

Primary Cutaneous Blastic Natural Killer-Cell Lymphoma

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Sir,

Blastic natural killer-cell lymphoma, also called “agranular CD4+ CD56+ haematodermic neoplasm” is an uncommon type of tumour, which is included in the new World Health Organization (WHO) classification as a malignancy derived from natural killer (NK) cells. It is very aggressive, affecting many organs, and skin involvement is highly characteristic. Several origins have been proposed, but recent studies have shown a relationship with plasmacytoid monocytes.

We report here a new case of this rare lymphoma, with skin infiltration as the first manifestation, and with early dissemination to bone marrow and central nervous system (CNS).

CASE REPORT

A 68-year-old man was referred to our department, with several purple nodules on his back (Fig. 1). These lesions had begun about 3 months earlier and had enlarged rapidly. A punch biopsy revealed a dense infiltrate located on the deep dermis, extending to the subcutis. Tumour infiltration spared the epidermis and subepidermal region with a Grenz zone (Fig. 2A). The dermal infiltrate was monotonous and composed of medium-sized pleomorphic cells. The nuclei were irregular, with finely dispersed chromatin and several small or medium-sized nucleoli (Fig. 2B). There were no obvious features of angiotropism or angiodestruction.



Fig. 1. Violaceous nodules on the back, some with central ulceration.

Immunohistochemical studies were performed on paraffin-embedded sections of skin lesions. The neoplastic cells reacted positively for CD56 (Fig. 3A), CD4, CD43 and CD68, and negatively for CD3, CD5, CD15, CD20 (Fig. 3B), CD30, CD34, TdT and myeloperoxidase.

Polymerase chain reactions showed polyclonal T-cell receptor gamma gene rearrangement. *In situ* hybridization for Epstein-Barr virus (EBV)-encoded RNAs did not exhibit signals indicating the presence of EBV mRNA within the malignant cells of the infiltrate.

A computed tomographic scan of the skull, chest and abdomen, and a bone marrow biopsy specimen revealed no extracutaneous involvement. Analysis of peripheral blood, liver function tests, beta-2-microglobulin, and white and red blood cell counts produced normal results. Specialist examinations did not indicate any involvement of the upper respiratory tract system.

During the period of examination (20 days), the skin lesions were fast growing, and anaemia and duplicated serum beta-2-microglobulin levels appeared. A second bone marrow biopsy was made, showing lymphomatous infiltration. Analysis of the cerebrospinal fluid revealed infiltration by lymphoma.

A diagnosis of primary cutaneous blastic NK-cell lymphoma with dissemination to bone marrow and CNS was made. High-dose aggressive chemotherapy was established with cyclophosphamide, vincristine, adriamycin, dexamethasone

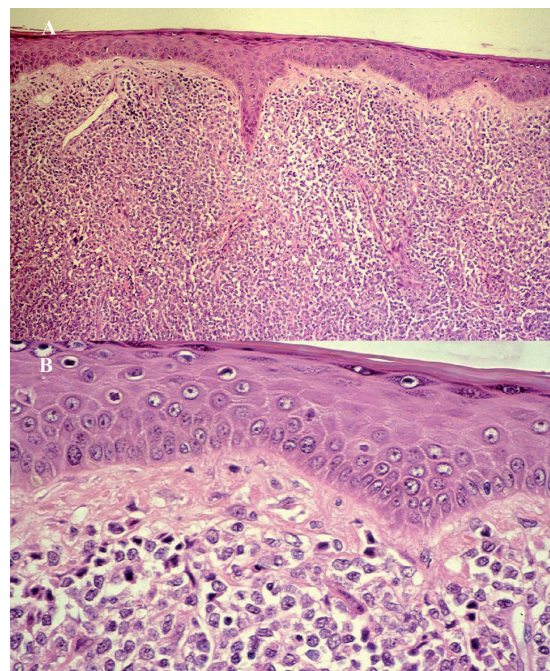


Fig. 2. Biopsy of a tumour. (A) Dense infiltrate in dermis, without epidermotropism, and a Grenz zone below the epidermis (haematoxylin-eosin $\times 40$). (B) At higher magnification medium-sized cells with irregular nuclei and some mitosis can be observed (haematoxylin-eosin $\times 100$).

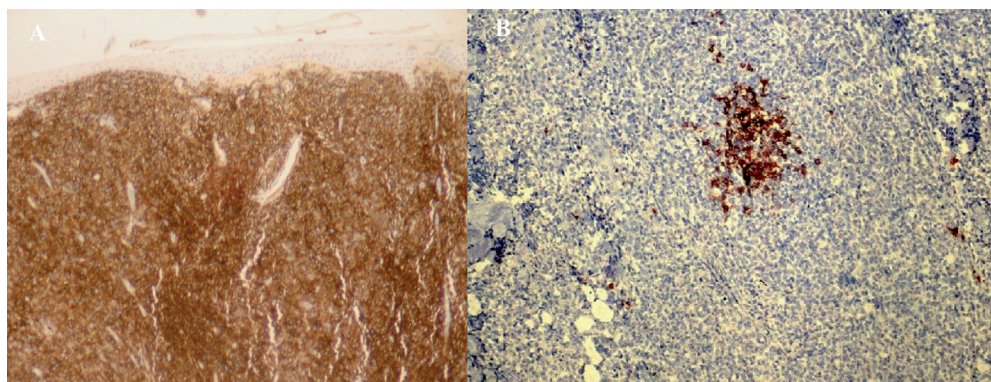


Fig. 3. Immunohistochemistry. (A) Neoplastic cells reacting positively for CD56. (B) Negative reaction of the neoplastic infiltrate to CD20, with a small amount of B-cells inside.

(hyperCVAD), methotrexate and Ara-C; intrathecal chemotherapy was associated. The patient presented complete remission after three cycles of chemotherapy, but with several complications, such as septic shock and infectious spondylitis. Twelve months after diagnosis the patient remains alive.

DISCUSSION

The issue of NK-cell neoplasm is complex. The most recent WHO classification recognizes the following NK-cell malignancies: aggressive NK-cell leukaemia, extranodal NK/T-cell lymphoma nasal type and blastic NK-cell lymphoma/leukaemia (1). Blastic NK-cell lymphoma/leukaemia is an aggressive neoplasm with multi-organ involvement (2). It is characterized by frequent skin involvement (which may be the first clinical manifestation of the disease) and a rapid course with bone marrow infiltration (3). There is a male predominance, and median age at diagnosis is about 60 years (4), but the disease may occur in younger adults or in children (3).

Clinically, violaceous lesions appear, with predilection for the trunk, but also involving extremities and the head and neck (4). Histopathological procedures usually show an infiltrate with monomorphous medium-sized cells with fine chromatin and scant cytoplasm. There are no granules within the cytoplasm of the cells. The neoplastic cells express CD4, CD56 and CD43. Expression of CD2, CD7, TdT, CD34 and CD68 is variable. Other T-cell markers, B-cell-associated markers and myelomonocytic markers are negative. There is no association with EBV infection (2).

The evolution of these neoplasms is rapidly fatal when polychemotherapy is not possible. When chemotherapy is applied there is an initial response, but relapse is a highly frequent event with CNS infiltration (3). The median survival of these malignancies is 14 months (5), with overall survival close to 0% after 5 years of follow-up (3). Some patients who benefited from allogenic bone marrow transplantation were still in complete remission after 60 months (3). The failure of conventional chemotherapy implies the necessity of

developing alternative therapies. Antibodies against CD123 could potentially be used for targeting drugs to tumour cells (6).

With regard to the origin of this neoplasm, although it was called blastic NK-cell lymphoma, its precise lineage was unresolved. Recent reports have presented a rare population of cells that expresses all the characteristic markers of this lymphoma. This population appears to be related to plasmacytoid monocytes, and these cells are called plasmacytoid dendritic cells, or type 2 dendritic cells (3, 6). Some authors have already proposed changing the name of this disease, calling it "early plasmacytoid dendritic cell leukaemia/lymphoma" (7).

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