

# Rosai-Dorfman Disease with Primary Cutaneous Manifestations— A Case Report

H Y Huang,\*<sup>MD</sup>, C L Yang,\*\*<sup>MD</sup>, W J Chen,\*\*<sup>MD</sup>

## Abstract

*Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is a benign systemic proliferative disorder of histiocytes resembling the sinus histiocytes of lymph nodes. The typical clinical features of this disease include bilateral painless lymphadenopathy, fever, and polyclonal hyperglobulinaemia. The condition may present with extranodal involvement in 43% of cases, and cutaneous lesions are the most common form of extranodal diseases. However, purely cutaneous Rosai-Dorfman diseases occur rarely, particularly among Orientals. We describe a 48-year-old female presenting with an erythematous dermal nodule on the abdomen. Complete physical examinations and laboratory tests demonstrated that the lesion was only limited to the skin. Histologically, the lesion consisted of proliferative large histiocytes frequently exhibiting emperipolesis. Immunohistochemical and ultrastructural studies were also performed. The former showed characteristic cytoplasmic staining of histiocytes against S-100 protein. Because cutaneous Rosai-Dorfman disease may be unfamiliar to most pathologists, cases limited to the skin are probably underestimated.*

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## Introduction

In 1969, Rosai and Dorfman first described a newly recognised benign systemic histioproliiferative disease characterised clinically by bilateral striking cervical lymphadenopathy, fever, leukocytosis, and pathologically by enlarged lymph nodal sinuses containing large histiocytes with intact phagocytosed lymphocytes (emperipolesis). They dubbed the entity "sinus histiocytosis with massive lymphadenopathy" (SHML or Rosai-Dorfman disease).<sup>1-3</sup> Since its original documentation, Rosai-Dorfman disease has become a well-established clinicopathological entity. Patients tend to be young at onset, have bilateral painless cervical massive lymphadenopathy, and usually have a protracted uncomplicated clinical course, despite various therapeutic interventions. Approximately half (43%) of the patients have concurrent extranodal involvement, most commonly on the skin, upper airway, and salivary glands.<sup>2,3</sup> Cutaneous lesions are the common form of extranodal diseases, but cases presenting as purely cutaneous lesions without nodal or other extranodal involvement are quite rare,<sup>4-9</sup> especially among Orientals. Only one Asian patient has been recorded.<sup>7</sup> The diagnosis is based upon the proliferation of large pale or foamy histiocytes exhibit-

ing enlarged vesicular nuclei, prominent nucleoli, and distinctive lymphophagocytosis or emperipolesis. The S-100 protein immunophenotype is useful in confirming the disease entity.<sup>10,11</sup>

## Case Report

An otherwise healthy 48-year-old woman complained of an erythematous indurated dermal nodule, measuring 2.0 x 2.0 cm, on the left lateral aspect of the abdomen (Fig. 1a). A thorough physical examination was normal. There was no lymphadenopathy, and neither liver nor spleen enlargement was noted. The presumptive diagnosis made by the dermatologist was a skin appendage tumour. Laboratory tests were all within normal limits, including erythrocyte sedimentation rate, complete blood count, antinuclear antibodies, rheumatoid factors, immunoelectrophoresis, and T-cell subset analysis (T4/T8 ratio). In addition, chest X-ray demonstrated no evidence of enlarged lymph nodes. The patient received incisional biopsy without other treatment and was quite well at the latest follow-up one year later.

Sections from skin biopsy were routinely processed and stained with haematoxylin and eosin, periodic acid-Schiff (PAS) and Fite stains. Immunohistochemical stud-

\* Chief Resident

\*\*\* Director

Department of Pathology

\*\* Chief Resident

Department of Dermatology

Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Address for Reprints: Dr Wei-jen Chen, Department of Pathology, Chang Gung Memorial Hospital, 123 Ta-Pei Road, Niao-Sung, Kaohsiung, Taiwan, ROC.

ies were performed with peroxidase-antiperoxidase staining procedure,<sup>10,11</sup> employing primary antibodies against S-100, lysozyme, alpha-1 antitrypsin (AAT), alpha-1 antichymotrypsin (AACT), L-26, UCHL-1, Ki-1 (CD30), and  $\kappa$  and  $\lambda$  light chains. For electron-microscopic study, tissue was recovered from the formaldehyde-fixed tissue, postfixed in 1% osmium tetroxide, dehydrated in graded ethanols, and embedded in epoxy resin (Epon). Ultrathin sections were stained with uranyl acetate-lead citrate, and then examined under electron microscope (Hitachi H-600).

Routine histologic examination of the lesion revealed that in the deep reticular dermis a nodular growth of polymorphic inflammatory cells composed mainly of proliferative large histiocytes, lymphocytes and plasma cells. The overlying epidermis and superficial dermis were intact. The most conspicuous feature was the proliferative large histiocytes which occupied the central portion of the lesion and imparted a moth-eaten appearance on low-powered magnification (Fig. 1b). At the periphery of the lesions were nodular lymphoid aggregates and the thick-walled venules possessing swollen endothelial cells surrounded by a cuff of lymphoplasmacytic cells (Fig. 2). The stromal fibrosis was moderate in degree and more prominent at the periphery.

At higher magnification, the proliferative histiocytes exhibited enlarged vesicular nuclei, prominent eosinophilic nucleoli, and abundant acidophilic or pale cytoplasm with feathery or indistinct cell borders. The phenomenon of emperipolesis was ubiquitously seen in this lesion, which exhibited presence of intact lymphocytes, plasma cells, and occasional neutrophils within the cytoplasm of large histiocytes (Fig. 3). Occasionally, there were scattered binucleated histiocytes and Touton giant cells, intermixed with lymphocytes, mature plasma cells, and even neutrophils. Russell bodies can be noted in the cytoplasm of some plasma cells.



Fig. 1a. The photograph showing an indurated erythematous dermal nodule on the lateral aspect of the abdomen.

The periodic acid-Schiff (PAS) and Fite stains were both negative.

The results of immunohistochemical studies are summarised in Table I and detailed as follows:

Strong nuclear and cytoplasmic staining was noted in

TABLE I: SUMMARY OF IMMUNOHISTOCHEMICAL STUDIES

	Large histiocytes	Other inflammatory cells
S-100	cytoplasm: +++ nucleus: occasionally +	(-), including ingested lymphocytes and plasma cells
AAT	cytoplasm: ++	(-)
AACT	cytoplasm: ++	(-)
Lysozyme	cytoplasm: ++	(-)
Ki-1	(-)	(-)
$\kappa$ light chain	(-)	++ in plasma cells
$\lambda$ light chain	(-)	++ in plasma cells
L-26	(-)	++ in lymphocytes
UCHL-1	(-)	++ in lymphocytes

+++ : strongly positive; ++ : focally positive; + : weakly positive; (-) : negative



Fig. 1b. Whole mount of the skin biopsy specimen revealing nodular infiltrate involving the deep reticular dermis with occasional lymphoid aggregates or follicles, more prominent at the periphery.

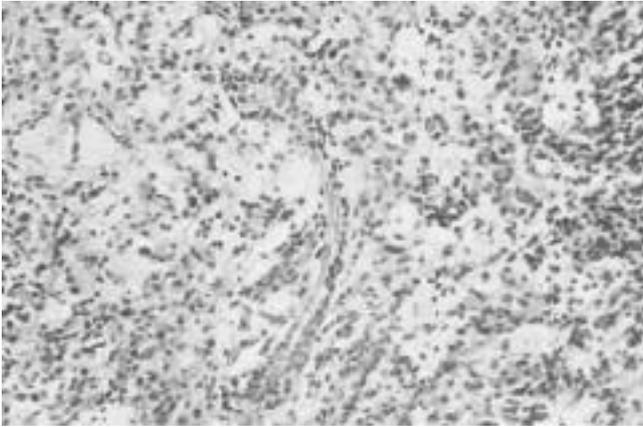


Fig. 2. On higher magnification, high endothelial venules with swollen endothelium were cuffed by lymphocytes and plasma cells (H & E x 200).

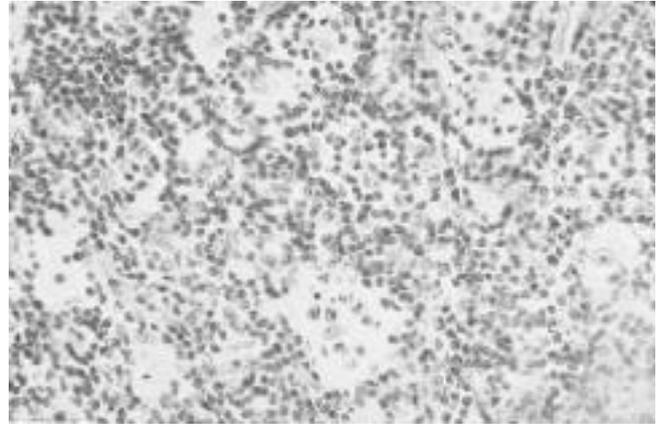


Fig. 3. High-power view demonstrating emperipolesis of histiocytes characterized by large vesicular nuclei and prominent nucleoli (H & E x 400).

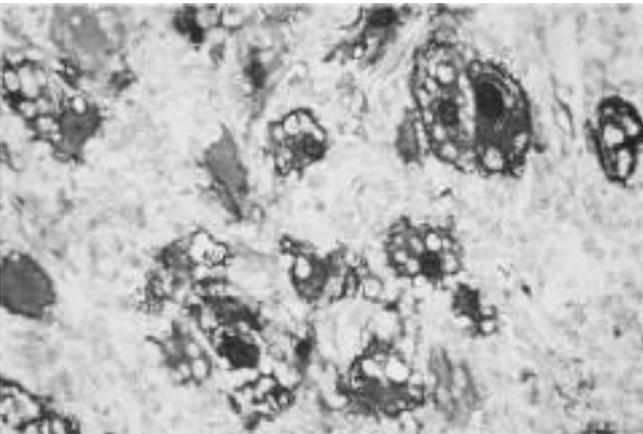


Fig. 4. Immunoperoxidase stain for S-100 revealing strong nuclear and cytoplasmic staining within histiocytes, whereas the ingested inflammatory cells remained unstained (labeled streptavidin biotin-peroxidase stain x 400).

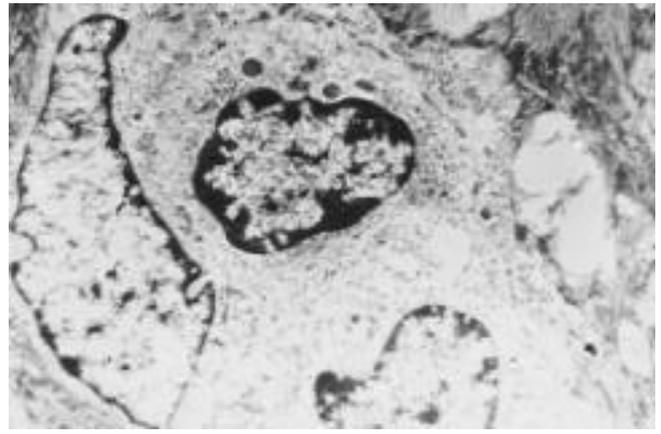


Fig. 5. Electron microscopy demonstrating a large histiocyte exhibiting emperipolesis with lymphocytes and plasma cells in the cytoplasm. Prominent extracellular collagen fibrils and cytoplasmic lipid are noted as well (uranyl acetate-lead citrate stain x 200).

the proliferative histiocytes with the S-100 protein, which easily highlighted the phenomenon of emperipolesis because of the negative staining of ingested lymphoplasmacytic cells (Fig. 4). In addition, other histiocytic markers, including lysozyme, alpha-1-antichymotrypsin (AACT), and alpha-1-antitrypsin (AAT) revealed positive reactivity within the cytoplasm of histiocytes. Positive reactivity for  $\kappa$  and  $\lambda$  light chains were demonstrated in the background plasma cells. Besides, L-26 and UCHL-1 positive lymphocytes were noted scattered in the lymphoid aggregates. Nonetheless, the reactivity for Ki-1 (CD30) was negative. This finding is in contrast to some previous reports.

Electron-microscopically, the most conspicuous element of the inflammatory infiltrate was the proliferative histiocytes which exhibited vesicular nuclei with faintly-distributed chromatin, focally indentated nuclear contour, and prominent nucleoli (Fig. 5). Within the abundant cytoplasm there were fat droplets, occasional lysosomes, dilated rough endoplasmic reticulum associated with Golgi apparatus, and more significantly various stages of emperipolesis, from envelopment of lympho-

plasmacytic cell by filiform processes of histiocytes to total encasement of these inflammatory cells within the histiocytic cytoplasm. Also noteworthy was that extracellular collagen fibrils were more prominent than those of nodal forms found in previous electron-microscopic study. In addition, neither Birbeck's granule or responsible microorganism was seen after thorough search.

## Discussion

Since the original description, Rosai-Dorfman disease has become a rare but distinct clinicopathological entity of idiopathic proliferation of histiocytes. It is currently defined by its diagnostic histopathological features, specifically the unique histiocytes. These cells are large and contain vesicular nuclei, delicate nuclear membranes, prominent nucleoli, and voluminous pale cytoplasm exhibiting lymphophagocytosis (emperipolesis).<sup>1-3</sup> People of all ages can be affected, but 80% of the patients are 20 years or younger at onset. Most patients are characterised by bilateral, painless cervical lymphadenopathy with or without constitutional manifestations and abnormalities such as anaemia, leukocytosis, polyclonal

hypergammaglobulinaemia, raised erythrocyte sedimentation rate (ESR), and even aberrant CD4/CD8 ratio.<sup>1-3</sup>

Because of gradual awareness of this disease entity, more and more extranodal cases with or without nodal involvement had been documented. To date, extranodal Rosai-Dorfman diseases are still on the rise and accounted for approximately 43% of 600 registry cases, which manifested at least one site of extranodal involvement.<sup>3</sup> Moreover, extranodal diseases may be the initial and sole manifestation of the disorder, making the eponym Rosai-Dorfman disease more appropriate than the original term "sinus histiocytosis with massive lymphadenopathy". The most common sites of extranodal diseases are the upper respiratory tract, skin, salivary gland, and bone, followed by the genitourinary system, oral cavity, and soft tissue.<sup>2,3</sup>

Despite common cutaneous involvement of extranodal cases, purely cutaneous Rosai-Dorfman diseases are indeed quite rare, particularly among Orientals, and often assume a spontaneously involuting course.<sup>4-9</sup> Previous reports on cutaneous manifestations of Rosai-Dorfman disease by Thawerani et al<sup>4</sup> and Chu and LeBoit<sup>8</sup> revealed a wide range of clinical presentations, such as exfoliate dermatitis, scaly erythematous lesions mimicking psoriasis, and pinhead-sized papules. Herein, we report a purely cutaneous Rosai-Dorfman disease in a middle-aged woman presenting as an erythematous dermal nodule on the abdomen, mimicking a skin appendage tumour but devoid of any constitutional symptoms or other systemic involvement.

Histologically, the skin biopsy specimen revealed an intradermal nodular growth of polymorphic inflammatory infiltrates with proliferative large histiocytes occupying the central portion and intermixed lymphocytes, plasma cells, and even neutrophils. The phenomenon of lymphophagocytosis was ubiquitous in our case. This finding is different from previous reports indicating that emperipolesis is often inconspicuous and stromal fibrosis more prominent in extranodal forms. Overall, the lesion recapitulated the nodal form of Rosai-Dorfman disease. Lymphoid aggregates were also noted at the periphery, but proliferative histiocytes within dilated venules were not found.

With respect to emperipolesis, it had been documented to be mediated by Fc receptor-bearing lymphocytes<sup>12</sup> and could be easily demonstrated by a strong positive reactivity for S-100 protein in the histiocytes, a unique feature of much aid in establishing the diagnosis in equivocal extranodal cases. In our case, other histiocytic markers, including lysozyme, alpha-1-antitrypsin, and alpha-1-antichymotrypsin all showed positive stainings within the cytoplasm of the histiocytes, consistent with previous reports.<sup>10,11</sup> In addition, polyclonal nature of the plasma cells and mixed population of lymphocytes

with T and B immunophenotypes could be unravelled by positive reactivity against both  $\kappa$  and  $\lambda$  light chains and UCHL-1 and L-26 antibodies, respectively. Nonetheless, Ki-1 (CD30), a marker indicative of activation antigen, was negative in our case, in contrast to some previous experiences.<sup>11</sup>

Recently, Perrin et al<sup>6</sup> reported a case of purely cutaneous Rosai-Dorfman disease to be positive for KP-1 (CD68), CD11c, Factor XIIIa, and even CD1a. The latter was a dendritic/Langerhans cell marker and probably negative in most published literatures.<sup>10,11</sup>

To date, most authors speculated that the histiocytes of Rosai-Dorfman disease were probably derived from circulating monocytes and a sort of distinctive activated histiocytes with co-expression of partial immunophenotypic characters of both monocyte/macrophage system and dendritic/Langerhans cell families.<sup>3,10</sup> Our own electron-microscopic observation was by and large consistent with previous studies performed in nodal forms with the exception of more prominent extracellular collagen fibrils.<sup>13</sup> A negative finding of significance was the absence of Birbeck's granules; this practically ruled out the possibility that Rosai-Dorfman disease belongs to a variant of Langerhans cell histiocytosis. Also consequential was failure to identify microorganisms such as viral particles or bacteria; nonetheless, we are aware that this observation does not necessarily exclude an infectious aetiology completely, because investigations demonstrating sporadic harbouring of Epstein-Barr virus (EBV) or human herpes virus 6 (HHV-6) genomes within the histiocytes by *in situ* hybridisation have been documented.<sup>3,13,14</sup>

On morphological ground, recognition of cutaneous Rosai-Dorfman disease should consider a variety of diseases in the differential diagnosis, including eruptive xanthoma, Tangier disease, Langerhans cell histiocytosis, reticulohistiocytoma, juvenile xanthogranuloma, lepraematous leprosy, Hodgkin's lymphoma, malignant histiocytosis, as well as inflammatory pseudotumour.<sup>3-5,15,16</sup> Since that the therapeutic schemes vary considerably among the aforementioned reactive or neoplastic cutaneous diseases and that Rosai-Dorfman diseases limited to the skin, as previous literature indicated, almost involute spontaneously, the value of accurate diagnosis of cutaneous Rosai-Dorfman diseases cannot be overemphasised for lack of time-honoured treatment other than removal of the lesion.<sup>4-9</sup>

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