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CD8-Positive Primary Cutaneous Anaplastic Large Cell Lymphoma with a Fair Prognosis

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Accepted April 19, 2002.

Sir,

Anaplastic large cell lymphoma (ALCL), also called Ki-1 lymphoma, is characterized by the proliferation of predominantly large neoplastic lymphoid cells with strong expression of the cytokine receptor CD30 and a characteristic growth pattern (1). A previous study reported that primary cutaneous CD30-positive (CD30+) cases of ALCL, regardless of their morphologic classification (anaplastic or non-anaplastic), can be considered as distinct types of cutaneous T-cell lymphoma (2). Most cases of ALCL have been reported to be CD4 positive (CD4+). We present here a case of a primary cutaneous ALCL with a CD8-positive (CD8+) phenotype, showing fairly good prognosis.

CASE REPORT

In February 2001 a 68-year-old man presented with a 1-month history of skin tumor on his right forearm (Fig. 1). The tumor had developed rapidly and presented as a solid, reddish-violet, circumscribed, 4.3×3.9 cm mass. In the center of the tumor there was a 1.4×1.9 cm ulcer. There was no lymphadenopathy.

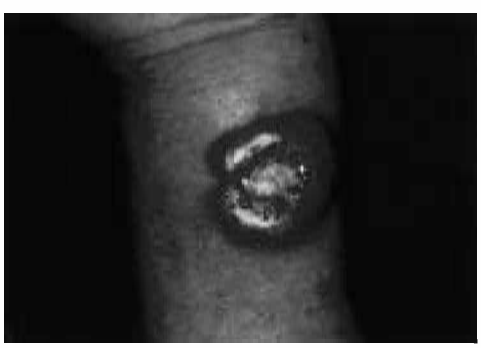

Fig. 1. Clinical appearance of the tumor on the patient's right wrist.

Laboratory investigations were almost normal, except for a mild renal dysfunction (creatinine clearance = 40 ml/min/1.73 m^2). No antibodies were detected against the human T-cell leukemia virus-1 (HTLV-1) or human immunodeficiency virus (HIV). The bone marrow did not show tumor cell involvement. A ^{67}Ga whole body scan showed a hot spot corresponding to the mass on the patient's right forearm. No evidence of lymphadenopathy or tumor mass was found by computerized tomography of his chest and abdomen and magnetic resonance imaging of his head and neck.

An incisional biopsy was performed. Histologically, the epidermis was slightly infiltrated by mononuclear cells. Irregularly shaped large cells with large atypical (often chromatin-poor, horseshoe-shaped) nuclei, prominent nucleoli and ample cytoplasm comprised the infiltrate, which extended from the papillary dermis to the subcutaneous fat (Fig. 2*a*). Medium-sized lymphoid cells with occasional atypical nuclei mingled with large cells were also observed. Adjacent areas showed a predominance of inflammatory cells consisting of normal lymphocytes and histiocytes. The tumor cells from the specimen were studied using a panel of monoclonal antibodies and they expressed leukocyte common antigen, CD2, CD3, CD5, CD7, CD8 (Fig. *2b*), CD30, CD45RO, CD68 and T-cell restricted intracellular antigen-1 (TIA-1). The cells tested negative for CD1a, CD4, CD16, CD20, CD56, CD57, anaplastic lymphoma kinase and TdT.

DNA hybridization analysis was performed using the T-cell antigen receptor gene (Cβ) probe, as described elsewhere (3), and rearranged bands were detected, indicating the proliferation of clonal T lymphocytes.

After the biopsy, a partial spontaneous resolution of the tumor was observed. The patient was treated for 20 days with local radiation therapy at 2 Gy per day for a total dose of 40 Gy, after which the tumor disappeared

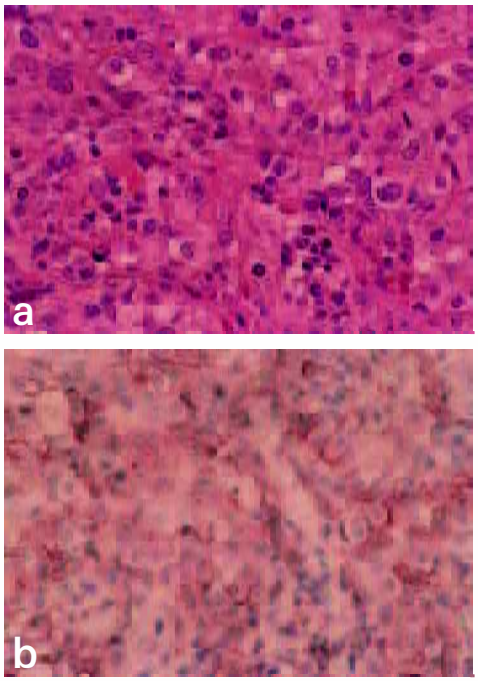

Fig. 2. Histopathologic findings: (*a*) cohesive sheets of large anaplastic cells with prominent nuclei and abundant cytoplasm (hematoxylin and eosin ×400). (*b*) Positive staining for CD8 antigen (×400).

and the ulceration healed with scar formation. The patient is still disease-free, more than a year after the therapy.

DISCUSSION

Because of the solitary cutaneous tumor, proliferation of large atypical cells, and CD30 expression, we diagnosed the present case as a primary cutaneous ALCL. ALCL was defined as a histological entity by Stein et al. (1) in 1985. This type of lymphoma is associated with expression of the immunological marker CD30. Most cases of primary ALCL in the skin have been reported as non-aggressive lymphomas. They arise *de novo* in the skin and may rarely affect other organs secondarily. Primary cutaneous ALCL is thought to differ from the systemic form owing to its site of origin, its clinical features and its frequent absence of anaplastic lymphoma kinase expression. The lesion usually presents as a solitary, asymptomatic, cutaneous or subcutaneous reddish-violet tumor which can be superficially ulcerated. It has a more favourable prognosis than nodal ALCL or secondary ALCL of mycosis fungoides and requires different treatment, at least in the early stages. Only in patients with generalized skin disease, who seem to have a greater risk of developing extracutaneous disease, should systemic polychemotherapy be administered.

Cutaneous T-cell lymphoma (CTCL) generally has the phenotype of CD3+ CD4+ and CD45RO+ memory T cells. Recent studies for CD30+ ALCL have demonstrated that primary non-cutaneous ALCL shows considerable variation in T-cell phenotypes including CD4+ CD8-, CD4- CD8+, CD4- CD8-, and CD4+ CD8+ (4, 5). In contrast, primary cutaneous CD30+ ALCL usually shows a CD4+ CD8− phenotype (6), but the present case showed a CD4- CD8+ phenotype. CTCL expressing a CD8+ T-cell phenotype is extremely rare and its clinicopathological features are ill-defined, although the outcome has been indicated to be poor, with resistance to various treatments and short survival (7). We found 6 cases of CD30+ CD8+ CTCL in the literature (8–10). Among these, 4 were ALCLs and the others were borderline cases considered as ALCLs with histological features of lymphomatoid papulosis. Three cases of ALCL showed a good clinical outcome (free of disease for 2 years, 30 months and 55 months, respectively). It is suggested that CD8+ expression alone cannot be a hallmark for a poor prognosis.

The vast majority of T/null ALCLs, including both the primary cutaneous and non-cutaneous types, were found to express the cytotoxic molecules perforin, granzyme B and T-cell intracellular antigen-1 (TIA-1), regardless of their expression of CD4 or CD8 (9–11). The expression of those cytotoxic granule proteins in the majority of ALCLs implies a cytotoxic lymphocyte phenotype and suggests that most cases originated from lymphocytes with cytotoxic potential. Our case was also positive for TIA-1.

Further investigation is warranted to elucidate the association between the immunophenotype and the clinical behavior of primary cutaneous ALCL.

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Disseminated Pagetoid Reticulosis Presenting as Cytotoxic CD4/CD8 Double Negative Cutaneous T-cell Lymphoma

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Accepted April 30, 2002.

Sir,

Disseminated pagetoid reticulosis (DPR) is a rare form of cutaneous T-cell lymphoma (CTCL) originally described by Ketron & Goodman in 1931 (1). This lymphoproliferative disorder usually presents as multiple erythematous, squamous patches, plaques, nodules, ulcerated skin tumours and, not infrequently, runs an aggressive course with dissemination of the lesions and progression to a fatal outcome (1, 2).

Cytotoxic cutaneous lymphomas are uncommon and usually express a CD8 and/or CD56 positive phenotype. They represent a heterogeneous group of lymphomas showing various features with regard to clinicopathologic profile, immunophenotypic features, clinical course and prognosis (3). All cytotoxic lymphocytes express a set of toxic proteins, e.g. perforins, granzymes A (GrA) and B (GrB), and the T-cell intracellular antigen-1 (TIA-1) (4), which are reliable markers of cells with activated cytotoxic function (2).

Gemcitabine is a nucleoside antimetabolite with established activity against several solid tumours showing promising results in the treatment of lymphoproliferative malignancies. Gemcitabine is a cytosine analogue that causes less myelosuppression as well as immunosuppression compared with other available nucleoside analogues (5).

We describe here a 35-year-old patient with a primary cutaneous T-cell lymphoma presenting with clinicopathologic features of DPR and showing a CD4/CD8 double negative, TIA-1/granzyme B cytotoxic positive phenotype. Furthermore, we report the efficacy of gemcitabine treatment in this aggressive lymphoproliferative disorder.

CASE REPORT

A 35-year-old man presented with a 1-year history of generalized, painful, erythematous, some ulcerated and exudative patches, plaques and nodules (Fig. 1). No hepatosplenomegaly or lymphadenopathy was detected. Past medical history and physical examination were unremarkable, and laboratory investigations were within normal limits. Staging procedures (total computed tomographic scans and bone marrow aspirate) showed no abnormalities. The patient's serum was negative for anti-HTLV-1 and anti-EBV antibodies and the levels of sIL-2 receptor and sTNF-α were within normal limits. Biopsy specimens from lesional skin were routinely processed for formalin fixation and paraffin embedding. Histopathologic examination showed a dense intraepidermal infiltrate of medium/large neoplastic lymphoid cells with clear, abundant cytoplasm, hyperchromatic nucleus and prominent nucleoli, scattered in the basal and suprabasal layers of the epidermis (Fig. 2). A few atypical lymphoid cells were also present around the blood vessels of the papillary dermis. The phenotypical profile of the intraepidermal lymphocytes was as fol-

Fig. 1. Erythemato-violaceous plaques and nodules at time of presentation.