Pink Papules on the Cheek

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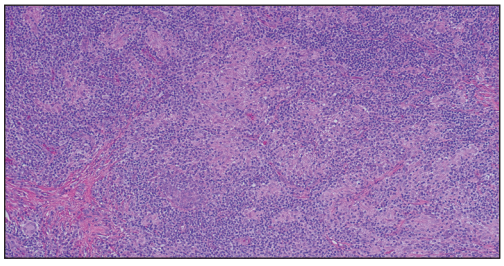
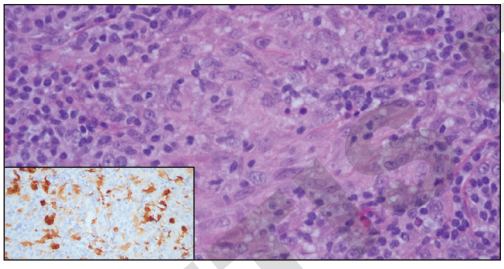


H&E, original magnification ×10. Photograph courtesy of Carla Stephan, MD (New York, New York).



H&E, original magnification ×40 (inset: S-100 stain, original magnification ×40). Photograph courtesy of Carla Stephan, MD (New York, New York).

A 31-year-old woman presented with a slow-growing, tender, pruritic lesion on the right cheek of 4 to 5 months' duration. She had been applying petroleum jelly and hydrocortisone cream 2.5% without any improvement. Physical examination revealed a 1×5-mm, pearly pink, erythematous, crusted papule with arborizing vessels surrounded by scattered pink papules with white dots within. No cervical lymphadenopathy was appreciated on physical examination, and the patient denied any other systemic symptoms. Shave and punch biopsies of the lesion were performed; stains for microorganisms were negative. The biopsy showed a dense reticular mixed inflammatory cell infiltrate comprised of a mixture of histiocytes (top), lymphocytes, neutrophils, and plasma cells that assumed a diffuse growth pattern within the dermis. The histiocytes exhibited abundant watery cytoplasms with ill-defined cytoplasmic membranes; intact leukocytes were found within the cytoplasms. The histiocytes demonstrated a unique phenotype characterized by S-100 (bottom) and CD68 positivity.

THE BEST **DIAGNOSIS IS:**

a. cutaneous Rosai-Dorfman disease
b. indeterminate cell histiocytosis
c. Langerhans cell histiocytosis
d. reticulohistiocytoma
e. xanthogranuloma

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THE **DIAGNOSIS:** Cutaneous Rosai-Dorfman Disease

Rosai-Dorfman disease is a rare benign non-Langerhans cell histiocytopathy that can manifest initially with lymph node involvement—classically, massive painless cervical lymphadenopathy.[1] Cutaneous Rosai-Dorfman disease (CRDD) is a variant that can be associated with lymph node and internal involvement, but more than 80% of cases lack extracutaneous involvement.[2,3] In cases with extracutaneous involvement, lymph node disease is most frequent.[3] Cutaneous Rosai-Dorfman disease unassociated with extracutaneous disease is a benign self-limiting histiocytopathy that manifests as painless red-brown, yellow, or flesh-colored nodules, plaques, or papules that may become tender or ulcerated.[4]

Cutaneous Rosai-Dorfman disease represents a benign histiocytopathy of resident dendritic cell derivation.[3] A characteristic immunohistochemical finding is S-100 positivity, which might suggest a Langerhans cell transdifferentiation phenotype, but other markers corroborative of a Langerhans cell phenotype—namely CD1a and langerin—will be negative. Biopsies typically show a mid to deep dermal histiocytic infiltration in a variably dense polymorphous inflammatory cell background comprised of a mixture of lymphocytes, plasma cells, and neutrophils.[3] At times the extent of lymphocytic infiltration can be to a magnitude that resembles a lymphoma on histopathology. In our patient, lymphoma was excluded based on clinical presentation, as this patient lacked the typical symptoms of lymphadenopathy or B symptoms that come with B-cell lymphoma.[5]

The histiocytes in CRDD are characteristically large mononuclear cells exhibiting a low nuclear to cytoplasmic ratio reflective of the voluminous, nonvacuolated, watery cytoplasm. They have ill-defined cytoplasmic membranes resulting in a seemingly syncytial growth pattern. A hallmark of the histiocytes is emperipolesis characterized by intracytoplasmic localization of intact inflammatory cells including neutrophils, lymphocytes, and plasma cells.[3]

The differential diagnosis of CRDD includes Langerhans cell histiocytosis (LCH), indeterminate cell histiocytosis, xanthogranuloma, and reticulohistiocytoma. All of these conditions can be differentiated by their unique histopathologic and phenotypic characteristics.

Langerhans cell histiocytosis is a distinct clonal histiocytopathy that has a varied presentation ranging from cutaneous confined cases manifesting as a solitary lesion to one of disseminated cutaneous disease with the potential for multiorgan involvement. Regardless of the variant of LCH, the hallmark cell is one showing an eccentrically disposed, reniform nucleus with an open chromatin and abundant eosinophilic cytoplasm (Figure 1).[6] Both LCH and CRDD stain positive for S-100. However, unlike the histiocytes in CRDD, those seen in LCH stain positive for CD1a and langerin and would not express factor XIIIA. Additionally, the neoplastic cells would not exhibit the same extent of CD68 positivity seen in CRDD.[6] Treatment of LCH depends on the extent of disease, especially for the presence or absence of extracutaneous disease.[7]

A variant of LCH is indeterminate cell histiocytosis, which can be seen in neonates or adults. It represents

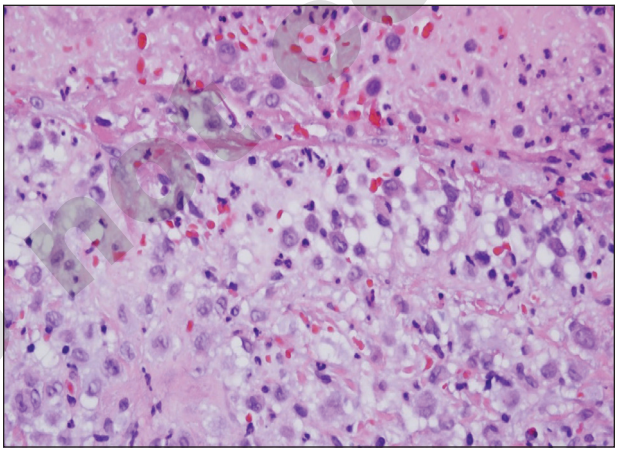

FIGURE 1. In Langerhans cell histiocytosis, Langerhans cells have a characteristic eccentrically disposed, reniform nucleus with abundant eosinophilic cytoplasm and do not show any scavenger properties, as revealed by a lack of phagocytosis of cells or cell remnants (H&E, original magnification ×400).

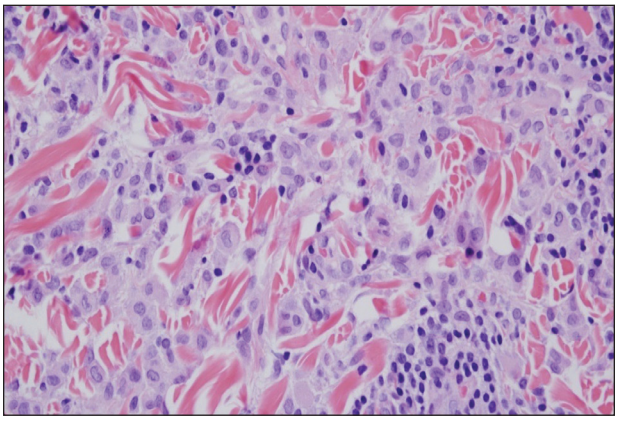

FIGURE 2. In indeterminate cell histiocytosis, the typical Langerhans cell cytomorphology demonstrates infiltrates that predominantly are dermal without notable epidermotropism (H&E, original magnification ×400).

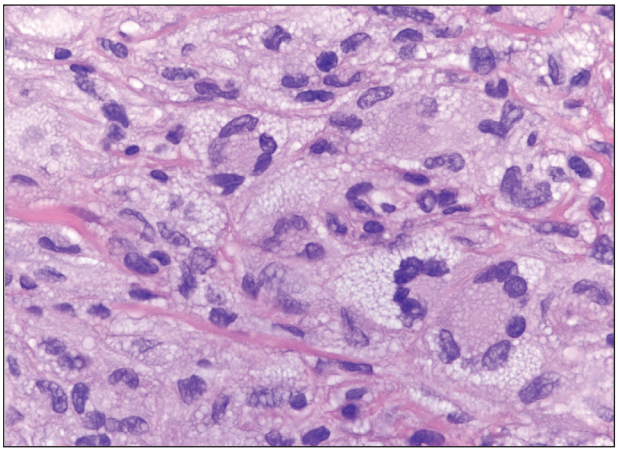

FIGURE 3. The Touton giant cell—a multinucleated histiocyte exhibiting a concentric wreathlike arrangement of nuclei with accompanying peripheral lipidization—is a characteristic hallmark cell encountered in xanthogranuloma (H&E, original magnification ×1000).

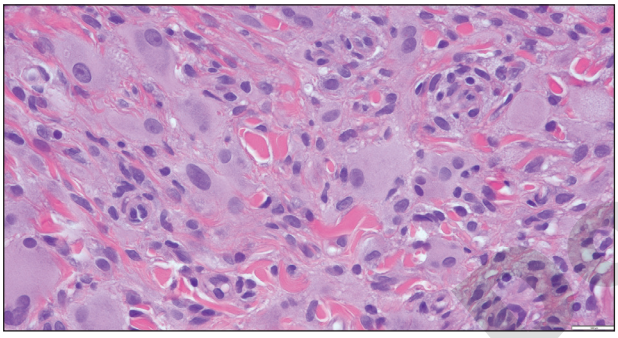

FIGURE 4. Large histiocytoid cells of reticulohistiocytoma with abundant eosinophilic to amphophilic cytoplasms, with a few of the neoplastic cellular elements exhibiting xanthomatous change (H&E, original magnification ×40).

a neoplastic proliferation of Langerhans cells that are devoid of Birbeck granules, reflective of an immature early phase of differentiation in the skin prior to the cells acquiring the Birbeck granule (as would be seen in neonates) or a later phase of differentiation after the mature Langerhans cell has encountered antigen and is en route to the lymph node (typically seen in adults).[8] The phenotypic profile is identical to conventional LCH except the cells do not express langerin. Microscopically, the infiltrates are composed of Langerhans cells that are morphologically indistinguishable from classic LCH but without epidermotropism and exhibit a dominant localization in the dermis typically unassociated with other inflammatory cell elements (Figure 2).[9]

Xanthogranuloma is seen in young children (juvenile xanthogranuloma) as a solitary lesion, though a multifocal cutaneous variant and extracutaneous presentations have been described. Similar lesions can be seen in adults.[10] These lesions are evolutionary in their morphology. In the inception of a juvenile xanthogranuloma, the lesions are highly cellular, and the histiocytes typically are poorly lipidized; there may be a dearth of other inflammatory cell elements. As the lesions mature, the histiocytes become lipidized, and characteristic Touton giant cells that exhibit a wreath of nuclei with peripheral lipidization may develop (Figure 3). In the later stages, there is considerable hyalinizing fibrosis, and the cells can acquire a spindled appearance. The absence of emperipolesis and the presence of notable lipidization are useful light microscopy features differentiating xanthogranuloma from CRDD.[11] Treatment of xanthogranuloma can range from a conservative monitoring approach to an aggressive approach combining various antineoplastic therapies with immunosuppressive agents.[12]

Solitary and multicentric reticulohistiocytoma is another form of resident dendritic cell histiocytopathy that can resemble Rosai-Dorfman disease. It is a dermal histiocytic infiltrate accompanied by a polymorphous inflammatory cell infiltrate (Figure 4) and can show variable fibrosis.[13] One of the hallmarks is the distinct amphophilic cytoplasms, possibly attributable to nuclear DNA released into the cytoplasm from effete nuclei.[13] The solitary form is unassociated with systemic disease, whereas the multicentric variant can be a paraneoplastic syndrome in the setting of solid and hematologic malignancies.[14] In addition, in the multicentric variant, similar lesions can affect any organ but there can be a proclivity to involve the hand and knee joints, leading to a crippling arthritis.[15]

We presented a case of CRDD, a benign resident dendritic cell histiocytopathy that can manifest as a cutaneous confined process in the skin where the clinical course is characteristically benign. It potentially can be confused with LCH, indeterminate cell histiocytosis, xanthogranuloma, and reticulohistiocytoma. For a solitary lesion, intralesional triamcinolone injection and excision are options. Multifocal cutaneous disease or CRDD with notable extracutaneous disease may require systemic treatment.[16] In our patient, one intralesional triamcinolone injection was performed with notable resolution.

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