A 13-year-old girl developed a non-pruritic pityriasis rosea-like rash, which did not respond to topical corticosteroids or UV therapy but persisted for 2 years. The lymphohistiocytic infiltrate in the upper dermis showed mononuclear cells immunoreactive with S100, CD68, factor XIIIa and CD1a. Electron microscopic evaluation of these cells demonstrated lamellated dense bodies but no Birbeck granules, lipid vacuoles or cholesterol crystals. Two diagnoses were made: a primarily clinical diagnosis of generalized eruptive histiocytosis and a more cell-biology-based diagnosis of an indeterminate cell histiocytosis. Three years later, the lesions are showing spontaneous resolution, with loss of erythema and flattening.

Our patient’s indeterminate cells fulfill Rowden’s classical definition (dendritically shaped epidermal non-keratinocytes without identifying cytoplasmic features), as well as Zelger’s newer definition (cells with features of both macrophages and dendritic cells). A Christmas tree pattern has not been previously described in indeterminate cell histiocytosis. Development of indeterminate cell histiocytosis in the lesions of a healing pityriasis rosea might explain the unusual distribution pattern. The development of a skin disorder at the site of an unrelated, already healed skin disease is known as an isotopic response. Key words: indeterminate cell; isotopic response; histiocytosis; pityriasis rosea.

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The classification of histiocytic diseases is an elusive and changing field. This is due to improved methods of investigation and a trend towards cell biological definitions as compared to morphological disease entities. We report the case of a young female with an unusual clinical presentation of cutaneous histiocytosis, and discuss the classification of her disease under clinical and cell biological aspects.

CASE REPORT

A 13-year-old girl developed a red plaque on her abdomen suggestive of the herald patch seen in pityriasis rosea, followed by other, smaller red macules on her trunk (Fig. 1). After 6 months, all individual lesions had persisted, grew slowly in size and became in part confluent, but neither itched nor caused any distress. A biopsy showed parakeratosis, extravascular and intraepidermal erythrocytes and spongiosis, more suggestive of pityriasis lichenoides but compatible with pityriasis rosea. Over the following 18 months, the lesions increased further in number and size. Topical corticosteroids and balneophototherapy were ineffective.

At 15 years of age, the patient was admitted to hospital with about 500, round to oval, confluent, infiltrated, reddish-brown macules and plaques ranging in size from 5 to 30 mm in a Christmas tree pattern on the trunk, upper arms and legs (Fig. 2). There was no lymphadenopathy. Histology now showed a focal lymphohistiocytic infiltrate in the upper dermis without exocytosis of red blood cells (Fig. 3). The histiocytic cells were immunoreactive with S100, CD68, factor...
pattern of the infiltrates and indeterminate cell histiocytosis based on the cell markers and electron microscopic findings (1). Because spontaneous regression is commonly seen in both disease entities, no aggressive treatment regimen was started, but regular follow-up visits were scheduled. Three years later, the lesions are fewer in number and have changed to barely infiltrated reddish macules, indicating an ongoing regression.

**DISCUSSION**

Our patient’s disease is unique, because it may be classified on clinical grounds as unusually large lesions of generalized eruptive histiocytosis, in which the distribution pattern followed that of pityriasis rosea, whereas ultrastructural and immunohistochemical data support the diagnosis of indeterminate cell histiocytosis. Generalized eruptive histiocytosis is a clinically defined disease entity with multiple symmetrical, frequently self-healing, brownish papules preferentially involving the trunk (2). The first case was reported by Cramer in 1963 (3), while the term generalized eruptive histiocytosis was made popular by Winkelmann & Müller (4). Generalized eruptive histiocytosis is best regarded as an initial stage of many different forms of non-Langerhans’ cell histiocytosis (non-LCH), also classified by Zelger et al. as xanthogranulomas (5). Most patients either resolve spontaneously or show waxing and waning of lesions. Others may advance to better-defined entities such as multicentric reticulohistiocytosis or even xanthoma disseminatum. Thus, generalized eruptive histiocytosis is a diagnosis made with caution early in a disease course but our patient’s long history and spontaneous resolution help seal the diagnosis. A case of histiocytic sarcoma mimicking generalized eruptive histiocytosis has been described recently (6), but in Caputo’s extensive experience, other patients with generalized eruptive histiocytosis tended to heal, often with hyperpigmented macules (1).
Indeterminate cell histiocytosis is a histologically and ultrastructurally defined disease entity with an infiltrate of so-called “indeterminate cells” (7, 8). The clinical manifestations range from a solitary nodule at birth (9) to widespread lesions in adults (10). Though only a few cases have been described, two clinical subtypes seem to predominate: a solitary nodular form and a multiple nodular or macular form. In our view, indeterminate cell histiocytosis is not a single disease. Indeterminate cell histiocytosis has also been described as a reactive process. The multiple nodular form is best documented as part of nodular scabies, a persistent reaction after acute scabies infestation (11).

The classical cell biological definition of indeterminate cells is dendritically shaped epidermal non-keratinocytes without identifying cytoplasmic features (melanosomes, Merkel cell granules or Birbeck granules) (12). Today, many immunobiologists think of indeterminate cells as truely dendritic, Langerhans’ cell-like cells expressing CD1a and S 100, but lacking Birbeck granules and LAG antigen. In this setting, they may represent a special maturation stage of interstitial type dendritic cells (13). Others use this term to describe cells with features of both macrophages and dendritic cells (7). Our patient’s cells fulfill all three of these definitions.

A minor population of these indeterminate cells is found in normal human skin (12). In atopic dermatitis, a major population of epidermal dendritic non-Langerhans’ cells has been demonstrated by immunophenotypical and ultrastructural analysis, and these so-called inflammatory dendritic epidermal cells (IDEC) and not the Langerhans’ cells are the relevant IgE binding population in atopic dermatitis (14). These findings have recently been extended through functional investigations (15).

Differential diagnostic possibilities include Langerhans’ cell histiocytosis (LCH), the other diseases included in the spectrum of non-Langerhans’ cell histiocytosis, mastocytosis and xanthoma (Fig. 5) (16). The histopathological examination excluded the last two diagnoses; the lack of Birbeck granules and LAG antigen rules out the diagnosis of LCH. Figure 5 shows our view of the classification of the histiocytes, as based on the results of the key findings of Birbeck granules, CD1a and S100 expression and attempts to arrange the historically defined, clinically meaningful disease entities by virtue of limited disease features.

Our patient’s rash started in the distribution pattern of pityriasis rosea. A Christmas tree pattern has not been previously described in indeterminate cell histiocytosis. It is possible that our patient’s indeterminate cell histiocytosis developed in the pre-existing lesions of a healing or already healed pityriasis rosea. We attempted to analyse the infiltrate in the initial biopsy diagnosed as pityriasis lichenoides but there was insufficient tissue remaining for immunohistochemical characterization. The development of a skin disorder at the site of an unrelated, already healed skin disease is known as an isotopic response (17). Development of indeterminate cell histiocytosis in the lesions of a healing pityriasis rosea might explain the unusual distribution pattern.
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