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Cutaneous Rosai-Dorfman Disease – A Pathologic Review of 2 Cases

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ABSTRACT

Rosai-Dorfman disease, also known as sinus histiocytosis with massive lymphadenopathy, is a rare but distinct clinicopathologic entity characterised histologically by a benign histiocytic proliferation. Isolated involvement of extranodal sites without concomitant nodal disease is rare. We describe the pathological features of 2 cases of Rosai-Dorfman disease that were clinically confined to the skin. In both male adult Chinese patients, proliferation of histiocytes was accompanied by S-100 protein expression demonstrated immunohistochemically within the histiocytes. The pathology of Rosai-Dorfman disease and its microscopic differential diagnoses are discussed.

Keywords: extranodal, skin, histiocytes, S-100 protein

INTRODUCTION

In 1969, Rosai and Dorfman described a clinicopathologic entity characterised by massive painless cervical lymph node enlargement, anaemia, fever, increased erythrocyte sedimentation rate (ESR), leukocytosis and hypergammaglobulinaemia[1]. Histologically, the enlarged lymph nodes showed sinus histiocytosis associated with emperipolesis and this condition was termed sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease (RDD). Initially thought to affect only the lymph nodes, it was subsequently documented to include a spectrum of nodal and extranodal manifestations[2]. Although the skin was the commonest site of extranodal disease in the SHML Registry published in 1990 that included 423 patients, purely cutaneous RDD is rare[2-6].

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CASE REPORTS

Case 1

A 32-year-old Chinese man presented with a 3 to 4 weeks history of 2 interscapular lumps. Clinical examination confirmed the presence of 2 discrete intradermal, hard, irregular lumps 1 cm and 3 cm in diameter. No lymphadenopathy or other significant abnormality was detected clinically and the lumps were excised.

Macroscopically, both lumps consisted of firm fibrous tissue measuring 4 cm and 2 cm in largest dimension with overlying skin noted in the smaller piece of tissue. Microscopic examination revealed sheets of histiocytes containing voluminous pale eosinophilic cytoplasm with indistinct cytoplasmic borders (Fig 1). Several histiocytes contained plasma cells and lymphocytes within the cytoplasm, a process termed "emperipolesis". A few multinucleated histiocytes were present. Surrounding plasma cells with Russell bodies and lymphocytes were present. Occasional neutrophils were identified but eosinophils were rare. Collagen bands and hyalinised stroma traversed the lesion resulting in a nodular appearance in some areas. Vascular channels surrounded by plasma cells were noted. There was no overlying pseudoepitheliomatous hyperplasia. No bacilli were demonstrated on the Wade Fite stain nor did the histiocytes stain with periodic acid Schiff (PAS).

Fig 1 – Sheets of histiocytes with "feathery" cytoplasmic borders and pale abundant cytoplasm, surrounded by chronic inflammatory cells. Magnification x100. (Haematoxylin and eosin stain).

Reticulin staining around individual histiocytes was absent. Immunohistochemical workup showed positive reactivity of the histiocytes with S-100 protein (Fig 2) while Factor VIII decorated lymphatic channels did not disclose luminal histiocytes. A diagnosis of cutaneous RDD was made. The patient was well 1.5 months later, but did not return for subsequent follow-up.

Case 2

A 35-year-old Chinese man who was otherwise well sought treatment for a persistent left buttock "rash" of a few months' duration. Clinical examination revealed 3 well-defined nodular lesions on the left buttock. There was no lymphadenopathy or other detectable abnormality.

The excised skin measuring 5 cm x 3 cm contained several nodular areas between 0.4 cm to 2.3 cm in diameter. The histological appearances were similar to those of Case 1 (Fig 3). The patient was well on review 14 days after the excision, but did not appear for the next outpatient appointment.

DISCUSSION

RDD or SHML is a rare but distinct clinicopathologic entity featuring a proliferation of benign histiocytes with a characteristic histology. It may affect any age group with a mean age of onset at approximately 20 years[2]. It occurs in both males and females, without racial predilection. Clinical manifestations include massive painless bilateral cervical lymphadenopathy associated with fever, anaemia, elevated ESR and polyclonal hypergammaglobulinaemia. Extranodal disease occurs in 43% of the cases in the SHML registry[2] with the commonest site of involvement being the skin. RDD has also been described in other locations like the nasal cavity/paranasal sinuses, soft tissues, eyelid/orbit, bone, salivary gland, central nervous system, oral cavity, and genitourinary system.

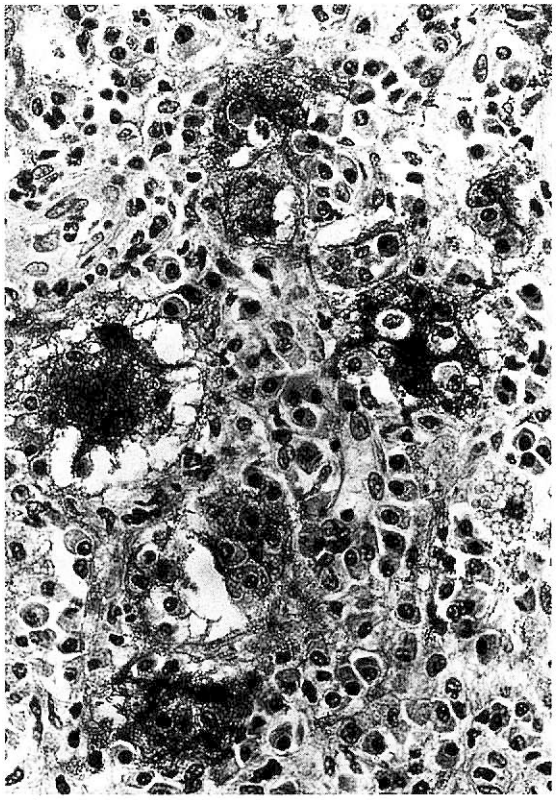

Fig 2 – The histiocytes exhibiting S-100 protein expression on immunostain (DAKO Corp). Note the presence of plasma cells and lymphocytes within the cytoplasm of the histiocytes (emperipolesis). Magnification x400. (Avidin biotin complex technique).

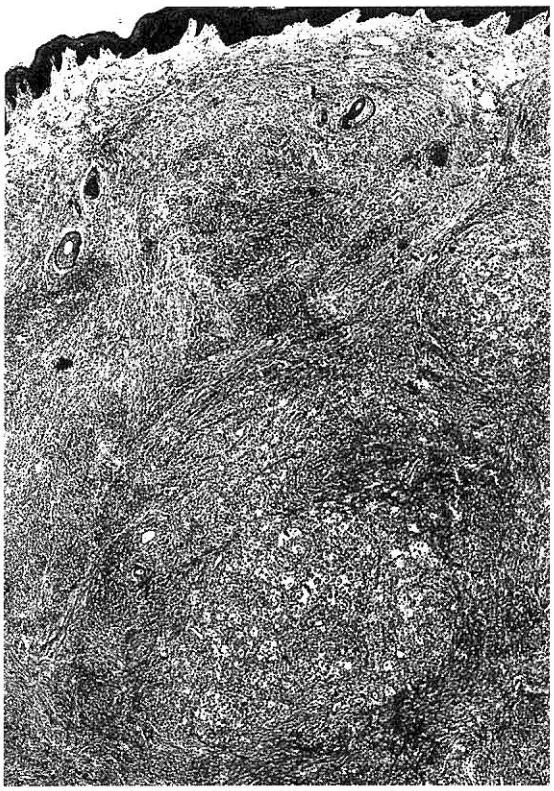

Fig 3 – The skin in case 2 shows nodular collections in the dermis comprising chronic inflammatory cells punctuated by pale histiocytes. Magnification x40. (Haematoxylin and eosin stain).

Cutaneous RDD may be associated with nodal disease or other extranodal site involvement. In the SHML registry, 13 of 49 patients with cutaneous disease had no evidence of lymph node involvement, hence the eponym Rosai-Dorfman disease is more apt than SHML. Half of this subpopulation of 13 patients had only cutaneous manifestation of RDD while the other half had other sites of involvement like the soft tissue. A further 6 patients[3-6] with only cutaneous RDD have been described in the English literature, with 1 patient presenting with a suspicious breast mass[5].

In our 2 cases, the disease was clinically limited to the skin, presenting as innocuous skin lumps that were excised. It was only on microscopic examination that the unusual pathologic entity of RDD was recognised. Histologically, the main feature of cutaneous RDD is the presence of large histiocytes with abundant pale eosinophilic cytoplasm, indistinct "feathery" cytoplasmic borders, vesicular nuclei and distinct nucleoli. These histiocytes exhibit the phenomenon of emperipolesis where lymphocytes, plasma cells and even neutrophils are found within the cytoplasm. S-100 protein expression in these histiocytes is characteristic. There is a surrounding inflammatory background of lymphocytes, plasma cells and some neutrophils. Foucar et al[2] considered the presence of

emperipolesis and S-100 protein expression by the histiocytes with feathery cytoplasmic borders to be diagnostic of RDD. Two other criteria stressed by Chu and LeBoit[3], namely the presence of histiocytes in dilated lymphatic spaces and nodular lymphoid aggregates at the periphery of the lesions are absent in our cases, findings similar to that in a previous report[4]. Cutaneous RDD differs histologically from nodal disease in that there is a greater degree of fibrosis, fewer histiocytes and diminished emperipolesis. Hence, cutaneous RDD can be overlooked if the index of suspicion for the disease is low.

The differential diagnoses include conditions that histologically exhibit emperipolesis like features. These include the so-called malignant histiocytosis, true histiocytic lymphoma, haemophagocytic syndrome and reticulohistiocytoma (reticulohistiocytic granuloma).

In the so called malignant histiocytosis[4,7], the "atypical histiocytes" usually show thick nuclear membranes, coarse chromatin and prominent nucleoli with varying degrees of anisonucleosis. Haemophagocytosis which may superficially resemble emperipolesis is usually confined to mature histiocytes. The presence of highly atypical cells associated with mitotic activity distinguishes the so-called malignant histiocytosis from RDD. With the advent of immunohistochemical and genotypic analysis, most cases of the so-called malignant histiocytosis can now be classified as large cell lymphoma (usually of T cell lineage with frequent expression of CD30). S-100 protein expression seen in the histiocytes of RDD is not a feature in the so-called malignant histiocytosis.

In true histiocytic lymphoma[7], haemophagocytosis is a rare feature and the presence of histiocyte-like cells with pleomorphic nuclei and abundant mitoses argues against the diagnosis of RDD. Although CD68 (a macrophage marker) expression may be present in histiocytic lymphoma, S-100 protein is absent.

In haemophagocytic syndrome associated with T cell lymphoma and infections eg. Epstein-Barr virus (EBV) infection, there is often septal and lobular panniculitis, termed cytophagic histiocytic panniculitis (CHP). In CHP, the histiocytes ingest erythrocytes, lymphocytes, platelets, plasma cells, nuclear debris and neutrophils resulting in "bean bag" shaped cells in a background of significant inflammation. The presence of subcutaneous inflammation is not in keeping with pure cutaneous RDD. In cases of cutaneous RDD with extension of the inflammatory process into the subcutaneous fat, hyaline fat necrosis, oedema and extensive haemorrhage seen in CPH[8,9] is absent. Furthermore, atypical lymphocytes found in cases of haemophagocytic syndrome associated with T cell lymphoma are absent. In problematic cases, the presence of S-100 protein expression by the histiocytes will favour a diagnosis of RDD.

In reticulohistiocytoma, the histiocytes show characteristic "ground glass" cytoplasm with sharp cellular outlines[10] whereas in RDD the histiocytes show pale foamy cytoplasm with indistinct cell borders. Plasma cells are numerous in RDD[4] and sparse in reticulohistiocytoma. The findings of PAS positive diastase resistant material and reticulin staining around the individual histiocytes[10] in reticulohistiocytoma distinguish it from RDD. S-100 protein expression and emperipolesis cannot be used as definitive criteria in distinguishing between reticulohistiocytoma and RDD because in some instances the histiocytes of reticulohistiocytoma have expressed S-100 protein[3,11] and may also contain inflammatory cells in the cytoplasm[3].

Langerhans cell histiocytosis (LCH) is another differential diagnosis to be considered in view of the presence of abundant cytoplasm of the Langerhans cells and the fact that both Langerhans cells and the histiocytes in RDD express S-100 protein. However the nuclei of Langerhans cells are usually smaller than those of RDD, frequently irregular and folded with central grooves, features absent in RDD. Emperipolesis is not a feature of LCH[7]. Eosinophils seen in RDD are never as numerous as those in LCH and do not form microabscesses. Ultrastructural demonstration of Birbeck granules confirms the diagnosis of LCH.

Other differential diagnoses like xanthoma and lepromatous leprosy[10] can be readily excluded by the negative S-100 reactivity of the foam cells in xanthoma and the presence of bacilli on the Wade Fite stain in lepromatous leprosy.

The exact aetiology of RDD is unknown. An underlying immune dysfunction has been postulated[12]. Possibly viruses like human herpes virus (HHV) 6[13] and EBV[14] may play a role, as HHV6 have been detected in some of the tissues involved by RDD while in one case, raised EBV titres was present.

RDD usually follows a course of spontaneous regression and recovery[2]. However, in a small percentage of cases, the disease may be persistent and progressive, associated with widespread dissemination and involvement of the kidneys, lower respiratory tract or liver. In such instances, autoimmune haemolytic anaemia, neutropenia, lymphocytopenia and immunologic abnormalities like antinuclear antibody expression are ominous findings[7]. When RDD is limited to the skin, most reports[2,3,6] indicate a favourable long-term prognosis with spontaneous regression although in one patient, roentgen therapy was administered for cosmetic reasons and upon the patient's request[6]. Most cutaneous lesions do not generally require any further treatment although roentgen therapy has been described as a useful therapeutic modality when the cutaneous disease runs a prolonged course or when the lesions are aesthetically unacceptable to the patient[6].

In summary, 2 rare cases of cutaneous RDD are documented and its differentials discussed. It is significant that these presented clinically as otherwise mundane skin lumps, stressing the importance of proper pathologic examination of excised tissues, as they may reveal histologic surprises. As RDD is not a commonly encountered entity, it is useful to note that certain ancillary investigations as mentioned above may aid in prognostication. The failure of the 2

patients to return for follow-up suggests that they suffered no untoward consequences after excision, corroborating the generally indolent course that cutaneous RDD pursues.

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