Pure Cutaneous form of Rosai Dorfmann disease- A cute surprise in the cutis

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Abstract
Rosai dorfmann disease (RDD) is a rare disease of histiocytic origin, with an obscure aetiology. Usually it manifests as bilateral cervical lymphadenopathy in young adults, with cutaneous involvement seen in 43% cases. Pure cutaneous from of RDD (PC - RDD) is very rare and amount for 3% of RDD. PC- RDD is enigmatic for the clinicians as the diagnosis is often delayed or missed due to its rarity, vague and overlapping presentations. We here in report a PC – RDD in a 53 year old male with a brief review of literature.

Keywords: Cutaneous, Rosai Dorfmann, Emperipolesis.

Introduction
RDD is a rare disease of histiocytic origin characterized by bilateral massive cervical lymphadenopathy and systemic involvement. The initial description of this disease was by Destombes in 1965, which was further documented as a distinct entity by Rosai and Dorfman in 1969.(1) The disease assumes three forms, nodal, extranodal and pure cutaneous. Extranodal form can coexist with nodal disease in 43% cases with skin being the most common site affected.(2) Other organs like respiratory tract, genitourinary tract, gastrointestinal tract, spleen, oral cavity can be involved. Pure cutaneous form indicates involvement of skin without any other organ being affected. Is very rare accounting for 3 % of RDD.(3) Clinically the pure cutaneous form can show myriad pattern ranging from macule to papule to nodule. Due to nonspecific clinical presentation, histopathology remains the key modality for definitive diagnosis.(4) Since PC-RDD is different from classic RDD in biologic, therapeutic and prognostic performance, accurate diagnosis is vital in patient management. We herein present a rare case of pure cutaneous RDD in a 53-year-old male and discuss in brief the literature.

Case Report
A 53-year-old male presented to dermatology outpatient department with complaint of a raised lesion on the left cheek of three months duration. There was no history of pain, itching or any discharge from the swelling. On local examination the lesion was a single pink colored non-tender nodule. There was a zone of hyperpigmentation and erythema around the nodule. The nodule measured 2 x 2 cm and was soft in consistency and nontender. (Fig. 1) There was no evidence of ulceration. The patient had no history of fever, cough, loss of appetite or any other specific symptoms. There was no evidence of any such lesion anywhere else on the body surface. Cardiovascular system, respiratory system, central nervous system and per abdomen examination were within normal limits. Based on these findings a provisional clinical diagnosis of lupus vulgaris was made. Incision biopsy was done and specimen sent for histopathology.

Gross: Consisted of single skin covered tissue bit measuring 0.5cm in length. Cut surface was grey white. At microscopy sections studied showed epidermis which was unremarkable. Dermis showed dense inflammatory cell infiltrate comprising of large histiocytes, plenty of plasma cells, lymphocytes and few neutrophils. These histiocytes had abundant pale eosinophilic cytoplasm and eccentrically place large nucleus with vesicular chromatin and prominent nucleoli, Many of the histiocytes showed emperipolesis i.e., histiocytes that had engulfed intact plasma cells, lymphocytes and occasionally neutrophils and RBC (erythrophagocytosis). At places plasma cells were seen to be emerging from the venules. Many multinucleated histiocytic giant cells were also noted. Special stains for mycobacteria and fungal infections were negative. AT immunohistochemistry, histiocytes showed strng positivity for S100 stain. (Fig. 2 to 4)

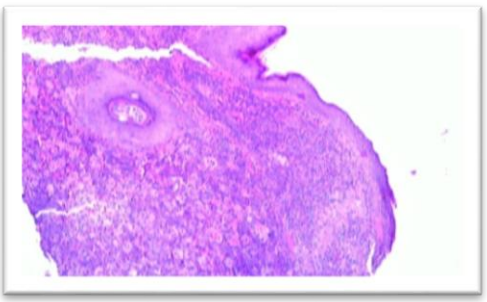

Fig. 2 A: Section through the nodule shows epidermis is atrophic. Dermis shows expansion by inflammatory cells resembling a lymph node. [Hematoxylin and Eosin (H&E), x 40]

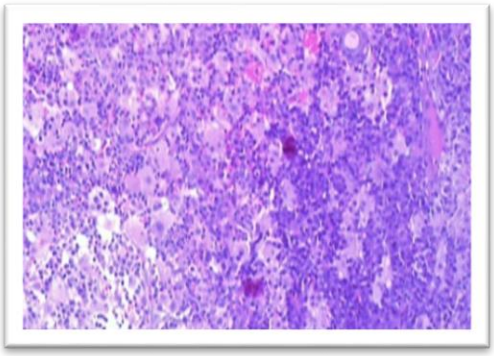

Fig. 2 B: A higher magnification highlights large histiocytes. (H & E, x 100)

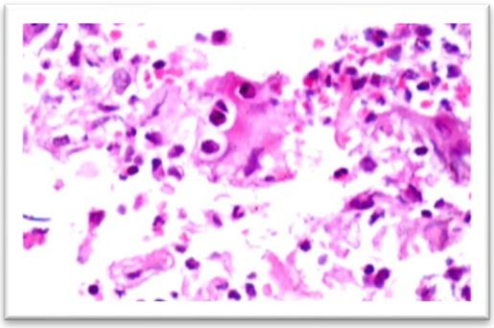

Fig. 2 C: Histiocyte engulfing intact plasma cell i.e., emperipolesis. Note- Clear space around engulfed plasma cell. (H & E, x 400)

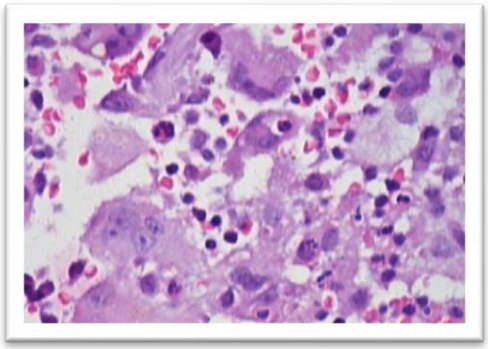

Fig. 2 D: Emperipolesis of neutrophils. (H&E, x 400)

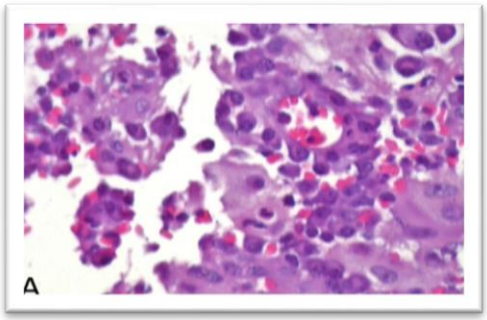

Fig. 3 A: Erythrophagocytosis by multinucleate histiocytic giant cell. (H & E, x 400)

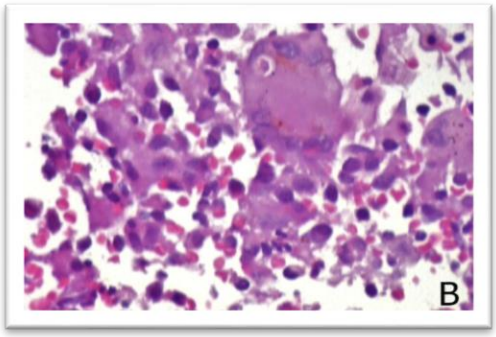

Fig. 3 B: Plasma cells surrounding blood vessels (H& E, x 400)

Hence a final diagnosis of Rosai Dorfmann disease in the skin was made.

Computed Tomography scan of the thorax and abdomen did not reveal any lymph node enlargement or any other visceral organ involvement. There was no other skin lesion identified. Hence a final diagnosis of PC - RDD was made. Later a wide excision was performed the histopathogy of which showed features consistent with RDD.

Patient is doing well and there is no evidence of recurrence six months post treatment.

Discussion

RDD is a rare disease of histiocytic origin, with an obscure etiology. The disease classically manifest in young adolescent or young adults with painless, bilateral cervical lymph node enlargement, although any lymph node organ many be affected. Cutaneous involvement in RDD is seen in 43% cases. However pure cutaneous from of RDD is very rare and amount for 3% of RDD.[2,3]

Pure cutaneous from of RDD are enigmatic for the clinicians as the diagnosis is often delayed or missed due to its rarity, vague and overlapping presentations. The cutaneous lesions may assume any from like a papule, nodule, plaque or an induration and the lesion may be solitary or multiple.[5]

In the present case, a single nodule on face with pink hue and soft consistency prompted the clinician towards a presumptive diagnosis of lupus vulgaris. Even at pathology, the diagnosis can be easily missed at first look due to its rarity. In a report of seven cases of cutaneous RDD, four cases were initially misinterpreted and accurate diagnosis was possible only after review by second pathologist.[6]

RDD is considered to be a benign disease which at time has a self-limiting course. The cell of origin is an abnormal histiocytes, whose activation has been driven by certain cytokines. Several theories have been proposed for its genesis like a dysregulated immune process, viruses like Epstein barr virus, human herpes virus 6 and autoimmune mechanisms.[7,8,9] However, none has been substantially proved. In a recent article

by Lui Get al, authors observed that the histiocytes of pure form of cutaneous RDD expressed markers of epithelial mesenchymal transition which led them to believe that RDD belongs to an intermediate category between inflammation and cancer.[10,11]

Liu G al in a report mentioned the presence of vascular invasion in a primary lesion of cutanaous RDD, which was followed by occurrence of another lesion probably metastatic, at a site distant from the primary lesion. This prompted the comptemplation of a metastatic process. Nevertheless, this is just a datum, further molecular studies with long term follow up are needed to unravel the etiopathogenesis and true nature of this rare entity.[10]

Morphology of cutaneous RDD is unique. The massive infiltration of dermis by lymphoid cells simulates a lymph node architecture on low power. On higher magnification the infiltrate is composed of plasma cells, large histiocytes, multinucleate giant cells and few lymphocytes. The histiocytes show the presence of intact lymphocytes and plasma cells in its cytoplasm, with a clear surrounding halo, a phenomenon called as emperipolesis. The halo implicates the anergy of engulfed cells to hydrolytic enzymes of histiocytes. Rarely neutrophils, eosinophils or RBC can be seen inside an histocyte. However, variations, based on the age of the lesion exists and can cause diagnostic dilemmas. In early lesions neutrophils may dominate the picture. In older lesions fibrosis may ensue and emperipolesis may be scarce. At such times, the presence of plasma cells around the venules and lymphoid aggregate at the periphery, pose important clues for the PC -RDD.[12,13] PC - RDD, fibrosis may obscure the histocytes, which may deter an accurate diagnosis. [14]

Though not pathogonomic of RDD, emperipolesis is an important pointer to the diagnosis of RDD. It must be noted that emperipolesis can be seen in other conditions like myelodysplastic syndromes, lymphoma and solid tumors. Hence careful examination of the background cell population and its correlation with clinical findings is imperative to prevent errors.

RDD has been reported to occur in association with other autoimmune disorders like systemic lupus erythematosus, rheumatoid arthritis, hypothyroidism, lymphoma and HIV infection.[15,16] These disorders can precede, occur concurrently or may follow RDD over a due course of time. Reports of RDD assuring synchronously with Langerhans cell histiocytosis at different sites as well as in single skin nodule are on record. A thorough evaluation coupled with long term follow up to look for systemic involvement is mandatory.[17]

Differential diagnosis include other histiocyte rich lesions of the skin like leprosy, atypical mycobacteria, fungal infections, xanthomas, LCH and histiocytic sarcomas.

Table 1: Depicts the morphologic and immune histochemical difference, between the morphologic differentials of cutaneous RDD.

Differential diagnosis	Morphology	Special stain / Immunohistochemistry
Leprosy.	Histocytes with foamy to clear cytoplasm. Neural involvement and or grenz zone	Fite Faraco positive
Atypical mycobacteria	Histiocytes with foamy cytoplasm. Neutrophils if immunocompromised host	Ziehl- Neelsen stain for acid fast bacilli
Fungal infections,	Eosinophils. Fungal organisms	Periodic Acid Schiff /Gomori Methenamine silver stain
Xanthomas	Foamy histiocytes, touton type giant cells, cholesterol clefts	
Langerhans cell histiocytosis	Eosinophils, histiocytes with lobulated nuclei and grooving	CD 1a Positive
Histiocytic sarcomas.	Histiocytes with atypical nuclei, bizzare cells and mitosis.	CD 163 Positive

Table 1: depicts the morphologic and immune histochemical difference, between the morphologic differentials of cutaneous RDD.

PC - RDD follows a self-limiting. Through recurrence occur, the disease is restricted to the site of origin. Due to the rarity of disease and limited studies available in literature, the treatment is challenging and is not standardized. [18] The treatment modalities include observation, local excision, local irradiation, steroids and chemotherapeutic drugs. Since the disease is self-limited, a less aggressive approach should be adopted. In a comprehensive review, involving 578 published cases of PC- RDD, A1 khateeb et. al., observed that surgical excision was the most effective method.[19]

What was unique in the present cases was the rarity of cutaneous form of RDD, presence of plasma cells around the venules – an important clue to RDD in the absence of emperipolesis and presence of erythrophagocytosis.

To conclude, dermatologist should consider cutaneous RDD as a rare but important differential in all skin and soft tissue lesions. Likewise pathologist must bear in mind this entity, while dealing with histiocytes rich lesions of the skin.

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