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CLINICAL REPORT

Cutaneous Rosai-Dorfman Disease: Histopathological Presentation as Inflammatory Pseudotumor. A Literature Review

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Purely cutaneous Rosai-Dorfman disease is exceptional. The disease is characterized histologically by large, proliferating histiocytes exhibiting inflammatory cells within their cytoplasm (emperipolesis). We present here a case of purely cutaneous generalized disease in which the routine histopathology was suggestive of an inflammatory pseudotumor. Positivity for S-100 protein, α1-antitrypsin, α1-antichymotrypsin, lysozyme, Mac387 and CD68 proteins, and negativity for CD1a protein confirmed the diagnosis of Rosai-Dorfman disease. The rarity of this case lies in the presence of conspicuous inflammatory pseudotumor-like histopathologic changes, masking an otherwise typical sinus histiocytosis cell infiltrate. This unusual presentation of the disease requires a high index of suspicion by clinicians and pathologists. ***Key words: cutaneous Rosai-Dorfman disease; inflammatory pseudotumor; S-100 protein.***

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Rosai-Dorfman disease (RDD) (sinus histiocytosis with massive lymphadenopathy) strictly confined to the skin is rare (26 published cases). Reported cases (1–23) to date suggest that when RDD is clinically limited to the skin, it follows a benign course, with only a small risk of systemic disease. We report on a patient who developed purely cutaneous generalized RDD. The routine histopathology was suggestive of an inflammatory pseudotumor, a benign fibroinflammatory tumor involving deep soft tissues, and rarely the skin (24). The clinical presentation, however, was atypical for inflammatory pseudotumor, which usually presents in the skin as a solitary, discrete, flesh-colored, usually asymptomatic nodule (24). The histopathology of inflammatory pseudotumor shows a circumscribed nodular mixed cell infiltrate with plasma cells, lymphocytes, eosinophils and neutrophils, and variable amounts of sclerosis. Positivity for S-100 protein is exceptional (24). In contrast to RDD, inflammatory pseudotumor never metastasizes, and is not associated with systemic involvement. Most cases of inflammatory pseudotumor have been treated with local excision.

The histopathologic differential diagnosis and management of this case are discussed, and reported cases of cutaneous RDD are reviewed.

CASE REPORT

A 41-year-old Haitian female presented with an acute onset of multiple cutaneous nodules over the trunk, buttocks, thighs, groin and popliteal fossae. The patient did not have a recent history of infection, vaccination, trauma, insect bites or drug intake. On physical examination, approximately 15 firm brownish, variably tender, occasionally lobulated, fixed, 1–15 cm nodules were noted (Fig. 1). There was no lymphadenopathy or hepatosplenomegaly. Over the following 3 years the lesions enlarged and increased in number. A laboratory work-up revealed mild normocytic anemia, decreased C3 and C4, and mildly elevated erythrocyte sedimentation rate. The T4/T8 ratio was within normal limits, and a syphilis test proved non-reactive. A total body CT scan, tuberculosis and HIV tests were negative. The lesions did not respond to intralesional corticosteroids or a 3-month course of thalidomide (50 mg/day). Many painful lesions were excised.

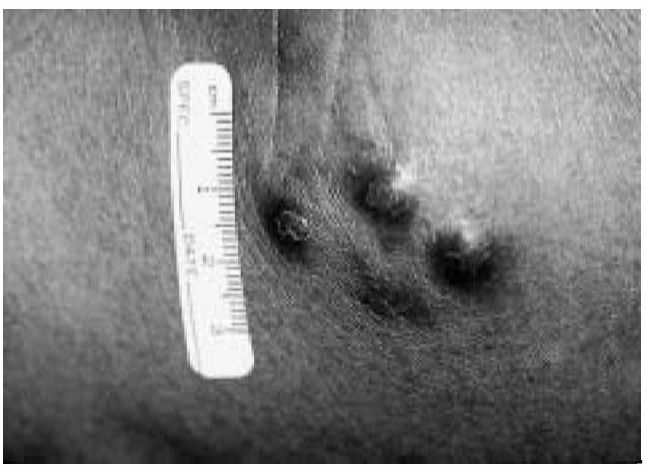

Fig. 1. Grouped hyperpigmented, firm, fixed cutaneous nodules on the back.

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Several biopsies were taken at presentation and follow-up visits. Hematoxylin-eosin stain (Figs. 2, 3) and stains for vimentin, muscle-specific actin and CD68 showed a myofibroblastic/histiocytic cell population associated with a diffuse and florid mixed inflammatory cell infiltrate of neutrophils, plasma cells and lymphocytes extending from the reticular dermis to the subcutis. The epidermis was intact. The lesions formed a focal multinodular pattern, and some nodules showed central accumulation of neutrophils. Occasional lymphoid follicle formation was seen. Large histiocytes with abundant cytoplasm were positive for S-100 (Fig. 4), α1-antitrypsin, α1-antichymotrypsin, lysozyme, Mac387 and CD68 proteins, and negative for CD1a protein. Emperipolesis was subtle on hematoxylin-eosin stain (Fig. 2) but could be clearly visualized on S-100 protein stain (Fig. 4). Only small foci in the histologic specimens were diagnostic of RDD as a result of extensive lymphoplasmacytic infiltrate and sclerosis. Histiocytes and lymphocytes were identified within vascular spaces. Special stains for bacteria and fungi were negative.

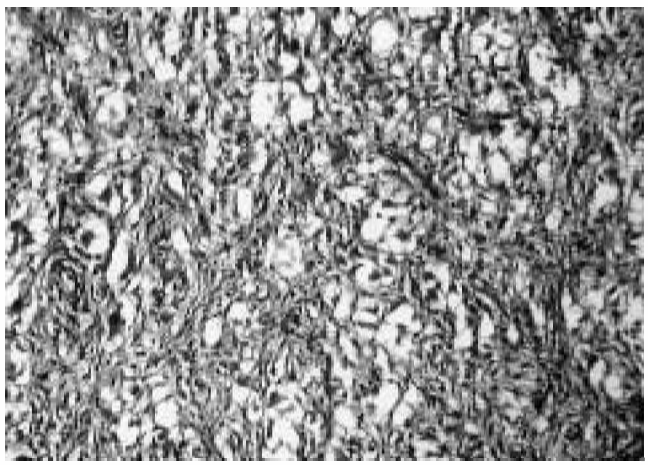

Fig. 2. Histopathologic section demonstrating a myofibroblastic/histiocytic cell population admixed with an inflammatory cell infiltrate. Lymphophagocytosis (emperipolesis) is subtle. (H&E-stain, original magnification ×40).

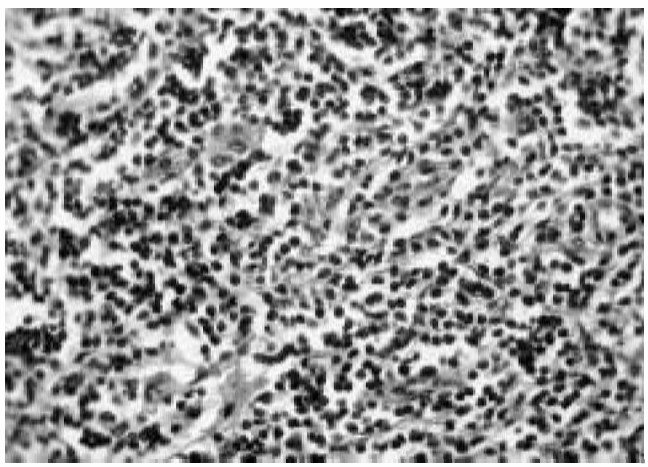

Fig. 3. Histopathologic section demonstrating a florid mixed inflammatory infiltrate consisting of neutrophils, plasma cells and lymphocytes (H&E-stain, original magnification ×20).

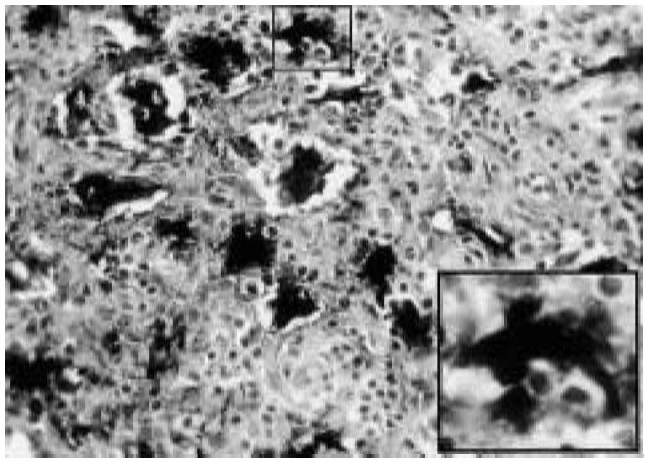

Fig. 4. Histopathologic section stained for S-100 protein. The histiocytes show strong nuclear and cytoplasmic staining. The pattern of alternating dark and brown areas is characteristically seen in cutaneous Rosai-Dorfman disease. The inset demonstrates lymphocytes within the cytoplasm of a histiocyte (emperipolesis). The lymphocytes remain unstained, and are surrounded by a clear halo (original magnification ×40).

DISCUSSION

The skin is the most common extranodal site in RDD (6). Although cutaneous involvement in RDD is common, RDD disease strictly confined to the skin has been reported in only 26 cases (1–23). When compared to nodal RDD, cutaneous RDD affects older people (median age 48 years, age range 15 to 77 years) with a preponderance of cases among white females (69.2%) (Table I). The lesions can be either solitary or multifocal, and run a variable clinical course. An association with herpes virus infection (10), Epstein-Barr virus (EBV) infection (2), varicella (12) and herpes zoster (19) has been reported.

Constant histologic features of cutaneous RDD include (6): (a) diffuse or nodular infiltrates of histiocytes with abundant cytoplasm and feathery borders, medium to large, round vesicular nuclei, and small nucleoli, (b) emperipolesis, (c) thick-walled venules surrounded by cuffs of plasma cells, more prominent at the periphery of the lesions, (d) lymphoid aggregates and germinal centers more prominent at the periphery of the lesions, and (e) histiocytes within dilated lymphatic spaces.

Although the histopathology of cutaneous RDD simulates nodal disease, the histologic hallmarks of the disease are less obvious than those seen in the lymph nodes (4, 22). Emperipolesis may be less conspicuous, the histiocytes being frequently spindled, arranged in a storiform pattern, and associated with fibrosis.

Table I. *Reported cases of cutaneous Rosai-Dorfman disease*

Ref.	Year	Cases	Age/Sex/Race	Skin lesions/anatomic site	Other disease	Evolution
1	1978	1	48/M/W	Solitary nodule (shoulder)		?
2	1987	1	15/F/B	Multiple nodules (trunk, arms, helix)	EBV	Exacerbation/remission
3	1987	1	45/F/W	Erythematous plaque (scapula)		Surgical removal
4	1988	1	48/M/Lebanese	Erythematous/xanthomatous papules (face, neck, legs)		Cure with thalidomide
5	1992	1	40/F/W?	Nodule (tragus)		Surgical removal
6	1992	3	59/F/W?	Erythematous papular eruption		
			32/M/W	Crusted nodule (scalp)		Surgical removal
			64/F/W	Red-orange papules (face, chest)		Chronic evolution (12 years)
7	1993	1	53/?	Red-brown papules (trunk, extremities)		Partial regression (3 years)
8	1994	1	34/M/W?	Painless breast mass		Surgical removal
9	1995	2	49/F	Tender red-violaceous nodule, satellite papules (thigh)	NIDDM hypothyroidism	Spontaneous resolution
			60/F	Tender red-violaceous		Spontaneous resolution nodule (leg)
10	1995	1	65/F/W	Red papules, nodules (back)	HSV	Spontaneous resolution (9 months)
11	1996	1	38/F/W	Red-brown papules, nodules (nose, back, extremities)		Cure with radiation
12	1997	1	16/F/B	Flesh-colored papules, nodules at varicella scars (chest)	Varicella	?
13	1997	1	35/F	Breast tumor		Recurrence
14	1997	1	44/M	Granuloma annulare-like plaques and subcutaneous nodules (face, neck, extremities)		Response to prednisone and chemotherapy
15	1998	1	15/F/W?	Tender enlarging mass (chest)		Surgical removal
16	1998	1	36/F/Indian	Indurated plaque (thigh)		Chronic evolution
17	1998	1	48/F/A	Indurated nodule (abdomen)		Incisional biopsy, no recurrence
18	1998	1	70/F/W	Red-orange plaques and nodules (face, arms, buttocks)		?
19	1998	1	77/M	Nodules at herpes zoster scars (abdomen)	Herpes zoster, lymphoma of the stomach	?
20	1998	1	77/F/W	Two dusky red nodules (thighs)		Surgical removal, no recurrence (1 year)
21	1999	1	55/F/W	Exanthematous/purpuric papules (back, thighs)		Spontaneous resolution (6 months)*
22	1999	1	35/M/A	Erythematous plaque (cheek)		Spontaneous resolution
23	2000	1	65/M/W	Generalized red-brown papules, plaques and nodules		No response to radiation, chemotherapy, intralesional steroids
Our case	2002	1	41/F/Haitian	Generalized tender brown nodules and tumors		Chronic evolution, no recurrence of excised lesions (3 years)

*Personal communication.
M: male; F: female; W: white; B: black; A: Asian; EBV: Epstein-Barr virus, HSV: herpes simplex virus; NIDDM: non-insulin-dependent diabetes mellitus.

The histopathologic differential diagnosis of this case is presented in Table II. Our case could not be reliably distinguished from inflammatory pseudotumor on the basis of routine histology alone because emperipolesis was only focally present (Fig. 2), and the most notable finding at presentation was a diffuse and florid mixed inflammatory infiltrate (Fig. 3). Nevertheless, the multifocality of lesions was rare for inflammatory pseudotumor (24). Positivity for S-100 protein confirmed the diagnosis of RDD and facilitated the search for emperipolesis, as it allowed the outline of the individual histiocytes to contrast with the negative image of the phagocytized cells (Fig. 4). The distinction between cutaneous lesions of RDD and cutaneous inflammatory pseudotumor is important, as the former may be associated with systemic involvement and necessitate a work-up for systemic disease. Furthermore, cutaneous lesions in RDD are often multiple, in contrast to cutaneous inflammatory pseudotumor which is usually a solitary lesion, never metastasizes, and can be cured with local excision.

Table II. *Histopathologic differential diagnosis of cutaneous Rosai-Dorfman disease*

Differential diagnosis	Features differentiating from cutaneous RDD
Inflammatory pseudotumor	Emperipolesis absent, positivity for S-100 protein rare
Malignant histiocytosis and lymphoma with feature of malignant histiocytosis	Atypia, cellular pleomorphism
Hemophagocytic syndrome associated with T-cell lymphoma and/or viral infection	Lymphomatous infiltrate, lobular panniculitis, negativity for S-100 protein
Langerhans' cell histiocytosis	Emperipolesis absent, Birbeck granules identified by electron microscopy
Reticulohistiocytoma cutis	Histiocytes with "ground glass" cytoplasmic appearance
Eruptive xanthoma	Emperipolesis and plasma cells absent
Generalized eruptive histiocytoma	
Juvenile xanthogranuloma	
Inflammatory malignant fibrous histiocytoma	Atypia, cellular pleomorphism
Lepromatous leprosy	Poorly defined infiltrate, plasma cells rare, positivity for organisms on Fite stain
Hodgkin's lymphoma	Atypical monocytes, Reed-Sternberg cells

Govender & Chetty (25) described a solitary lesion with combined histologic and immunophenotypic features of inflammatory pseudotumor and RDD of soft tissue. The authors suggested that these two lesions are part of a spectrum of inflammatory or reactive conditions. They postulated that the morphological and immunophenotypic features of their lesion could be secondary to aberrant cytokine expression in an inflammatory pseudotumor, resulting in transformation of histiocytes to resemble those seen in RDD. Nevertheless, the presence of morphologic similarities between cutaneous RDD and inflammatory pseudotumor does not necessarily represent evidence that these entities should be grouped together. Stain for S-100 protein can reliably differentiate inflammatory pseudotumor from cutaneous RDD. Although S-100 stain has not been performed in many cases of inflammatory pseudotumor, in a few reported cases of S-100-positive inflammatory pseudotumor (24), the histiocytes did not show the characteristic morphology of those seen in RDD.

This report indicates that lesions of a relatively discrete entity (RDD) can readily and incorrectly be assigned to the less well-defined diagnostic category of inflammatory pseudotumor. This case also presents a therapeutic challenge, as many lesions were symptomatic and/or located in uncomfortable sites, thus interfering with the patient's daily activities. Experience in the treatment of cutaneous RDD is limited and remains largely empirical and/or symptomatic. Solitary lesions have been treated with local excision (3, 5, 8). Systemic or intralesional steroids and chemotherapy have been administered in cutaneous RDD with minimal response (14, 23). Responses to radiation therapy (11) and thalidomide (11) have been reported. Our patient did not respond to intralesional steroids or a 3-month course of thalidomide. Surgical excision of painful lesions provided symptomatic relief. With a 3-year follow-up, the lesions have not recurred while several others persist.

REFERENCES

1. Thawerani H, Sanchez RL, Rosai J, Dorfman RF. The cutaneous manifestations of sinus histiocytosis with massive lymphadenopathy. Arch Dermatol 1978; 114: 191–197.
2. Lasar AP, Esterly NB, Gonzalez-Crussi F. Sinus histiocytosis clinically limited to skin. Pediatr Dermatol 1987; 4: 247–253.
3. Aso M, Hagari Y, Shimao S, Kimura R, Shimuzi Y. A case of cutaneous involvement by sinus histiocytosis with massive lymphadenopathy. J Dermatol 1987; 14: 253–257.
4. Viraben R, Dupre A, Gorguet B. Pure cutaneous histiocytosis resembling sinus histiocytosis. Clin Exp Dermatol 1988; 13: 197–199.
5. Tsang WYW, Chan JKC, Ho WK, Yu HC, Chow LTC. Extranodal Rosai-Dorfman disease: an uncommon cause of persistent nodule in the ear. J Laryngol Otol 1992; 106: 249–251.
6. Chu P, LeBoit PE. Histologic features of cutaneous sinus histiocytosis (Rosai-Dorfman disease): study of cases both with and without systemic involvement. J Cutan Pathol 1992; 19: 201–206.
7. Perrin C, Michiels JF, Lacour JP, Chagnon A, Fuzibet JG. Sinus histiocytosis (Rosai-Dorfman disease) clinically limited to the skin. J Cutan Pathol 1993; 20: 368–374.
8. Mac-Moune Lai F, Lam WY, Chin CW, Ng WL. Cutaneous Rosai-Dorfman disease presenting as a suspicious breast mass. J Cutan Pathol 1994; 21: 377–382.
9. Skiljo M, Garcia-Lora E, Tercedor J, Massare E, Esquivias J, Garcia-Mellado V. Purely cutaneous Rosai-Dorfman disease. Dermatology 1995; 191: 49–51.
10. Perez A, Rodriguez M, Febrer I, Aliaga A. Sinus histiocytosis confined to skin. Am J Dermatopathol 1995; 17: 384–388.
11. Annessi G, Giannetti A. Purely cutaneous Rosai-Dorfman disease. Br J Dermatol 1996; 134: 749–753.
12. Saenz-Santamaria MC, Reed JA, Ochs RL, McNutt NS. Asymptomatic nodules on the chest. Arch Dermatol 1997; 133: 231–236.
13. Wang JS, Hsieh SP, Shih DF, Tseng HH. Cutaneous Rosai-Dorfman disease manifesting as recurrent breast tumor: a case report. Chinese Med J 1997; 59: 269–273.
14. Scheel MM, Rady PL, Tyring SK, Pandya AG. Sinus histiocytosis with massive lymphadenopathy: presentation

as giant granuloma annulare and detection of human herpesvirus 6. J Am Acad Dermatol 1997; 37: 643–646.
15. Carrington PR, Reed RJ, Sanusi D, Fowler M. Extranodal Rosai-Dorfman disease of the skin. Int J Dermatol 1998; 37: 267–727.
16. Child FJ, Fuller LC, Salisbury J, Higgins EM. Cutaneous Rosai-Dorfman disease. Clin Exp Dermatol 1998; 23: 40–42.
17. Huang HY, Yang CL, Chen WJ. Rosai-Dorfman disease with primary cutaneous manifestations – a case report. Ann Acad Med Singapore 1998; 27: 589–593.
18. Quaglino P, Tomasini C, Novelli M, Colonna S, Bernengo MG. Immunohistologic findings and adhesion molecule pattern in primary pure cutaneous Rosai-Dorfman disease with xanthomatous features. Am J Dermatopathol 1998; 20: 393–398.
19. Requena L, Kutzner H, Escalonilla P, Ortiz S, Schaller J, Rohwedder A. Cutaneous reactions at sites of herpes zoster scars: an expanded spectrum. Br J Dermatol 1998; 138: 161–166.
20. Hafner O, Gerstel C, Bertsch HP, Vakilzadeh F. Cutaneous sinus histiocytosis (Rosai-Dorfman disease). Hautarzt 1998; 49: 392–396.
21. Stefanato CM, Ellerin P, Bhawan J. Cutaneous sinus histiocytosis (Rosai-Dorfman disease): a benign reactive process mimicking Langerhans' cell histiocytosis. J Cutan Pathol 1999; 26: 451.
22. Kang JM, Yang WI, Kim SM, Lee M-G. Sinus histiocytosis (Rosai-Dorfman disease) clinically limited to the skin. Acta Derm Venereol 1999; 79: 363–365.
23. West SW, Bridges AG, DiCaudo DJ. Purely cutaneous Rosai-Dorfman disease. J Cut Pathol 2000; 27: 543.
24. Ramachandra S, Hollowood K, Bisceglia M, Fletcher CDM. Inflammatory pseudotumor of soft tissues: a clinicopathological and immunohistochemical analysis of 18 cases. Histopathol 1995; 27: 313–323.
25. Govender D, Chetty R. Inflammatory pseudotumor and Rosai-Dorfman disease of soft tissue: a histological continuum? J Clin Pathol 1997; 50: 79–81.