

CLINICAL REPORT

Blastic CD56+ Natural Killer-cell Lymphoma with Primary Cutaneous Manifestation

 THOMAS G. BERGER¹, REINHARD E. VOLL², MIKLOS SIMON JR.¹ and FRANKLIN KIESEWETTER¹

 Departments of ¹Dermatology and ²Internal Medicine III, University Hospital of Erlangen, Erlangen, Germany

T/natural killer-cell lymphomas belong to a heterogeneous group of non-Hodgkin lymphomas with predominant extranodal, often cutaneous, manifestations. In contrast to B- and T-cell lymphomas, T/NK-cell lymphomas were only recently regarded as a distinct entity. These rather aggressive malignancies arise from cytotoxic T cells, NK-cells or NK-like T cells, which share several phenotypic and functional properties. We report a man with a blastic NK-cell lymphoma with nodular skin infiltrations as the leading clinical manifestation of the disease. Complicated of tuberculosis, the patient died within 9 months of diagnosis, despite aggressive polychemotherapy. **Key words:** cytotoxic lymphoma; lymphoma classification; NK cells.

(Accepted August 11, 2003.)

Acta Derm Venereol 2004; 84: 53–56.

Thomas Georg Berger, Department of Dermatology, University Hospital of Erlangen, Hartmannstr. 14, D-91052 Erlangen, Germany.
E-mail: thomas.berger@derma.imed.uni-erlangen.de

T/natural killer (NK)-cell lymphomas are a rare and heterogeneous subset of non-Hodgkin lymphomas. They are characterized by the expression of typical NK-cell markers, most importantly CD56. Lymphomas derived from NK cells typically lack a rearrangement of the T-cell receptor genes. They usually present as extranodal diseases with an unfavourable prognosis. The current WHO classification (1, 2) differentiates “nasal type” T/NK-cell lymphoma, blastic NK-cell lymphoma and aggressive T/NK-cell leukaemia. Most T/NK-cell lymphomas, especially in patients of Asian or native American origin, affect the nasopharyngeal region; however, cutaneous involvement displaying erythematous papules, plaques and tumours is common. In some cases, the skin is the only manifestation of the disease at the time of diagnosis. We report here a man with a blastic NK-cell lymphoma with cutaneous involvement as the initial disease manifestation.

CASE REPORT

A 79-year-old man was referred to the Department of Dermatology with multiple plaques and nodules which

first appeared on the head and the shoulder one year previously. Later, numerous non-itching, painless lesions appeared on the trunk and the extremities and increased dramatically during the 4 weeks prior to admittance. After a time the lesions began to itch. He complained of general malaise, but was otherwise healthy without fever, night-sweats, loss of weight or any known chronic disease. A physical examination showed more than a hundred red to purple plaques and tumours, with a maximal diameter of 5 cm, disseminated on the head, trunk and the extremities (Fig. 1). There were findings of cervical and axillary lymphadenopathy, splenomegaly and testicular pain without palpable masses. Blood examinations showed haemoglobin 12.0 g/dl, platelets $116 \times 10^9/l$ and a white blood cell count of $7.4 \times 10^9/l$. The blood smear revealed 9% atypical lymphocytes, but no blasts. The serum parameters, including immunoglobulin concentrations and protein electrophoresis, were within their reference values, apart from a slightly increased lactate dehydrogenase (259 U/l) most likely caused by the lymphoma. Blood coagulation tests and urine analysis were normal. A delayed type hypersensitivity test (multitest Merieux) did not result in any skin reactions against 7 common recall antigens including tuberculin. The phenotyping of peripheral blood leucocytes by flow cytometry exhibited normal numbers of T cells, B cells, monocytes and NK cells. Serologically, there were no signs of an active infection with Epstein-Barr virus (EBV) or cytomegalovirus.

Repeated skin biopsies uniformly showed, under a normal epidermis, a dense dermal infiltrate of medium-sized basophilic lymphoid cells with distinct cytoplasm, pleomorphic nuclei and frequent atypical mitoses. The cells did not form follicular centres (Fig. 2). Immunohistopathology revealed reactivity of approximately 90% of the cells with CD56 and a homogeneous and a strong expression of bcl-2 and Ki-67. Many cells also stained positive for CD4; only 10% of the cells were positive for CD8. Immunostainings for CD3, CD3ε, CD19, CD20, CD30, CD68, CD79a and TIA 1 were either very weak or negative (Fig. 3). Clonal rearrangement of the T-cell receptor (TCR)-γ-chain or the immunoglobulin heavy chain was not detected by polymerase chain reaction (PCR). The histopathological and immunohistopathological examinations of an

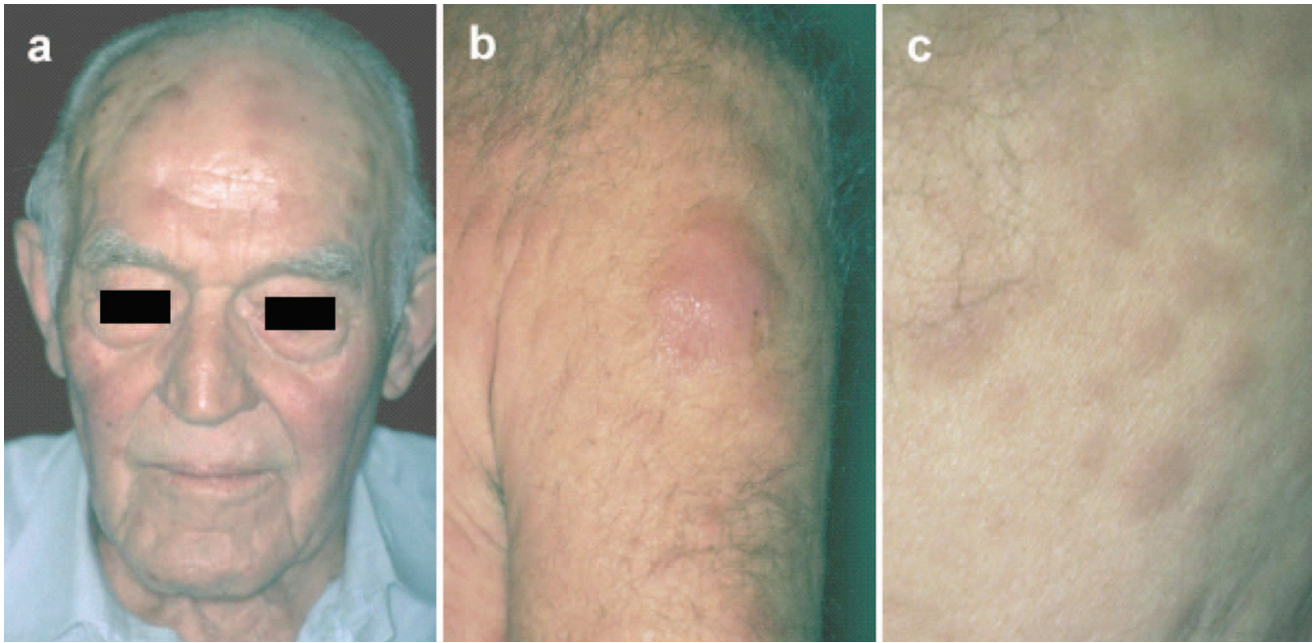


Fig. 1. Multiple nodules and plaques on the forehead (a), shoulder (b) and buttock (c).

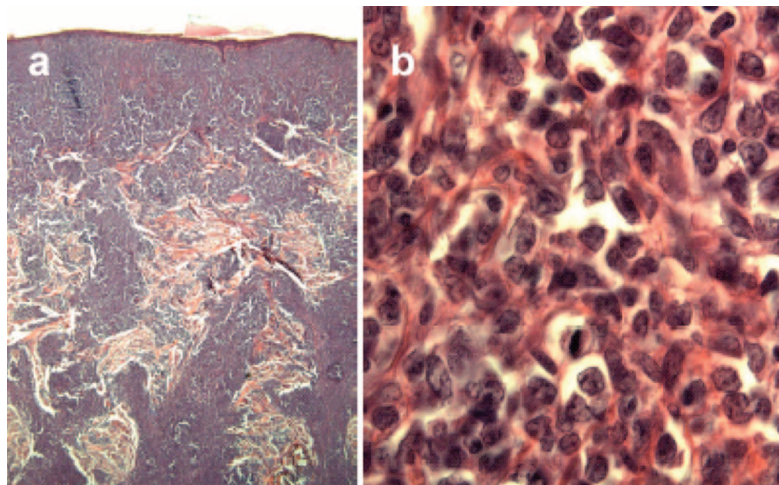


Fig. 2. Photomicrograph showing (a) a dense dermal infiltrate composed of (b) medium-sized lymphoid cells with distinct cytoplasm and pleomorphic nuclei (haematoxylin/eosin-staining, original magnification (a) $\times 40$; (b) $\times 400$).

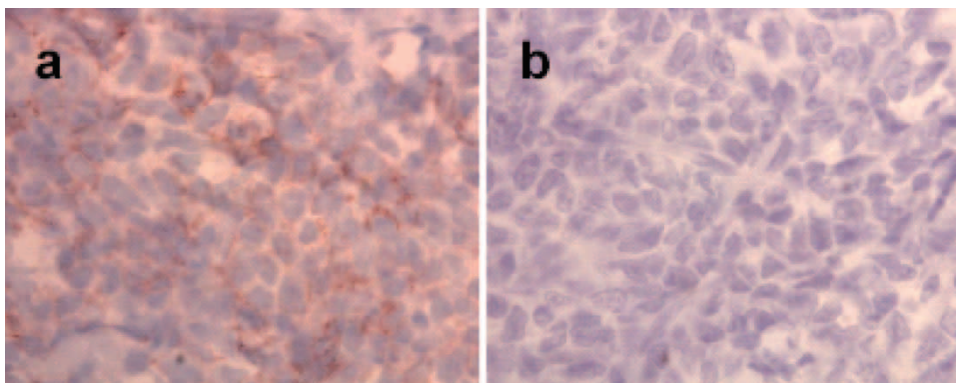


Fig. 3. Immunostaining (original magnification $\times 400$): tumour cells are CD56 positive (a), but CD3 negative (b).

excised lymph node from the left axilla gave similar results.

A CT scan of the head was normal, whereas in the neck, axillary and inguinal region multiple enlarged lymph nodes were detectable. A hypodense lesion identified in the spleen was most likely a lymphoma infiltration. Characteristic signs of an old tuberculosis lesion were detected in the upper lobe of the right lung. However, the old lesions were surrounded by dull nodular infiltrates, leading to suspicion of a reactivation of tuberculosis. Repeated microbiological examinations of sputum and urine were negative for acid-fast bacilli in direct microscopy after Ziehl-Neelsen staining, but revealed mycobacterium tuberculosis complex after 3 weeks of culture.

After diagnosis of a highly malignant, CD56+ blastic NK-cell lymphoma with nodal and cutaneous involvement, the patient received six courses of polychemotherapy with cyclophosphamide, vincristine and prednisolone (COP). This treatment resulted in partial remission. The smaller nodular skin infiltrates virtually disappeared one week after application of the first course of COP, leaving hyperpigmented areas. The pruritus stopped immediately with the initiation of steroid therapy. In addition, the patient had to be treated for reactivated pulmonary tuberculosis, which most likely developed due to a lymphoma-caused immunosuppression. Initially, the patient received isoniazid as a prophylaxis; however, when we received notice of the positive mycobacterium tuberculosis culture after the first application of the COP polychemotherapy, combination therapy with isoniazid, rifampicin, ethambutol and pyrazinamide was started immediately. The second course of COP was delayed until the PCR for mycobacterial DNA was negative in a bronchoalveolar lavage. Six months after initiation of the lymphoma therapy, shortly after application of the 6th course of COP, the patient had relapsed with cutaneous lymphoma infiltrations, itching, generalized lymphadenopathy and a dramatic deterioration of his general condition. Despite receiving a second-line therapy with pentostatin, the patient died 2 months later, i.e. within 9 months of the primary diagnosis.

DISCUSSION

NK-cell lymphomas have only recently become the subject of more attention, as reflected by the increasing numbers of reports in the literature (3–10). This may be due to the fact that older classifications, such as the Kiel classification, and even more recent ones, such as the Revised European-American (REAL) (11) and European Organization for Research and Treatment of Cancer (EORTC) classifications for lymphomas (12), have not recognized NK-cell lymphomas as a separate entity. Since subsets of cytotoxic T cells can acquire some features of NK cells ("NK-like T cells"), which

may give rise to lymphomas similar to NK-cell lymphomas, both of these are now grouped together under the term T/NK-cell lymphoma in the actual WHO classification (1). Sometimes T/NK-cell lymphomas are also referred to as "cytotoxic lymphomas" (13), which may not be adequate in the light of CD4 expression.

The classical prototypes of T/NK-cell lymphomas are the "nasal" (with its primary manifestation localized in the nasopharynx, formerly designated as lethal midline granuloma (14)) and the "nasal type" T/NK-cell lymphoma (with histopathologically indistinguishable features, but a primary manifestation other than the nasopharynx, e.g. skin, testis, gastrointestinal and upper respiratory tract). EBV-DNA is present in the majority of these tumours (9, 15), which predominantly affect patients from Asia or native Americans, but rarely Caucasians.

The source for "blastic" NK-cell lymphomas is immature NK cells. Patients are often elderly, there is no association with EBV infection and the clinical course is aggressive; some progress to a NK-cell leukaemia (9).

T/NK-cell lymphomas are, in general, rare, and virtually all arise from extranodal sites where they occasionally resemble reactive processes and can be difficult to diagnose. Cutaneous involvement with diverse characteristics, including erythema, papules, plaques and nodules, is common, and in some cases is the primary or sole manifestation (16, 17). The classification is still a matter of debate, since T/NK-cell lymphomas can be morphologically heterogeneous and there is, other than for T and B cell lymphomas, no phenotypic marker for clonality. Subtypes of extranodal T/NK-cell lymphomas can be distinguished by different expression of surface markers, association with EBV infection and racial predisposition. The cells of origin can be NK cells (CD56+, CD3ε±, surface CD3-, no clonal TCR rearrangements), NK-like T cells or certain cytotoxic T cells (also CD56+, but CD3+ and with clonal rearrangement of TCR genes). It is noteworthy that detection of the CD56 expression, an isoform of the neural cell adhesion molecule (18), is most important in diagnosing T/NK-cell lymphomas and should not be missed. However, it is not totally specific (7).

In our case report of a blastic NK-cell lymphoma, the NK-lineage could be proven by the virtually exclusive CD56 expression of the tumour cells and the absence of T-cell markers or a clonal TCR-rearrangement. Unfortunately, but as expected, there was only a temporary response even to aggressive treatment and the patient died within 9 months of primary diagnosis, underlining the aggressive nature of these malignancies. While polychemotherapy is currently the standard therapy in younger patients with a

stem cell donor, allogeneic stem cell transplantation may be considered to potentially achieve long-term remissions, or even to cure these aggressive non-Hodgkin lymphomas with unfavourable prognosis.

REFERENCES

- Jaffe E, Harris N, Stein H, Vardiman J. WHO classification of tumors: pathology and genetics of tumors of hematopoietic and lymphoid tissues. Lyon: IARC Press, 2001.
- Russel-Jones R. World Health Organization classification of hematopoietic and lymphoid tissues: implications for dermatology. *J Am Acad Dermatol* 2003; 48: 93–102.
- Natkunam Y, Smoller BR, Zehnder JL, Dorfman RF, Warnke RA. Aggressive cutaneous NK and NK-like T-cell lymphomas: clinicopathologic, immunohistochemical, and molecular analyses of 12 cases. *Am J Surg Pathol* 1999; 23: 571–581.
- Kato N, Yasukawa K, Onozuka T, Kikuta H. Nasal and nasal-type T/NK-cell lymphoma with cutaneous involvement. *J Am Acad Dermatol* 1999; 40: 850–856.
- Ginarte M, Abalde MT, Peteiro C, Fraga M, Alonso N, Toribio J. Blastoid NK cell leukemia/lymphoma with cutaneous involvement. *Dermatology* 2000; 201: 268–271.
- Amo Y, Yonemoto K, Ohkawa T, Sasaki M, Isobe Y, Sugimoto K, et al. CD56 and terminal deoxynucleotidyl transferase positive cutaneous lymphoblastic lymphoma. *Br J Dermatol* 2000; 143: 666–668.
- Slater DN. Cutaneous CD56 natural killer and natural killer-like T-cell lymphoma: Editorial comments. *Br J Dermatol* 2000; 142: 853–855.
- Hofbauer GFL, Kamarachev J, Kempf W, Burg G, Pestalozzi BC, Dummer R. A CD4+CD56+natural killer-like T-cell systemic lymphoma with haemorrhagic cutaneous manifestations. *Br J Dermatol* 2001; 144: 432–434.
- Greer JP, Kinney MC, Loughran TP Jr. T cell and NK cell lymphoproliferative disorders. *Hematology (Am Soc Hematol Educ Program)* 2001; 259–281.
- Ling TC, Harris M, Craven NM. Epstein-Barr virus-positive blastoid nasal T/natural killer-cell lymphoma in a Caucasian. *Br J Dermatol* 2002; 146: 700–703.
- Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361–1392.
- Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood* 1997; 90: 354–371.
- Shabrawi-Caelen L, Cerroni L, Sterry W, Audring H, Kerl H. Cytotoxic lymphomas. *Hautarzt* 2000; 51: 390–395.
- Chim CS, Ooi GC, Shek TWH, Liang R, Kwong YL. Lethal midline granuloma revisited: nasal T natural-killer cell lymphoma. *J Clin Oncol* 1999; 17: 1322–1325.
- Chiang AKS, Chan ACL, Srivastava G, Ho FCS. Nasal T natural killer (NK)-cell lymphomas are derived from Epstein-Barr virus-infected cytotoxic lymphocytes of both NK- and T-cell lineage. *Int J Cancer* 1997; 73: 332–338.
- Dummer R, Potoczna N, Haffner AC, Zimmermann DR, Gilardi S, Burg G. A primary cutaneous non-T, non-B CD4(+), CD56(+) lymphoma. *Arch Dermatol* 1996; 132: 550–553.
- Bastian BC, Ott G, Muller-Deubert S, Brocker EB, Muller-Hermelink HK. Primary cutaneous natural killer/T-cell lymphoma. *Arch Dermatol* 1998; 134: 109–111.
- Lanier LL, Testi R, Bindl J, Phillips JH. Identity of Leu-19 (CD56) leukocyte differentiation antigen and neural cell adhesion molecule. *J Exp Med* 1989; 169: 2233–2238.