

A case of cutaneous Rosai-Dorfman disease (CRDD) with underlying calvarial involvement and absence of BRAF^{V600E} mutation

Nadine M. Kaskas, MD,^a Malan Kern, BA,^f Andrew Johnson, MD,^b Matthew P. Hughes, MD,^b Matthew Hardee, MD, PhD,^c John Day, MD,^d Murat Gokden, MD,^e Sara C. Shalin, MD, PhD,^{b,c} and Ling Gao, MD, PhD^b
Baton Rouge, Louisiana, and Little Rock, Arkansas

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Rosai-Dorfman disease (RDD) is a benign histiocytic proliferation that most commonly presents with painless bilateral lymphadenopathy and constitutional symptoms such as fever, fatigue, and night sweats.¹ RDD is considered by many to be a reaction pattern with several different manifestations, especially as clonality has not been documented to support it representing a neoplasm per se. Classic histologic features include histiocytes that are S100 protein positive, are CD1a⁻, and demonstrate emperipolesis. Cutaneous lesions can occur in about 10% of patients, however, RDD limited only to cutaneous involvement is particularly rare.^{2,3} Moreover, concomitant cutaneous RDD (CRDD) and bone RDD has rarely been reported in the English-language literature.^{4,5} Here, we presented a case of CRDD on the scalp with underlying bony involvement.

CASE REPORT

A 53-year-old African American woman presented for evaluation of asymptomatic growths on her scalp that had been progressively enlarging over a 6-month period of time. She denied any constitutional symptoms and her medical, family, and social history, medications, and allergies were

Abbreviations used:

CRDD: cutaneous Rosai-Dorfman disease
 LCH: Langerhans cell histiocytosis
 RDD: Rosai-Dorfman disease

noncontributory. Physical examination revealed a cluster of 5 erythematous to yellow nodules ranging in size from 0.5 to 1.5 cm each on the midline vertex of the scalp (Fig 1, A). No lymphadenopathy was appreciated on physical examination. Previous evaluation by an outside provider included a deep shave biopsy specimen interpreted as granulation tissue with inflammation, deemed negative for malignancy. Bacterial and fungal stains were negative. To rule out any lymphoproliferative process, a subsequent excisional biopsy specimen revealed a dense dermal infiltrate of histiocytes with abundant light eosinophilic cytoplasm and distinct nucleoli extending from the papillary to the reticular dermis (Fig 1, B and C). Foam cells, lymphoid aggregates, focally prominent plasma cells, and sparse intermixed granulocytes were noted. Immunohistochemical stains demonstrated uniform, strong positivity for S100 protein in the histiocytic cells, and highlighted

From Louisiana State University Health^a; and Departments of Dermatology,^b Radiation Oncology,^c Neurosurgery,^d and Pathology,^e and College of Medicine,^f University of Arkansas for Medical Sciences.

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Correspondence to: Ling Gao, MD, PhD, University of Arkansas for Medical Sciences, Slot 576, 4301 W Markham St, Little Rock, AR 72205. E-mail: lgao@uams.edu.

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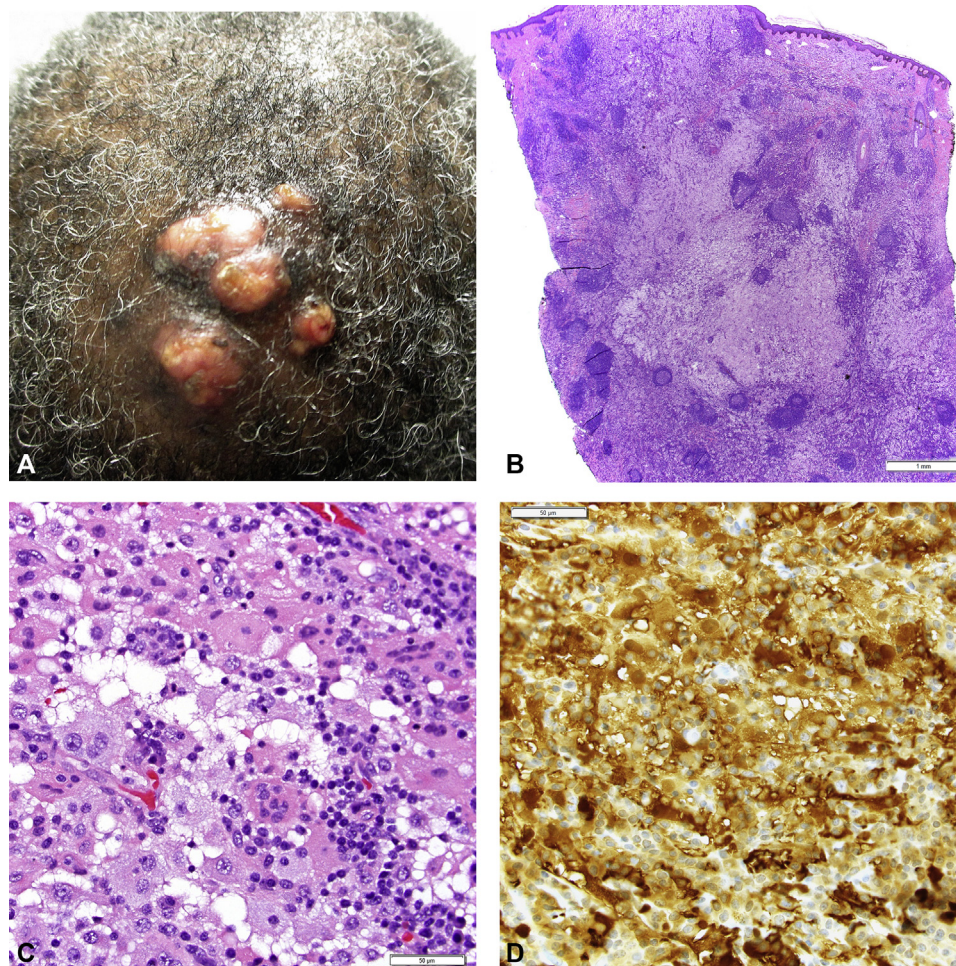


Fig 1. Cutaneous Rosai-Dorfman disease. **A**, The clinical manifestation on presentation included erythematous pustular nodules on the midline vertex of the scalp. **B**, Histologic examination revealed a histiocytic and lymphocytic infiltrate. **C**, High magnification reveals histiocytes with abundant eosinophilic to foamy cytoplasm engulfing other inflammatory cells (emperipolesis). Plasma cells are also part of the infiltrate. (**B** and **C**, Hematoxylin-eosin stain; original magnifications: **B**, $\times 20$; **C**, $\times 400$.) **D**, Numerous histiocytes demonstrating emperipolesis. (S100 stain; original magnification: $\times 40$.)

many emperipoletic histiocytes (Fig 1, D). CD1a was negative in the lesional cells. Interestingly, magnetic resonance imaging of the brain indicated the underlying bony involvement with a small focus of full-thickness calvarial erosion and no intracranial lesion was appreciated. A computed tomography scan of the neck, chest, abdomen, and pelvis was unrevealing. Lactate dehydrogenase and erythrocyte sedimentation rate were elevated. Both urine and serum protein electrophoresis revealed normal findings.

Recently, BRAF^{V600E} mutation has been detected in Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease, but not in other histiocytic disorders such as juvenile xanthogranuloma and RDD.⁶⁻⁸ However, it is unlikely the RDD cases included in the studies were cases with concurrent skin and

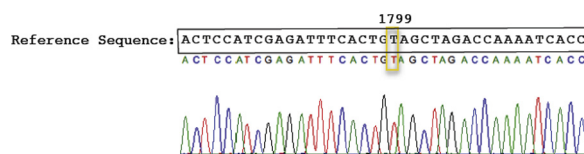


Fig 2. BRAF V600E (c. 1799 T>A) sequencing. Chromatogram represents the relevant Rosai-Dorfman sample nucleotide sequence; reference sequence represents the wild type BRAF gene (*Homo sapiens* BRAF proto-oncogene, National Center for Biotechnology Information, National Institutes of Health). Highlighted nucleotide in yellow denotes the position of interest (c. 1799) with lack of T>A nucleotide transversion.

bone involvement, simply because of the rarity of this condition. Given this unusual bony involvement in our patient, we decided to examine whether our

case harbored BRAF^{V600E} mutation. Similar to other cases of RDD, a wild type BRAF was revealed by direct DNA sequencing of extracted genomic DNA as described previously⁷ (Fig 2).

DISCUSSION

RDD limited only to the skin, referred to as “cutaneous” RDD, is a rare variant and involves a distinct demographic distribution.^{1,3} Although systemic RDD is most common in Caucasian and African American men younger than 20 years, CRDD is usually found in Caucasian and Asian women in the fifth decade of life.¹ CRDD is especially rare in African Americans, as seen in our patient.¹ The clinical presentation of CRDD varies from solitary or multiple erythematous, yellow, or brown papules, nodules, or plaques that typically involve the torso or face. CRDD presenting on the scalp is rare with only 4 cases reported.⁹⁻¹² The clinical differential diagnosis includes necrobiotic xanthogranuloma, which can present as a yellow plaque, and multicentric reticulohistiocytosis. Primary RDD of the bone is particularly uncommon. It typically affects long bones and causes lytic bone lesions.⁴ Interestingly, a few cases with RDD in both cutaneous and bony involvement have been reported.⁵ Yoon et al⁵ reported a patient with an initial bone lesion in the fibula who developed subcutaneous lesions on upper extremities several months later. Similar to our patient, 2 patients who presented with subcutaneous lesions on the scalp and underlying calvarial RDD have been reported recently^{10,13}; 1 of the patients also developed a lesion in the spine later.¹³ Although it is unlikely the cutaneous lesion was derived from RDD of the bone in our patient, it is impossible to discriminate whether cranial erosion is a result of the local destruction of CRDD or concomitant primary RDD of the bone involving the overlying skin without obtaining a sample from cranium. Nevertheless, the patient will need to be followed up closely with imaging studies to monitor the development of additional bone lesions.

Unlike some reported cases of LCH,⁶⁻⁸ there is no BRAF^{V600E} detected even though there is bony involvement in our patient, suggesting a distinct cause in CRDD as compared with LCH. The lack of BRAF^{V600E} mutation in our patient also further supports that RDD may represent a reactive, rather than neoplastic, condition, and is clinically significant as it illustrates no role for targeted therapy with BRAF/mitogen-activated protein kinase pathway inhibitors. Although the exact origin of RDD is unknown, it is postulated to reflect a hyperstimulation of humoral immunity,^{2,3,14} which is evidenced by coexistence of RDD with autoimmune disease,

hematologic malignancies, and postinfectious conditions. Histology plays an essential role in obtaining a definitive diagnosis. On low-power magnification, CRDD is recognized by a dense dermal infiltrate of foamy to pink histiocytes. The large, polygonal histiocytes have voluminous cytoplasm and vesicular nuclei. An intact cell engulfed within the cytoplasm of a histiocyte, termed “emperipolesis,” is classically identified in RDD.^{1,2} Immunophenotypically, the histiocytes in RDD express S100 protein but are negative for CD1a. These histopathologic findings and the immunophenotype are essential to differentiate RDD from LCH and malignant histiocytosis, particularly when there is bony involvement. In contrast to RDD, LCH is composed of clusters and sheets of ovoid histiocytoid cells with a reniform or coffee bean–shaped nucleus that often invade and extend into the epidermis, frequent accompanying eosinophils, and CD1a and/or Langerin protein expression in the histiocytes.

Although there is no broad consensus on best practice therapy for CRDD, a variety of therapeutic interventions have been reported, including topical and systemic corticosteroids, acyclovir, interferon, antibiotics, imatinib mesylate, retinoids, dapsone, methotrexate, thalidomide, cryotherapy, surgical excision, and radiation.^{1,3,14,15} Although some cases may persist and progress despite treatment, the prognosis is generally favorable, with many reported cases following a generally indolent course with spontaneous self-remittance within 3 years.^{1,14} After detailed review of treatment options, our patient elected for surgical excision of the lesions on the scalp and declined radiation.

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