Xanthomatous cutaneous Rosai-Dorfman disease with overlapping features of IgG4-related disease

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INTRODUCTION

Rosai-Dorfman disease (RDD) is a rare, benign non-Langerhans cell histiocytosis. Cutaneous involvement represents 10 percent of extranodal disease. RDD is characterized by S-100–positive and CD1a-negative histiocytes that exhibit emperipolesis, defined as the presence of leukocytes within the cytoplasm of histiocytes, in a background of fibrosis and a lymphoplasmacytic infiltrate. Given the potentially nonspecific clinical findings of RDD, diagnosis is strongly dependent on histopathologic identification of classic S-100 histiocytes with emperipolesis. Herein, we describe a case of cutaneous RDD with prominent xanthomatous infiltrates and overlapping features of IgG4-related disease.

Abbreviations used:

CRDD:	Cutaneous Rosai-Dorfman disease
IgG4RD:	IgG4-related disease
RD:	Rosai-Dorfman
RDD:	Rosai-Dorfman disease

CASE REPORT

A 39-year-old woman presented with a 5-month history of an asymptomatic rash on the bilateral legs. Her past medical history was significant for HIV infection with a CD4 count of 560 cells/mm^3 and an undetectable viral load. Physical examination demonstrated indurated, hyperpigmented papules and nodules that coalesced into plaques on the bilateral lower extremities (Fig 1, *A* and *B*). The clinical differential diagnosis included morphea, deep fungal infection, and atypical mycobacterial infection in the setting of HIV. Tissue cultures for bacteria, fungi, and acid-fast bacilli were obtained and were negative. Punch biopsy revealed a characteristic alternating light and dark appearance at scanning magnification due to the presence of histiocytic and lymphoplasmacytic infiltrates that spanned the dermis and the lobules of the subcutis. There was also fibrosis, lobular panniculitis with fat necrosis, and edema. Obliterative phlebitis was not identified. There were numerous dense lymphoplasmacytic aggregates with plasma cells (Fig 2, *A* and *B*) containing Russell bodies. Lipidized mononuclear cells comprised most of the histiocytic infiltrate (Fig 2, *C*). Fite-Faraco, Ziehl-Neelsen, Grocott methenamine silver, periodic acid-Schiff, Von Kossa, human herpesvirus 8, and Gram stains were negative. Kappa and lambda in situ hybridization reflected a polytypic plasmacytoid population. The IgG4/IgG ratio was 50 percent with 80 IgG4-positive cells per high-power field. The histiocytic infiltrate was diffusely positive for CD68 and negative for CD1a. Focally identified on deeper levels, there were clusters of

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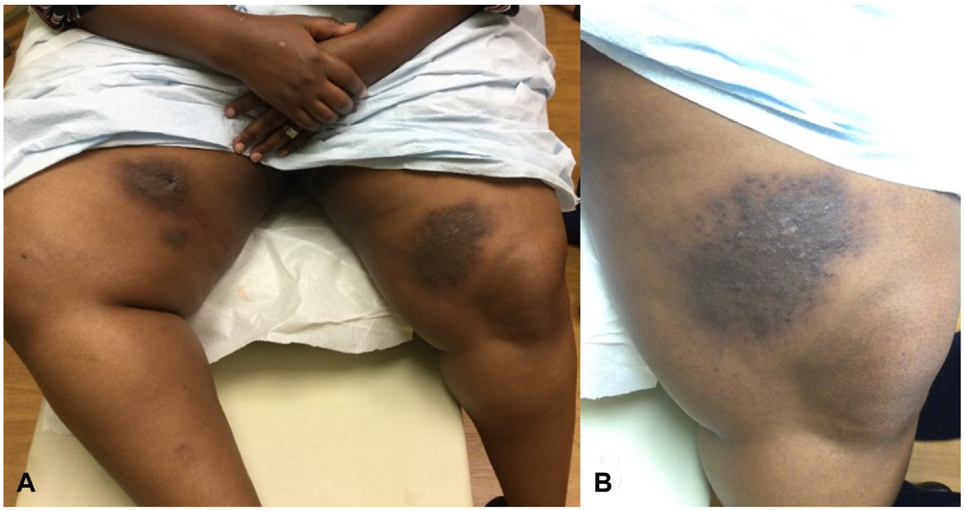

Fig 1. Rosai-Dorfman disease. (**A** and **B**): Hyperpigmented papules and nodules coalescing into plaques on the bilateral thighs.

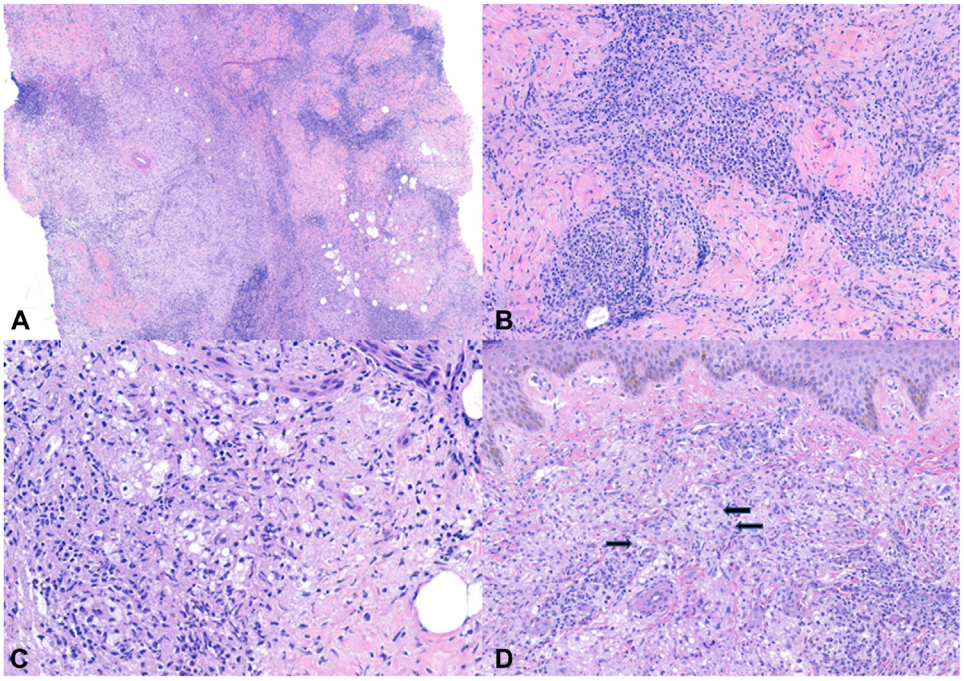

Fig 2. Rosai-Dorfman disease. Histiocytic and lymphoplasmacytic infiltrates within a fibrotic stroma (**A**: H&E, 50× magnification). Abundant plasma cellular aggregates (**B**: H&E, 200× magnification). Lipidized mononuclear cells comprise the majority of the histiocytic infiltrate (**C**: H&E, 400× magnification). Focally, there are large histiocytes (*arrows*) with large nuclei and abundant eosinophilic cytoplasm (**D**: H&E, 200× magnification).

large histiocytes with abundant eosinophilic cytoplasm (Fig 2, *D*) which contained lymphocytes and plasma cells within their cytoplasm (emperipolesis) (Fig 3, *A*). These larger histiocytes with emperipolesis were S-100 positive, but the smaller lipidized histiocytes comprising most of the infiltrate were S-100 negative (Fig 3, *B*).

DISCUSSION

RDD is a rare, benign non-Langerhans cell histiocytosis of unknown etiology. RDD is classified under the "R" group of histiocytoses according to the Histiocyte Society revised classification system.[1] RDD most commonly presents as cervical lymphadenopathy, with associated fever, night sweats, and

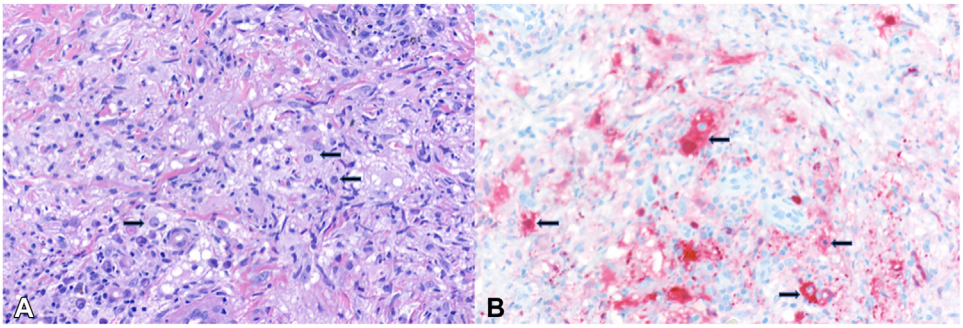

Fig 3. Rosai-Dorfman disease. Large histiocytes with large nuclei and abundant eosinophilic cytoplasm (*arrows*), some of which contained lymphocytes within their cytoplasm (**A**: H&E, 400× magnification). S-100 immunostaining demonstrates nuclear and cytoplasmic expression as well as emperipolesis within these larger histiocytes (*arrows*), but the smaller lipidized histiocytes comprising the majority of the infiltrate are S-100 negative (**B**: S-100, 400× magnification).

weight loss.[2] Laboratory alterations including elevated erythrocyte sedimentation rate, leukocytosis, polyclonal hypergammaglobulinemia, and anemia can be observed.[2] Extranodal involvement occurs in 40% of cases with cutaneous involvement representing 10% of extranodal disease.[2] Cutaneous RDD (CRDD) is a distinct entity from classic RDD and is classified under the "C" group of histiocytoses.[1] Unlike classic RDD, laboratory alterations are typically absent, and the disease tends to remain localized to the skin in CRDD.[2]

The clinical presentation of CRDD is variable. Papulonodular lesions are most common, but indurated plaques, acneiform lesions, tumor-like lesions, flat-topped papules, vesicles, and pustules have all been described.[2,3] In a case series of 25 patients with CRDD, lesions were most commonly found on the extremities and torso. However, the chest, face, and buttocks may also be involved.[3] The color ranges from violaceous to red and brown or pink.[3] On histopathology, CRDD typically involves the dermis and subcutis. It is characterized by polygonal proliferating histiocytes with a pale cytoplasm, large nuclei, and prominent nucleoli known as Rosai-Dorfman (RD) cells, surrounded by an infiltrate with lymphocytes, neutrophils, and abundant polytypic plasma cells.[3] The presence of large, pale histiocytes alternating with lymphoplasmacytic cell infiltrates give rise to the characteristic light and dark (blue) areas, respectively, at scanning magnification. Strong diffuse cytoplasmic and nuclear S-100 positivity highlights emperipolesis.[3] CD1a negativity helps differentiate RD cells from the histiocytes of Langerhans cell histiocytosis and indeterminate cell histiocytosis.[2] Fibrosis is common, and the presence of histiocytes within lymphatic and vascular spaces is another helpful diagnostic clue.[3]

The diagnosis was complicated by the presence of a dermal xanthomatous infiltrate and features of IgG4-related disease (IgG4RD). Given the dense infiltrate of foamy histiocytes and the plasmacellular aggregates, infectious etiologies producing parasitized histiocytes were considered and excluded. Von Kossa stain was utilized to exclude cutaneous malakoplakia, which demonstrates laminated concentric calcifications (Michaelis-Gutmann bodies) within lipidized histiocytes (von Hansemann cells). The presence of numerous S-100–negative lipidized histiocytes within the inflammatory infiltrate initially obscured the classic RD cells. The xanthomatous change exhibited here is an atypical presentation of CRRD that has rarely been described.[3-6] In this context, xanthohistiocytic diseases—such as necrobiotic xanthrogranuloma, xanthoma disseminatum, xanthomas associated with hyperlipidemia, Langerhans cell histiocytosis, and Erdheim-Chester disease—should be excluded.[2,4] In this case, the focal presence of S-100–positive histiocytes, emperipolesis, and negative staining for CD1a aided in differential diagnosis.[4]

It has been suggested that xanthomatous change may reflect a degenerative process within RD cells. Wang et al[7] observed a "transition zone" of regressing histiocytes that exhibited xanthomatous change in a 30-month-old lesion. The authors suggested that an area of granular, S-100–positive RD cells represented degenerating cells because it spanned a xanthomatous area and a mixed focus, both of which contained typical RD cells. A similar finding was observed by Quaglino et al[4] in a longstanding lesion in another patient with multiple lesions of varying ages. A 1-year-old lesion on the patient's left arm exhibited characteristic findings of CRRD—namely a dense nodular and diffuse dermal infiltrate

Table I. Previously reported cases of xanthomatous cutaneous Rosai-Dorfman disease

Study	Study type	Number of patients	Age of lesion(s) when xanthomatous change noted	Pertinent histopathologic indings
Wang et al[5]	Case series	6	30 mo	One patient had an infiltrate consisting of a large number of S-100−negative lipidized histiocytes with a transition zone of eosinophilic S-100−positive degenerating RD cells separating the xanthomatous infiltrate from a nodular infiltrate containing classic S-100−positive RD cells
Kong et al[3]	Case series	25	Unknown	Two cases exhibited xanthomatous S-100−negative, CD68-positive macrophages
Quaglino et al[4]	Case report	1	10 y	Overwhelming presence of foamy histiocytes with scattered S-100−positive RD cells within a long-standing nodule
Pitamber et al[6]	Case series	5	24 mo	One patient demonstrated aggregates of xanthomatous histiocytes within follow-up biopsies obtained 6 and 12 mo after initial presentation

RD, Rosai-Dorfman.

consisting of sheets of S-100−positive RD cells with prominent emperipolesis. Conversely, the oldest lesion, which had been present for 10 years, was characterized by an abundance of large, round lipidized histiocytes with indistinct margins among which were interspersed occasional S-100−positive RD cells. Kong et al[3] reported 2 cases of CRDD exhibiting aggregation of foamy histiocytes, but they did not report the age of these lesions. Finally, Pitamber and Grayson[6] reported the appearance of aggregates of xanthomatous macrophages present on follow-up biopsies at 6 and 12 months after initial presentation in a patient who had an 18-month-old hyperpigmented plaque on the right groin. A list of previously reported cases of xanthomatous CRDD can be found in Table I. The self-limited nature of RDD and the observation of xanthomatous changes in other histiocytic disorders also support the idea of a degenerative or regressive phenomenon. Xanthomatous infiltrates seemed to appear more rapidly in the patient presented here (5 months after onset) than in previously reported cases.

IgG4RD was considered given the presence of stromal fibrosis, prominent lymphoplasmascytic infiltrates, presence of 80 IgG4-positive cells per high power field and an IgG4/IgG ratio of 50 percent. IgG4RD is characterized histopathologically by a triad of dense lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis.[8] Other features that support the diagnosis of IgG4RD include eosinophilic infiltrates, an abundance of IgG4-positive plasma cells, an increased ratio of IgG4 to IgG, and elevated serum levels of IgG4.[7,8] However, RDD and IgG4RD can exhibit overlapping clinical and histopathologic features. The presence of IgG4-expressing plasma cells has been shown to be comparable between RDD and IgG4RD, and this can complicate the diagnosis initially.[7,9] So too can the ratio of IgG4 to IgG expression, which can be elevated in RDD. An IgG4/IgG ratio >40 percent has previously been described as a criterion for the diagnosis of IgG4RD.[8] However, in 1 series, IgG4/IgG ratios of >40 percent were found in 41.2 percent of patients with RDD.[7] In another series of patients with CRDD, the mean IgG4/IgG ratio was found to be 34 percent, with 1 patient exhibiting a ratio of 51 percent.[9] Serum IgG4 concentrations are usually elevated in IgG4RD, but this finding is nonspecific and can be seen in RDD as well.[7,8] Conversely, up to 40% of patients with biopsy proven IgG4RD can have normal serum IgG4 levels.[8] Wang et al[7] demonstrated that the presence of eosinophilic infiltrates, obliterative phlebitis, and/or storiform fibrosis was the findings most helpful in distinguishing IgG4RD from RDD. In the patient presented here, eosinophilic infiltrates and obliterative phlebitis were not identified. Additionally, while there was fibrosis, it was not storiform. Serum IgG4 levels were not obtained. Because many of the

histopathologic features of IgG4RD overlap with RDD, diagnosis requires clinical, histopathologic, and serological correlation. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4RD (ACR/EULAR IgG4RD criteria) integrates these 3 domains and allows for diagnosis of patients with IgG4RD with an 82% to 89% reported sensitivity.[10] According to the ACR/EULAR IgG4RD criteria, the presence of S-100–positive histiocytes allows exclusion of IgG4RD.[10] To our knowledge, this represents the first reported case of CRDD with both xanthomatous features and features of IgG4RD within the same biopsy specimen.

Management in RDD is individualized. Observation is often an appropriate first step as up to 50% of patients will achieve spontaneous remission.[2] Alternative treatments that have been described include surgical excision, corticosteroids, sirolimus, radiotherapy, chemotherapy, and targeted immunotherapy.[2] Prognosis is generally favorable, especially for cutaneous disease.[2] Our patient was subsequently lost to follow-up, and despite multiple attempts, we were unable to contact her to assess the progression of her disease.

Conflicts of interest

None disclosed.

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