Refractory Cutaneous Rosai-Dorfman Disease Responsive to Cryotherapy

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Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare, acquired, idiopathic, nonneoplastic histiocytosis. In many cases the skin is involved and treatment is indicated. Various treatment options have been attempted with variable success. We report a case of cutaneous Rosai-Dorfman disease (CRDD) refractory to both topical and intralesional corticosteroid therapy that showed a rapid and remarkable response to cryotherapy. These observations suggest that cryotherapy should be considered as a therapeutic option for CRDD.

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Case Report

A 50-year-old woman presented with erythematous papules on the right cheek of 4 months' duration and a plaque on her right flank of 2 months' duration. These lesions were mildly pruritic. There was no joint involvement. The patient's medical history included cardiac palpitations and hypertension. Medications included only atenolol and she reported no medical allergies. Her personal and family dermatologic history was negative. Review of systems did not reveal other symptoms.

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The authors report no conflict of interest.

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Physical examination revealed the following abnormalities: red indurated papules and plaques on the right cheek and back. There was no lymphadenopathy or hepatosplenomegaly. The initial differential diagnosis included pseudolymphoma, lupus, chronic folliculitis, morphea, and panniculitis. A biopsy specimen was obtained from the right cheek and right flank revealing a dense dermal infiltrate of large histiocytes with abundant eosinophilic cytoplasm and vesicular nuclei. Prominent lymphoid hyperplasia and emperipolesis were noted (Figures 1A and 1B).

Plasma cells were present. Immunohistochemical staining revealed that histiocytes were positive for S100 and CD68 (Figures 1C and 1D). CD1a staining was negative. These findings were consistent with Rosai-Dorfman disease (RDD).

Complete blood cell count with differential and peripheral smear were both normal and antinuclear antibody was negative. Serum protein electrophoresis revealed mild hypergammaglobulinemia. Chest x-ray was normal.

The lesions slowly became more numerous and coalesced to form confluent plaques, particularly on the right cheek. The patient found the lesions to be pruritic and aesthetically disfiguring, which resulted in her request for treatment.

Because of the indolent nature of RDD for most patients, any benefit achieved from treatment must be weighed against possible risks such as scarring and long-term complications. The patient declined surgical excision to avoid cosmetically unacceptable scarring, especially on the cheek. Radiation therapy was inappropriate because of potential long-term complications including secondary malignancies. Topical and intralesional corticosteroids were initially attempted. Betamethasone valerate cream 0.1% was applied twice daily for 2 months, and a single intralesional injection of 0.3 mL of triamcinolone acetonide (10 mg/mL) was administered to the patient. However, no notable improvement was achieved. Therefore, an effective alternative treatment was required.

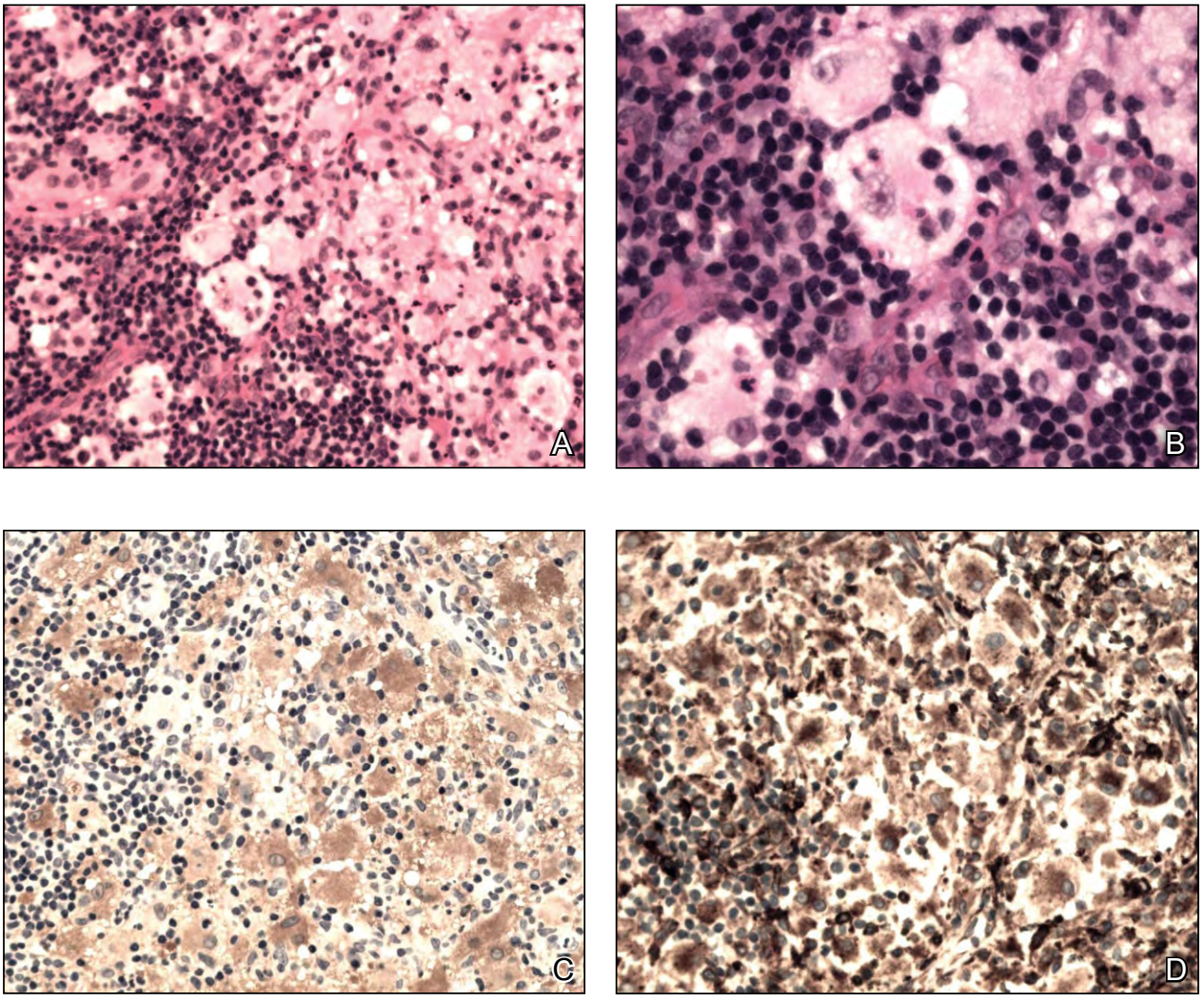

Figure 1. Histology of cutaneous Rosai-Dorfman disease demonstrated emperipolesis and prominent foamy histiocytes admixed with inflammatory cells (A)(H&E, original magnification ×20) as well as emperipolesis at high power (B)(H&E, original magnification ×40). Immunohistochemical staining revealed histiocytes positive for S100 (C) (original magnification ×20) and CD68 (D)(original magnification ×20).

Cryotherapy was attempted, first using the right mid back as a test site for 20 seconds. At reassessment 2 weeks later, the red papule on the right mid back was completely resolved. This therapy was then applied to all remaining lesions on the back and the right cheek for 20 seconds each session every 2 weeks for a total of 3 sessions. Considerable improvement on the face (Figure 2) and near complete resolution on the back was achieved. Unfortunately, some visible scarring and/or residual lesions persisted. The disease remained stable with no further development of new lesions over 12 months. Repeated serum protein electrophoresis did not show progression of the hypergammaglobulinemia.

Comment

Also known as sinus histiocytosis with massive lymphadenopathy, RDD is a rare, acquired, benign, idiopathic histiocytosis first recognized as a distinct clinical entity by Rosai and Dorfman[1] in 1969.[1-3] This disorder commonly presents with painless lymphadenopathy and also is associated with fever, leukocytosis, elevated erythrocyte sedimentation rate, and polyclonal hypergammaglobulinemia.[2,4] It is thought to have a male predominance and primarily affects children and young adults.[2,4]

Approximately 40% of patients have extranodal involvement, particularly on the skin.[3-7] Morphology of the skin lesions is variable; they may present as

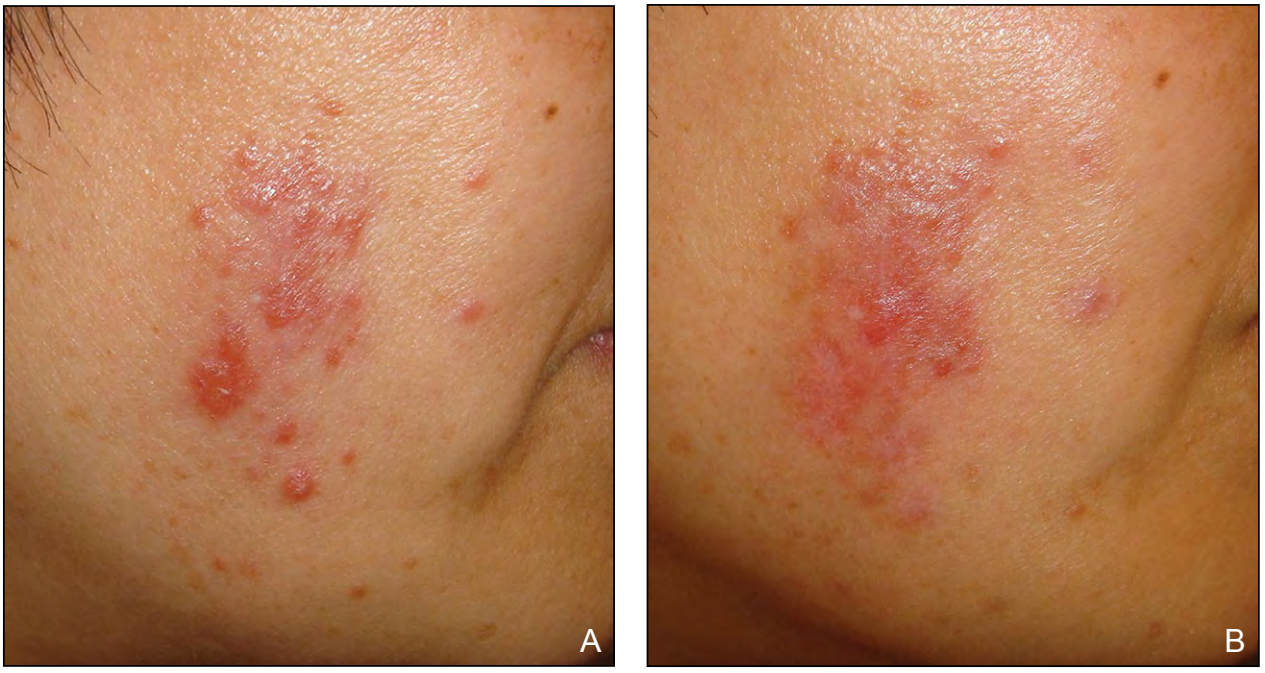

Figure 2. Red nodules on the face characteristic of cutaneous Rosai-Dorfman disease before (A) and 2 months after cryotherapy (B).

macules, plaques, papules, or nodules, ranging in color from yellow to red-brown.[4,8,9] Rosai-Dorfman disease exhibits a diverse range of clinical presentations and often is associated with immunologic abnormalities. A literature review published in 2007 suggested the etiology of RDD could be immune mediated.[2]

Most RDD patients experience a benign and self-limiting course. A small minority of patients manifest considerable systemic disease and even death. Poor prognosis has been associated with anemia; immunologic abnormalities; and dissemination to multiple organs, such as the kidneys, liver, and lower respiratory tract.[2]

Histologically, RDD is characterized by large, pale S100 positive and CD1a negative histiocytes with large vesicular nuclei. Inflammatory cells are present within the histiocytes, a process termed *emperipolesis*. A mixed inflammatory infiltrate also is demonstrated.[3,4]

Rosai-Dorfman disease involving only the skin is known as cutaneous Rosai-Dorfman disease (CRDD) and is exceedingly rare.[3,5-7] The gross and histologic morphology of the skin manifestations in classic RDD and CRDD are identical.[8] However, in contrast to RDD, CRDD usually is not associated with constitutional symptoms or laboratory abnormalities, though uveitis has been reported to be associated with CRDD.[8,9] In contrast to systemic RDD, CRDD is more common in older adults, females, and Asian populations.[3,8,9] Cutaneous Rosai-Dorfman disease usually has a limited distribution, most commonly affecting the extremities, back, and face.[3,8-10] In one study of 21 patients from Taiwan, the most common lesion was a central noduloplaque with satellite papules.[9] In another study involving 25 cases of CRDD, the most common lesions were clusters of slowly growing, discrete, erythematous to violaceous papules with or without nodules.[3] The clinical course is variable, with some cases spontaneously resolving and others persisting despite multiple treatment efforts.[9]

Various treatments of the skin manifestations of RDD and CRDD have been described with variable effectiveness including topical, intralesional, and systemic steroids[8,9,11-14]; oral isotretinoin[3,9,11]; topical retinoic acid[9]; hydroxychloroquine[11]; dapsone[9,11]; thalidomide[9,12]; antibiotics[3,8,9]; pulsed dye laser and intense pulsed light[9]; interferon[3]; cryotherapy[3,8,10,15]; superficial irradiation therapy[8,9,13]; and surgical excision.[3,8,9]

Some authors suggest that surgical excision is the most effective treatment of solitary lesions.[3,9] Other treatment modalities also have been shown to be effective in specific cases.[3,8,9,11,13,14] However, excision is not a reasonable option in cases involving multiple lesions or large lesions. Currently, a safe and effective alternative to surgical excision remains unclear.[9]

The use and efficacy of cryotherapy in CRDD is not well-established and has produced mixed results.[3,8,10] Case studies have reported that although

spontaneous resolution is the rule, cryotherapy may considerably decrease lesion size or accelerate the complete resolution of lesions.[10,15]

The authors acknowledge that spontaneous regression cannot be ruled out in this case. However, our observation further supports the administration of cryotherapy as a potentially effective therapeutic option for CRDD, particularly for cases that do not spontaneously resolve. Further trials investigating the effectiveness of cryotherapy for CRDD would be beneficial to further clarify the effectiveness of this treatment.

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