Acquired Mucosal Indeterminate Cell Histocytoma

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Abstract: Indeterminate cell histiocytosis is an exceptional and controversial entity with variable clinical, histopathologic or immunohistochemical findings, sharing morphologic and immunophenotypic features from both Langerhans and non-Langerhans cell histiocytoses. Neoplastic cells express S-100 and CD1a antigens, but lack Birbeck granules. It has been reported in both adults and children, as solitary or multiple cutaneous lesions with rare extracutaneous involvement. We describe a 12-year-old boy with an indeterminate cell histiocytosis manifesting as a solitary verrucous papule on the mucosa of the glans penis. The morphologic features and diagnostic criteria of cutaneous indeterminate cell histiocytic proliferations are reviewed. The possible relationship between indeterminate cell and Langerhans cell histiocytoses is discussed.

Indeterminate cells are normal dendritic accessory cells, usually located in the dermis. According to the classical definition, they constantly lack intracytoplasmic Birbeck granules but share morphologic and immunophenotypic features with Langerhans cells (LC). Since its original identification, the exact relationship between the two types of cells has been a matter of controversy. Indeterminate cells migrate into the epidermis, and some authors have suggested that their organelles may be modified and may become LC (1). Conversely, when cultured, LC usually lose Birbeck granules, resembling indeterminate cells, and some authors have also postulated that indeterminate cells may represent a more mature form of LC (2–4).

Indeterminate cell histiocytosis (ICH) represents a rare and heterogeneous group of proliferations of indeterminate cells usually involving the skin and, exceptionally, extracutaneous sites. A possible relationship between indeterminate cell histiocytosis and LC histiocytosis, as well as other dendritic cell tumors, has been postulated (4–5).

CASE REPORT

A 12-year-old boy, with an irrelevant medical and family history was referred to our Department for evaluation of a solitary lesion on the glans penis which had appeared 1 month before. No previous history of trauma or pre-existing lesions was recorded.

Physical examination disclosed an apparently healthy boy with an erythematous, papule, 6 mm in diameter, with a moist and slightly verrucous surface, which was located on the lateral aspect of the glans penis (Fig. 1). The rest of the physical examination was unremarkable, and no similar lesions were noted elsewhere.
An excisional biopsy was performed. Histopathology examination disclosed an eroded mucosa and a dense inflammatory infiltrate in the upper and middle submucosa. This infiltrate was composed of histiocytic cells, with large eosinophilic cytoplasm and a round, elliptic or kidney-shaped nucleus, and numerous polymorphonuclear eosinophils (Fig. 2). No mitotic figures were observed. Immunohistochemical stains disclosed that histiocytic cells expressed CD68, S-100, and CD1a (Fig. 3) antigens. A similar proportion of cellular expression of these antigens was noted. In situ hybridization study for Epstein–Barr virus genome using a RNA probe (Inform EBER, from Ventana Medical Systems Inc., Tucson, AZ) yielded negative results.

Ultrastructural study of dermal histiocytes showed cells with large cytoplasms containing lysosomal dense bodies and a convoluted, intended, elongated nucleus (Fig. 4). No intracytoplasmatic Birbeck granules were identified after systematic evaluation of multiple cells, although several coated vesicular and tubular structures near the cellular membrane were noted.

A complete survey including hematologic and biochemical studies, chest X-ray film, abdominal echography, a whole body bone scan, and a cranial computed tomography disclosed no abnormalities.

After the excision, no recurrence of the lesion has been detected during a follow-up period of 2 years. No similar cutaneous or other extracutaneous lesions have developed elsewhere.

**DISCUSSION**

The histiocytoses are a heterogeneous group of histiocytic cell proliferations with diverse clinical features,
prognosis, and evolution. According to the clinicopathologic features and ultrastructural aspects of the histiocytic cell, they can be differentiated into three main groups: Langerhans cell (LCH), non-Langerhans cell (NLCH), and indeterminate cell histiocytoses (ICH).

Indeterminate cell histiocytosis was first defined in 1985 as a proliferation of histiocytic cells (6) that share morphologic and immunohistochemical characteristics with both LC and non-LC. Neoplastic cells have a large eosinophilic cytoplasm and an irregularly shaped nucleus. No cellular atypia, epidermotropism, or intercellular edema is observed. Indeterminate cells usually express S-100 and CD1a antigens. However, they always lack Birbeck granules. This latter feature is the diagnostic hallmark to differentiate ICH from LCH. Nevertheless, Ratzinger et al (7) have recently reported that histiocytic cells in ICH have the characteristics of both LC and macrophages, expressing CD68 and S-100 antigens and showing variable reactivity for CD1a. Therefore, unlike the classical definition, in which histiocytic cells are considered a variant of LC without Birbeck granules, current definition would stress the overlap between LC and macrophages.

Indeterminate cell histiocytosis is usually manifested as solitary (5,8,9) or multiple (6,10–26) asymptomatic maculo-papular or papulo-nodular lesions, both in adults and children. In most patients, the lesions are located on the trunk, face, neck, or extremities, although a generalized distribution has also been described (13,14). As far as we know, no previous reports of ICH involving the genital area have been published.

Extracutaneous lesions and systemic symptoms have rarely been reported. Isolated instances of ICH involving the lymph nodes (9,22,23), bones (7,24) and cornea (21) have been observed. Recently, an additional pediatric patient with multiple conjunctival lesions has been described (7).

The etiology of ICH remains unknown. Some authors have postulated that indeterminate cell histiocytic proliferations can represent a reactive disorder, secondary to antigenic exposure (7). A proliferation of indeterminate cells has been detected in isolated occurrences of nodular scabies (18), in healing lesions of pityriasis rosea (11) and even in association with generalized eruptive histiocytosis (10). Exceptional instances of ICH arising in patients with a history of a low-grade B-cell lymphoproliferative disorder (9,22,23) have also been described. Nevertheless, in the vast majority of patients, ICH develops spontaneously and no triggering factors can be identified.

The evolution of the disease is variable. It is usually an indolent or self-limiting disorder, with persistence of the lesions, development of new ones, or even spontaneous regression (7). As solitary lesions are usually removed, it is difficult to predict their natural evolution. Conversely, two adult patients who developed acute leukemia have been described (9,22,23), as well as a child with a malignant histiocytic outcome (24).

Although ICH appears to be a well-defined disorder, a broad spectrum of clinical and histopathologic features has been reported. Patients with clinical and histopathologic features identical to either LCH (16,24), Hashimoto-Pritzker syndrome (5,17), NLCH (7,11,14,26) or even dendritic cell tumors (25) have been documented. In such instances, the definitive diagnosis was established on the basis of immunohistochemical stains and ultrastructural features. Those presentations clinically or histologically closer to NLCH would fit in the recent definition of ICH, whereas those similar to LCH would be included in the classic definition.

In our patient, histopathologic and immunohistochemical features indistinguishable from those of LCH were observed. Transmission electron microscopy disclosed a nuclear morphology highly suggestive of LCH and coated vesicular and tubular structures near the cellular membrane were noted. However, no intracytoplasmic Birbeck granules were detected. Based on this latter feature, the definitive diagnosis of solitary ICH was established.

Some observers seem to question the diagnostic value of Birbeck granules: LC lose their Birbeck granules in tissue culture (2,3). In some clear-cut LCH series, electron microscopy was not performed and diagnosis was established on the basis of immunohistochemical results. In others, no evidence of Birbeck granules on the ultrastructural examination was detected (27,28). This latter feature has been related to a naturally occurring point mutation in the human Langerin gene (29,30). A possible relationship between LCH and other dendritic cell tumors or reactive proliferations has been suggested. Both LC and dermal dendritic cells derive from a common myeloid precursor cell (4). Therefore, the possibility that indeterminate cells and LC could correspond to different evolutionary stages of a unique cell has been proposed.

In conclusion, as indeterminate cell proliferations have heterogeneous clinical and histopathologic features often similar to those of LCH and NLCH, it could be questioned whether ICH represents an individualized disorder not related to other forms of histiocytosis. The observation of some instances of clear-cut LC histiocytosis lacking Birbeck granules and the histopathologic similarities between LCH and ICH seem to suggest that a continuum between these disorders may exist.
REFERENCES