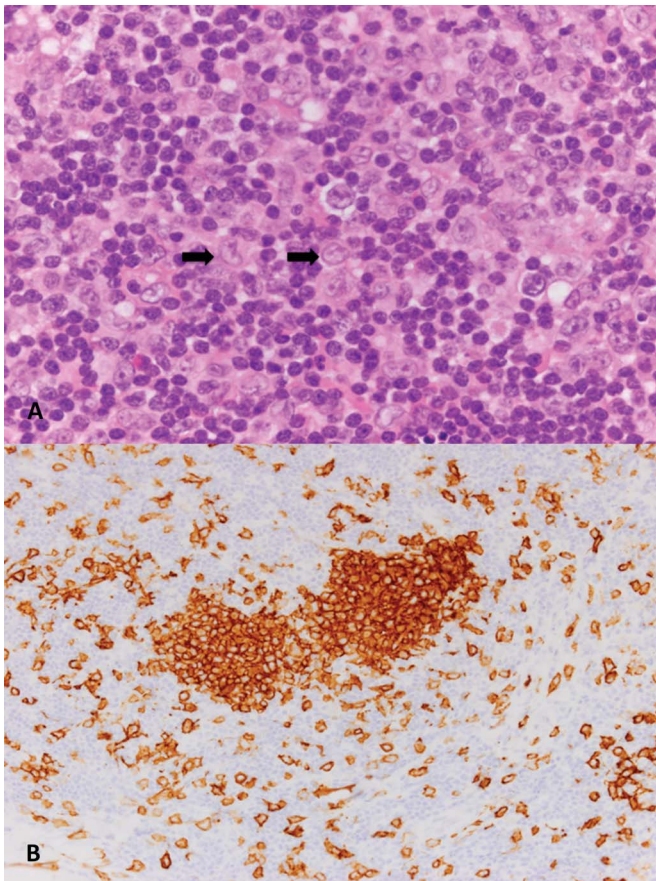
features. As with previous cases, these lesions followed a benign course clinically.

Llamas-Velasco et al<sup>11</sup> reported the first case with an aggressive clinical presentation. They identified a patient with concurrent RDD, LCH, and splenic marginal zone lymphoma. Of note, the patient presented with multiple skin lesions of both RDD and LCH but did not have any combined lesions. The patient’s disease remained stable for several years until he developed massive hepatosplenomegaly. The patient rapidly progressed and died within several days, and a premortem liver biopsy revealed a histiocytic sarcoma.

The most recent case was reported by Cohen-Barak et al<sup>9</sup> and involved a 10-year-old boy that had multifocal LCH of bone and subsequently developed RDD affecting the skin. The LCH was successfully treated with chemotherapy; however, his skin lesions worsened despite the good response of the LCH. He was started on azathioprine for treatment of cutaneous RDD, but did not have significant follow-up regarding the effectiveness of this treatment at the time of publication.

RDD is considered to be a reactive condition, which is supported by data suggesting that RDD is a polyclonal process.<sup>14</sup> A recent study suggested that RDD may represent an intermediate step between reactive inflammation and





**FIGURE 3.** A, Hematoxylin and eosin stain ( $\times 400$ ), showing mononuclear cells with reniform and coffee bean-shaped nuclei (arrows). B, CD1a immunohistochemical stain ( $\times 200$ ), showing strong positivity within focal aggregates.

neoplasia.<sup>15</sup> In contrast, there is growing evidence that LCH represents a neoplastic process, including the identification that LCH is a clonal process and the presence of BRAF<sup>V600E</sup> mutations within marrow dendritic cell progenitors in approximately half of LCH cases.<sup>16</sup>

Although the histiocytic precursors of both LCH and RDD originate in the bone marrow, a definitive mechanism linking these 2 processes has not been described. One proposed mechanism has been that concurrent LCH and RDD represent a biphenotypic presentation whereby a common precursor cell develops along 2 divergent pathways. Some support for this theory was provided in 1 case where cells displaying a transitional phenotype between RDD and LCH were identified (these cells displayed morphologic features consistent with RDD but an immunohistochemical phenotype consistent with LCH).<sup>13</sup> A second proposed mechanism posits that these combined lesions begin as a polyclonal reactive histiocytic proliferation (RDD) that secondarily develops clonality (LCH). A final proposed mechanism suggests that RDD and LCH develop concurrently because they are driven by similar cytokines. Initial studies suggested that the Langerhans cells in LCH expressed tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) with

occasional cells expressing interleukin-1 $\beta$  and reactive background cells expressing interleukin-6. All 3 cytokines were expressed by the large reactive histiocytes in RDD suggesting that TNF- $\alpha$  expression may represent a common link between the 2 conditions.<sup>17</sup> More recent data have suggested that LCH may actually be driven by interleukin-17A.<sup>16</sup>

Given the scarcity of published cases, definitive guidelines regarding the follow-up and management of these cases are lacking. It seems reasonable to combine the recommended baseline laboratory and radiographic studies for both conditions that would include complete blood count, complete metabolic profile, coagulation studies, thyroid stimulating hormone, and free T4 serum levels, morning urinalysis, including morning urine osmolality, serum protein electrophoreses, and whole-body positron emission tomography-computed tomography.<sup>18,19</sup> Fortunately, most of the reported cases, particularly the subset of cases with localized cutaneous involvement, have favorable long-term outcome with stable disease or resolution; however, 1 reported case had a fatal outcome because of progression to histiocytic sarcoma. This patient initially presented with widespread cutaneous lesions. Treatment options for localized cutaneous LCH and RDD include surgical excision, cryotherapy, intralesional corticosteroid injection, radiotherapy, dapsone, acitretin, pulsed-dye laser, and close clinical monitoring.<sup>8,12,20</sup>

Although rare, it is important to be aware of this unusual combined presentation because it requires a modified laboratory and imaging evaluation when compared with cutaneous RDD and has the potential for a more aggressive course. Future studies on these lesions should focus on gathering larger case series with long-term follow-up, so we can better understand the long-term prognosis and develop evidence-based guidelines for laboratory/imaging evaluation and treatment. As we develop a more thorough understanding of the pathogenesis of each individual disease, we may also define a definitive mechanism underlying the pathogenesis of this unique combined presentation.

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