Case Study

Primary Cutaneous True Histiocytic Sarcoma: A Case with an Indolent Course

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True histiocytic sarcoma (THS) is a rare form of malignant neoplasm, which is thought to have a poor prognosis. We report the case of a 47-year-old woman who presented with a solitary cutaneous tumor on the forehead. After excision of the tumor, she had no recurrence or metastasis for 10 years. Microscopic observation showed massive infiltration of histiocytoid tumor cells from the dermis without epidermotropism to the deep muscle layer. The large histiocytoid tumor cells contained folded nuclei with frequent mitoses and abundant cytoplasm, but showed no phagocytosis. Muscle fibers were destroyed by infiltration of the tumor cells. Immunohistochemically, the tumor cells were positive for histiocytic markers (CD68 and lysozyme), but negative for lymphoid and epithelial markers. No rearrangement of the immunoglobulin heavy chain and T-cell receptor β/γ chain genes was demonstrated. Therefore, the lesion was diagnosed as primary cutaneous true histiocytic sarcoma (PCTHS) based on the current, strict definition of histiocytic malignancies. In reviewing the literature, we found that some PCTHSs had an indolent clinical course; therefore, we propose that PCTHSs may have variable prognoses.

Key Words: histiocytic sarcoma, cutaneous lymphoma, CD68

INTRODUCTION

Cutaneous neoplasms morphologically suggestive of a histiocytic lineage include heterogeneous, distinctive entities such as monocyte/macrophage lesions, Langerhans cell/dendritic cell lesions, fibrohistiocytic tumors, and CD30(+) anaplastic large cell lymphomas. Fibrohistiocytic tumors including dermatofibroma and atypical fibroxanthoma are mesenchymal neoplasms with a histiocytoid appearance. Langerhans cell/dendritic cell neoplasms and anaplastic large cell lymphomas express characteristic immunohistochemical markers for histiocytes and lymphoid cells, respectively. According to the current definition, only neoplasms derived from the monocyte/macrophage series are recognized as true histiocytic tumors. In the skin, true histiocytic malignancies may manifest themselves as cutaneous involvement of generalized malignant histiocytosis (MH) or primary cutaneous true histiocytic sarcoma (PCTHS). In general, the latter is recognized as a localized form of the former1-5. Here, we report a case of PCTHS which showed no relapse for 10 years, its indolent clinical behavior differing from the usual aggressive course of MH.

CASE REPORT

A 47-year-old woman, who was not from an HTLV-I endemic area, presented with a three-week history of rapidly growing nodule on the right forehead without any antecedent episode such as insect bite or trauma. The lesion was 1.2 cm in size, red and dome-shaped (Fig. 1), and was movable without periosteal adhesion. The patient lacked constitutional symptoms such as fever and wasting, and physical examination failed to demonstrate any enlargement of the superficial lymph nodes, liver and spleen.

There were no abnormal hematopoietic cells in the peripheral blood or bone marrow (aspiration...
Fig. 1. Dome-shaped tumor on the right forehead.

and biopsy). Other laboratory parameters were unremarkable. Antibodies against both HTLV-1 and EB viruses were negative. Image analyses including chest X-ray, Ga-scintigraphy, and abdominal CT showed no abnormalities. The forehead lesion was locally excised, and no additional treatment was given. The postoperative course was uneventful, and for 10 years the patient had no evidence of relapse at the primary site, metastasis or hematologic abnormality.

MATERIALS AND METHODS

The resected specimen was fixed in 10% buffered formalin and embedded in paraffin. Five-micrometer-thick sections were stained with hematoxylin-eosin and Masson’s trichrome. Immunohistochemical studies were performed by the immunoperoxidase method as described previously. The primary antibodies used were as follows: CD1a (O10, Immunootech, Marseille, ×1), CD3 (PS-1, Novocastra, Newcastle, ×100), CD4 (1F6, Novocastra, ×40), CD8 (C8/144B, Dakopatts, ×100), CD15 (Leu M1, Beckon Dickinson, Mountain View, ×100), CD20 (L26, Dakopatts, ×100), CD30 (BerH2, Dakopatts, ×80), CD45 (2B11+PD7/26, Dakopatts, ×50), CD45RO (UCHL-1, Dakopatts, ×50), CD68 (KP-1, Dakopatts, ×40), CD68 (PG-M1, Dakopatts, ×200), CD79a (JCB117, Dakopatts, ×100), latent membrane protein (LMP) (CSI-4, Dakopatts, ×40), epithelial membrane antigen (EMA) (E29, Dakopatts, ×100), carcinoembryonic antigen (CEA) (II-7, Dakopatts, ×25), neuron-specific enolase (NSE) (BBS/NC/V1-H14, Dakopatts, ×100), cytokeratin (CAM 5.2, Beckon Dickinson, ×1), cytokeratin (AE1/AE3, Dakopatts, ×50), S-100 protein (Dakopatts, ×300), and lysozyme (Dakopatts, ×200).

Paraffin sections were processed for ultrastructural studies. After deparaffinization and dehydration, sections on glass slides were covered with gelatin capsules filled with epoxy resin. After polymerization, the capsules were removed from the glass slides, and sliced into ultrathin sections. Double-stained ultrathin sections were then observed by electron microscopy.

For genotypic studies, deoxyribonucleic acid was extracted from paraffin sections by proteinase K (200 μg/mL) digestion. The supernatant containing DNA was used directly for PCR amplification. The polymerase chain reaction was used to detect rearrangements of (1) the immunoglobulin heavy chain (IgH) gene using three VH primers (FR1c, FR2a and FR3a) and two JH primers (LJH and VLJH)‡, (2) the T-cell receptor (TCR) γ-chain gene using eight V primers (V2/V8, V3, V4, V5, V9, V10, V11) and three J primers (J1.3/2.3, J1.1/2.1, J1.2)§, and (3) the TCR β-chain gene using five primers (V, D1, D2, J1 and J2)‡.

RESULTS

Microscopically, the lesion consisted of a massive infiltration of large histiocytoid cells from the upper dermis into the tunicus muscularis through the subcutaneous adipose tissue, and exhibited a circumscribed bottom-heavy pattern (Fig. 2A). In addition, muscle fibers were destroyed by the infiltrating tumor cells (Fig. 2B). Large tumor cells showing pleomorphism contained irregular indented nuclei with a fine chromatin and an abundant cytoplasm. Mitotic figures were frequently observed (Fig. 2C). In spite of the histiocytic appearance, no phagocytosis was evident. Although epidermotropism was lacking, the epidermis was depressed.
Fig. 2. Hematoxyline and eosin-stained morphological appearance compatible with primary cutaneous true histiocytic sarcoma. A: Low-power view. There is a massive infiltration from the upper dermis into the deep muscle layer (×10). B: Middle-power view. Muscle fibers have been destroyed by the infiltrating tumor cells (×260). C: High-power view. Large tumor cells show pleomorphic infiltration with frequent mitoses. Small amount of reactive lymphocytes are mingled (lower right area, ×550). D: Electron microscopic examination. Large tumor cells have an abundant cytoplasm and an irregular nuclear envelope (×2000).
and atrophic without a clear Grenz zone. The tumor cells were accompanied by patchy reactive small lymphocytes in the dermis and the upper subcutis (Fig 2C).

Almost all tumor cells were positive for CD68 (KP-1 and PG-M1) (Fig. 3A) and lysozyme (Fig. 3B), and some were also positive for CD15 (Fig. 3C). None were immunoreactive for CD1a, CD3, CD4, CD8, CD20, CD30, CD45, CD45RO, CD79a, S-100 protein, NSE, EMA, CEA, cytokeratins (CAM5.2 and AE1/AE3) or LMP.

Ultrastructural examination clearly demonstrated nuclear foldings and abundant cytoplasm (Fig. 2D). Although the ultrastructure was not well preserved, no tumor cells appeared to contain cerebriform nuclei, well developed rough endoplasmic reticulum or Birbeck granules.

In the genotypic analysis, there were no clonal amplification products for IgH, TCR γ-chain, or TCR β-chain.

**DISCUSSION**

"Histiocytes" include two different cell lineages: the monocyte/macrophage and the Langerhans cell/dendritic cell series. Histiocytes from the monocyte/macrophage lineage exhibit high phagocytic activity, but play little part in the immunologic response. They also lack Birbeck granules. The Langerhans cell/dendritic cell series show poor phagocytosis and actively work as immunocompetent cells. Only the former are designated as "true" histiocytes. Therefore, the diagnosis of true histiocytic neoplasm should be made only when characteristics of the monocyte/macrophage series are strictly established. The current criteria for true histiocytic sarcoma (THS) are as follows: 1) the tumor cells show histiocytoid features such as nuclear foldings, abundant cytoplasm and occasional phagocytosis; 2) they should be immunoreactive for two or more histiocyte-associated markers; 3) they lack reactivity for B cell- and T cell-specific markers; 4) they also lack Birbeck granules and reactivity for CD1a; 5) they are negative for CD30, which is a characteristic marker of anaplastic large cell lymphoma; 6) there is no evidence of immunoglobulin or T-cell-receptor gene rearrangement.

The above criteria are still controversial to some extent. First, evidence of phagocytosis is not always essential for diagnosis of THS. Some investigators have also reported cases of CD30-positive THS. Furthermore, exceptional cases of THS showing clonal rearrangement of the immunoglobulin or the T-cell receptor genes have been reported. Since the morphologic and phenotypic criteria of THS were fulfilled, the authors suggested the possibility of biphenotypic, lymphocytic and histiocytic differentiation in these lesions.

The tumor cells of the present case showed histiocytoid features, such as folded nuclei with a fine chromatin and an abundant cytoplasm, although phagocytosis was apparently absent. The lesion also showed a destructive growth in the muscle layer and the cytologic atypia with numerous mitoses. Immunohistochemically, the tumor cells were positive for CD68 (KP-1 and PG-M1) and lysozyme but negative for other lymphoid and epithelial markers. Electron microscopy failed to demonstrate the presence of Birbeck granules. Clonal rearrangement of the IgH and TCR β- and γ-chain genes was not demonstrated. Therefore, the present tumor fulfilled the strict criteria of THS.

THS is very uncommon, occurring in lymph nodes as well as at extranodal sites such as the gastrointestinal tract, the liver, the kidneys, the lungs, the central nervous system, the bone marrow, the bones, the soft tissues and the skin. THS usually shows an aggressive clinical course and a poor prognosis. To our knowledge, 38 cases have been reported previously (Table). Eight (21.1%) of these cases initially involved the skin. Four were solitary, each one occurring in the supraclavicular, the abdominal, the back and the lumbarosacral regions respectively, three had multiple or disseminated lesions, and one was of unspecified localization. The patients ranged in age from 7 to 85 years (median: 60 years; mean: 53.4 years), and included five men and three women. During follow-up (0.5-96 months), which was possible in seven cases, four patients died from the tumor within 6 months, one died from infectious complications without tumor 96 months later, and two were alive without disease 10 months and 26 months later. Two of the three who lived more than 6 months were children aged 7 and 10 years. Secondary involvement of the skin was also described in seven cases (Table). Therefore, the skin is one of the most common sites of THS involvement (15 of 38 cases, or 39.5%).

There are several skeptical opinions on THS as a distinct entity. Since THS is difficult to distinguish from monocytic leukemia (MoL) even by morphologic, cytochemical, immunocytochemical
Fig. 3. Immunohistochemical appearance of histiocytic markers for primary cutaneous histiocytic sarcoma. A: Almost all the tumor cells are positive for CD68 (KP-1, ×550). B: Almost all the tumor cells are positive for lysozyme (×550). C: Some tumor cells are positive for CD15 (×550).
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Table. Localized true histiocytic malignancies: Review of the literature

<table>
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<tr>
<th>Reference</th>
<th>Total number of cases</th>
<th>Number of cases with cutaneous involvement</th>
<th>Number of cases initiated in the skin</th>
<th>Age(Years)/Sex</th>
<th>Survival (Months)</th>
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<td>Total</td>
<td>38</td>
<td>15</td>
<td>8</td>
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M. male; F. female; DF, disease-free; NA, not available; 1) died of complications; 2) alive

and molecular methods, Elghetany proposed that cutaneous THS should be regarded as an extramedullary cutaneous expression of MoL, i.e., aleukemic leukemia cutis of monocytic origin<sup>23</sup>. However, PCTHS is localized to the primary site and behaves like malignant lymphoma rather than leukemia. Therefore, PCTHS may be derived from tissue-fixed histiocytes<sup>24</sup>, in contrast to MH, which is thought to originate from migrated free histiocytes. Some cases of PCTHS, including the present one, behave less aggressively than previously thought, indicating that this rare lesion may have a widely variable prognosis.

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