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# Primary high-grade malignant lymphomas of bone*

**T. Radaszkiewicz**[1] **and M.-L. Hansmann**[2]

[1] Institute of Pathology, University of Vienna, Spitalgasse 4, A-1090 Vienna, Austria
[2] Institute of Pathology, University of Kiel, Hospitalstrasse 42, D-2300 Kiel, Federal Republic of Germany

**Summary.** Five cases of primary high-grade malignant lymphoma of bone are presented. The tumours occurred at a single site in all the cases and produced osteopathic lesions. Histologically, they were large cell tumours characterized by round to irregularly shaped nuclei with finely distributed heterochromatin and small to medium-sized nucleoli. The cytoplasm was moderate and slightly to moderately basophilic. In one case, giant cells similar to Hodgkin and Sternberg-Reed cells occured. The tumour cells bore B-cell markers but did not express immunoglobulin. Three of the bone tumours were polymorphic centroblastic lymphomas. The remaining two cases were also high-grade malignant B-cell lymphomas which may also be derived from germinal center cells but this could not be further substantiated.

**Key words:** High-grade malignant B-cell lymphoma – Primary bone involvement

## Introduction

The different morphological features of non-Hodgkin's lymphomas (NHL) originating in lymph nodes have provided the basis for systems of classification (Dorfman 1974; Lennert et al. 1975; Lukes and Collins 1974; Nathwani et al. 1978). Among these the Kiel classification (Lennert et al. 1975) correlates well with the clinical behavior (Brittinger et al. 1984) and to a great extent with the immunological phenotype of the tumour cells. Similarly, most extranodal malignant NHL can be characterized on the basis of the Kiel classification (Dragosics et al. 1985; Jellinger et al. 1975; Schwarze 1984).

Primary NHLs of the bone are well recognized but rare disorders. Unlike nodal lymphomas, they have been mostly classified as reticulum cell sarcoma and lymphosarcoma of the bone (Boston et al. 1974; Shoji and Miller 1971; Wang and Fleischli 1968). These tumours may therefore, encompass all of the different entities (Reimer et al. 1977) recognized in lymph node lymphomas, perhaps presenting a different clinical course, or may be restricted to only a few lymphoma categories. Several recent papers have dealt with primary NHLs of bone (Bacci et al. 1986; Dosoretz et al. 1982; Dumont and Mazabraud 1979; Howat et al. 1987) but only two papers (Dumont and Mazabraud 1979; Vassallo et al. 1987) applied the Lukes and Collins classification and the Kiel classification, respectively. This, and the scarcity of detailed immunomorphological studies (Vassallo et al. 1987) prompted us to report on five morphologically unusual cases of primary NHL of the bone.

## Case report

The first patient was a 66-year-old female who presented with a four week history of painless swelling of the ventral iliac crest. X-rays exhibited an oval shaped osteolytic process $3 \times 2$ cm in diameter. The patient had no other symptoms. All physical and biochemical and haematological investigations revealed normal values. A grey tumour mass surrounded by bone and infiltrating the adjacent connective and fatty tissue was biopsied and diagnosed histologically as high-grade malignant lymphoma (polymorphic centroblastic lymphoma). No other manifestation of the lymphoma could be found. Radiation therapy was given and one year later the patient was still in complete remission.

The second patient was also a 66-year-old woman who suffered from pain in the left groin. X-rays showed a parasymphyseal cystic destruction of the left pubic bone and computer tomography revealed additionally a continuous infiltration of the adjacent connective tissue and adductor muscle. Biopsy revealed a partly necrotic malignant lymphoma of high-grade malignancy (polymorphic centroblastic lymphoma). No other

*Offprint requests to:* M.-L. Hansmann

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manifestation of the lymphoma could be found by clinical investigations. Radiation therapy was initiated.

The third patient was a 44-year-old man who complained of a 6-month history of slight cinesalgia in the left hip-joint which was initially interpreted as tendopathy. X-ray and scintigraphic investigations revealed a $6 \times 4 \times 4$ cm sized area of destruction of the proximal diaphysis of the left femur surrounded by slightly sclerotic bone. No other tumourous infiltration in the skeleton and organs was detected. Blood and bone marrow smears, a trephine biopsy and blood chemistry were all normal. Two biopsies of the tumour were performed and interpreted as high-grade malignant lymphoma of B-type. Local irradiation (50 Gy) and one cycle of chemotherapy (VIM/Bleo-CHOP) were administered. Following this therapy the proximal part of the femur was resected because of statical problems of the bone and a prosthetic restoration was performed. The resected part of the femur contained no tumour masses as judged by extensive microscopic investigations. A few small areas of necroses in an oedematous, slightly fibrotic area, measuring 6 cm were found.

The last two patients were younger. A 25-year-old man presented with a tumour mass of at least 5 cm in diameter destroying the bone of the left ileum and infiltrating the adjacent connective tissue. Clinically, the tumour was suspicious of a chondrosarcoma. Biopsy revealed a high-grade malignant lymphoma of B-cell type. No other tumour manifestation was found clinically.

In one ischium of a further 22-year-old female a tumour mass was found destroying the bone. The tumour grew rapidly infiltrating the adjacent connective tissue and the major labium. This tumour was finally classified as a high-grade malignant lymphoma of B-type. No other manifestation was detected by clinical investigations.

## Material and methods

The biopsy specimens were fixed in phosphate buffered formalin, embedded in paraffin and the sections stained with H&E, Giemsa, Gomori's silver impregnation, and PAS.

Immunoperoxidase staining on paraffin sections of the five tumours was performed using the PAP technique according to the method of Mepham et al. (1979) utilizing the monoclonal leukocyte common antigen and polyclonal antibodies against light and heavy chains (DAKO, Copenhagen/Denmark). A new monoclonal antibody (Ki-B3) recognizing B cells was also applied on paraffin sections. Details on the production and specificity of the latter are given elsewhere (Feller et al. 1987). In addition, parts of the biopsy specimens of patient 3 were snap frozen in liquid nitrogen and stored at $-70°$ C. Cryostat sections of these specimens were immunostained as described by Stein et al. (1982).

Polyclonal antibodies against human heavy and light chains (DAKO, Copenhagen/Denmark) and the following monoclonal antibodies were applied: To15(CD22) (DAKO, Copenhagen/Denmark), HD39(CD22) (Moldenhauer et al. 1986), HD37(CD19) (Pezzutto et al. 1986) and Ki-B3 (Feller et al. 1987) as pan-B-cell reagents; OKT11(CD2) for the sheep red blood cell associated antigen, OKT4(CD4) for the helper/inducer T-cell-associated antigen, OKT8(CD8) for the suppressor/cytotoxic T-cell-associated antigen, OKT6(CD1) for the cortical thymocyte associated antigen (all from Ortho Diagnostics, Heidelberg/FRG) and anti-Leu1 (CD5) (Becton-Dickinson, Heidelberg/FRG) as pan-T reagent; Ki-M1, Ki-M6 (Parwaresch et al. 1986) and Ki-M8 (Radzun et al. 1987) (own laboratory; for specificity see also Radzun et al. 1983; Radzun et al. 1985) for antigens on cells of the myelomonocytic and monocyte/macrophage lineage. In addition, VIL-A1(CD10) for common ALL antigen (Knapp et al. 1982), Ki1(CD35) for the Hodgkin's disease associated antigen (Stein et al. 1985) and Ki67, a nuclear proliferation associated antigen (Gerdes et al. 1983) were applied.

## Results

In the first case the diffuse tumour infiltration consisted largely of medium-sized blasts with round to oval nuclei with a prominent nuclear membrane and several small to medium-sized nucleoli located partly at the nuclear membrane. The cytoplasm was moderate and basophilic. Small to medium-sized blasts containing sometimes indented nuclei with finely dispersed chromatin, small nucleoli and a narrow to moderate rim of slightly basophilic cytoplasm were intermingled (Fig. 1). These cells resembled so-called centrocyte-like centroblasts (Hui et al. 1988). All tumour cells were consistently PAS negative; in particular no intranuclear PAS-positive inclusions were found. Numerous mitoses were visible. Some histiocytes and a few isolated epithelioid cells were interspersed. Reticular fibers were rare. There was no nodular arrangement. The infiltration contained some high-endothelial venules with thickened PAS-positive basement membranes, but without any arborization. Only a few residues of the spongiosa which showed some lacunar resorption of the bone. Based on this morphology the diagnosis of a high-grade malignant NHL of B-cell origin probably a polymorphic centroblastic lymphoma was established.

In patient 2 the diffuse tumour infiltration consisted mostly of medium-sized somewhat pleomorphic blasts containing oval or round, sometimes elongated, sometimes kidney-shaped or indented nuclei with finely dispersed chromatin and mostly small nucleoli (Fig. 2). The moderate cytoplasm was slightly basophilic. Only a few large blasts with vesicular round nuclei and a narrow rim of basophilic cytoplasm were intermingled. Again the tumour cells were PAS-negative. Mitoses were frequent and some histiocytes were scattered throughout the area of infiltration. Reticular fibers were increased and formed a coarse alveolar network in some areas; a nodular pattern was completely absent. Some randomly intermingled high endothelial venules showed thickened basement membranes but were not arborized. A slight hyalinization of collagen fibers were visible in some areas. The spongiosa was largely destroyed. A high-grade malignant NHL belonging to the group of polymorphic centroblastic lymphoma was diagnosed.

In the third patient the excised tumour pieces showed diffuse infiltration by numerous medium-sized to large blasts containing round to oval nuclei with delicate, finely dispersed chromatin, promi-

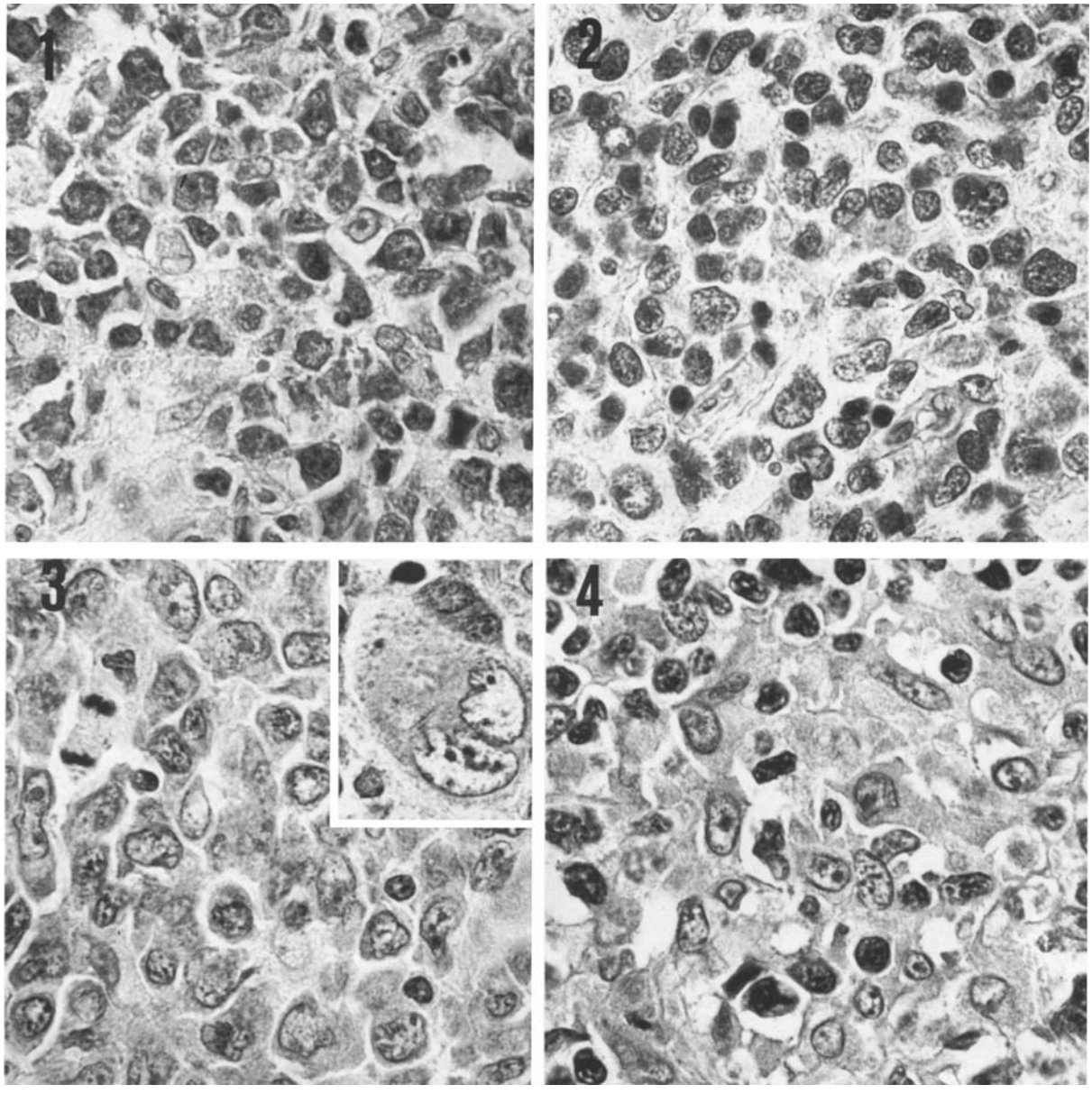


**Fig. 1.** Malignant lymphoma of the iliac crest (Patient 1). The tumour consists of small to medium-sized blasts containing occasionally indented nuclei and a narrow rim of slightly basophilic cytoplasm. Giemsa, ×880

**Fig. 2.** Patient 2. Medium-sized blasts with oval to irregularly shaped nuclei and moderate basophilic cytoplasm. H&E, ×880

**Fig. 3.** Malignant lymphoma of the left femur (Patient 3). Medium-sized to large blasts with round to oval, somewhat polymorphic nuclei, thin nuclear membrane, small nucleoli and medium-sized, slightly basophilic cytoplasm. Inset: multinucleated giant cells. Giemsa, ×880

**Fig. 4.** Patient 4. Tumour composed of centroblast-like tumor cells. Intermingled a few cells resembling larger centrocytes. H&E, ×880

nent thin nuclear membrane and sometimes a few small nucleoli. The moderate cytoplasm was slightly basophilic. These cells were randomly scattered or grouped in small clusters (Fig. 3). Single areas of necrosis and a few uni- or multinucleated tumour cells somewhat reminiscent of Hodgkin and Sternberg-Reed cells but with irregularly shaped nuclei and coarse chromatin and mostly without prominent nucleoli were intermingled (Fig. 3). All tumour cells were PAS-negative. Mitoses were frequent. Some small lymphocytes and numerous epithelioid cells sometimes arranged in small clusters were distributed throughout the infiltration. Eosinophils were absent. In the silver

strain the fibers were increased and slightly thickened but no nodular pattern was found. Some areas were slightly hyalinized. Venules with flat epithelium and thick PAS-positive basement membranes were frequent; they were not arborized. Small residual spongiosa fragments were largely destroyed and the adjacent tissue showed fibrosis. The tumour infiltration was diagnosed as a B-cell NHL of high-grade malignancy, unclassified.

In patient 4 the tumour was similar to that of patient 1. In some areas numerous blasts were intermingled by a considerable number of histiocytes. Other areas contained many small centrocyte-like cells (Fig. 4). A high-grade malignant NHL of B-cell origin, especially a polymorphic centroblastic lymphoma, was diagnosed.

The tumour of patient 5 resembled the tumour in patient 3. The medium-sized to large blasts contained vesicular, polymorphic nuclei with medium-sized nucleoli and slightly basophilic cytoplasm. Several histiocytes and a few multinucleated giant cells were intermingled. The tumour could not be further classified but based on immunohistochemistry it was diagnosed as a NHL of high-grade malignancy of B-cell type, unclassified.

*Immunohistochemistry*

In immunohistology on paraffin sections the membranes of the tumour cells of all five specimens were positively stained with the monoclonal panleukocyte antibody and the pan-B-cell antibody Ki-B3, thus proving the diagnosis of a malignant NHL deriving from the B-cell lineage. No intracytoplasmic immunoglobulin could be detected in the tumour cells. Frozen sections of the tumour of patient 3 were available for investigation with a panel of monoclonal antibodies. The blasts stained positive with the B-cell antibodies To15(CD22), Ki-B3, HD37(CD19) and HD39(CD22), but were negative for heavy and light chains. No T-cell markers OKT6(CD1), OKT11(CD2), Leu1(CD5), OKT4 (CD4), OKT8(CD8) or myelomonocytic antigens (Ki-M1, Ki-M6, Ki-M8) were detected on the tumour cells. They were also consistently negative for CALLA (VIL-A1)(CD10) and the Hodgkin's disease associated antigen Ki1. About 70% of the nuclei of the tumour cells stained positive with the nuclear proliferation associated antigen Ki67, indicating a high proliferation rate. Thus, the diagnosis of a high-grade malignant NHL of B-cell type was established.

## Discussion

Primary NHL of the bone are rare disorders. They may involve any bone but occur more frequently in the femur, pelvic girdle (Schajowicz 1981; Shoji et al. 1971) and in the skull and mandible (Dahlin 1978). Four of our five cases occurred in the pelvic girdle and one in the femur. Skull and mandible lymphomas were excluded from this study. The most common symptoms reported in large series (Dahlin 1978; Schajowicz 1981) are pain and swelling around the destructive lesion accompanied by a general well-being of the patients. This was also true in our patients.

With few exceptions (Bacci et al. 1986; Dosoretz et al. 1982; Dumont and Mazabraud 1979; Vassallo et al. 1987) large studies concerning the morphological classification according to the major classification systems do not exist. Like other extranodal lymphomas (Schwarze 1984), most of the tumours in our experience and as shown by Vassallo et al. (1987) can be well characterized using the Kiel classification. However, at least two of the described cases (3 and 5) of the large cell lymphomas presented here show an unusual morphology which caused some diagnostic difficulties. The tumour cells showed some resemblance to epithelial cells. The chromatin was finely dispersed and the cytoplasm slightly or moderately basophilic. However, in cases 1, 2, and 4 areas were found in which the tumour showed a centroblastic differentiation with the typical morphology of this entity. A few immunoblasts were also recognized. Additionally, all five tumours expressed B-cell markers. This accords with Vassallo et al. (1987), who found 7 centroblastic lymphomas in their series of 13 NHL with primary bone manifestation but only two immunoblastic, two lymphoblastic and one centrocytic lymphomas. Multinucleated giant cells resembling Sternberg-Reed cells as seen in patient 3 and the diffuse increase of venules with thickened basement membranes are an unusual finding in typical centroblastic lymphomas. However, some of the medium-sized lymphoid cells in the tumours of patient 1 and 4 contained indented nuclei with small to medium-sized nucleoli and thus resembled large centrocytes. However, their narrow rim of basophilic cytoplasm is not consistent with centrocytes, which usually show only a slightly basophilic, often hardly detectable, cytoplasm. These cells resemble the centrocyte-like centroblasts (Hui et al. 1988) recently identified in a subtype of centroblastic lymphomas.

The increase of venules and the pleomorphic tumour cells predominantly seen in patient 3 as well as the epithelioid cell clusters could be interpreted as a feature consistent with a peripheral T-cell lymphoma of angioimmunoblastic (AILD)-(Shimoyama et al. 1979) or lymphogranulomatosis X (Lgr-X)-type (Lennert et al. 1985) or of Len-

nert's lymphoma (Lennert et al. 1982) transforming into a T-cell lymphoma of large cell type. The dense storage of the tumour cells, the lack of clusters of "clear cells" (Suchi 1974) and the absence of arborization of the vessels are uncommon in most peripheral T-cell lymphomas. In addition, the tumour cells of all five tumours showed a positive reaction with the pan-B antibody Ki-B3, thus underlining their B-cell nature. Furthermore, the lack of T-cell antigens and the presence of several B-cell markers on the tumour cells of patient 3 left no doubt as to its B-cell character of despite the fact that no heavy and light chains could be detected. In our experience, however, this is not an uncommon finding in large cell lymphomas of B-cell type.

Differential diagnostically Hodgkin's disease of mixed cellularity was considered in patient 3. Despite the lack of cells typical of the "cellular background" of mixed cellularity like eosinophils and plasma cells and the unusual chromatin structure of the giant cells, the immunostaining with the antibody against Hodgkin's disease associated antigen Ki1 was consistently negative. The morphological picture in combination with the negativity for Ki1 (Stein et al. 1985) of the tumour cells excluded the diagnosis of HD mixed cellularity type.

It is possible to speculate on the origin of these highly malignant B-cell lymphomas. Since the lymphoid cells of the bone marrow are predominantly B cells and even small germinal centers are present in normal marrow (Rohr 1960) these cells could be the target of a malignant transformation event. The presence of a few centroblasts and immunoblasts argues for the derivation of this tumour from germinal center cells. Nevertheless, the uncommon morphology of the infiltrations in patient 3 and 5 compared with the typical centroblastic lymphomas of lymph nodes presents difficulties in classifying the tumour. Unfortunately, no specific antigen for large germinal center cells yet exists which confirms the germinal center cell derivation by immunohistochemical methods. The common ALL antigen found in reactive germinal centers and in most centroblastic/centrocytic lymphomas (Stein et al. 1982) may or may not be present in centroblastic lymphomas of lymph nodes (Stein et al. 1984).

In this context, a more recent study of 33 primary lymphomas of the bone (Dosoretz et al. 1982) should be mentioned. Only three histological subgroups were found: eight cases of the non-cleaved cell type, 22 cases of the cleaved cell type, and three of a "pleomorphic" variant with multiple lobulations and infoldings of the tumour cell nuclei. None of these tumours seemed to consist of a "pure" cell population and cleaved and non-cleaved cells seemed to be present in all cases. Since cleaved and non-cleaved cells in the Lukes and Collins classification (Lukes and Collins 1974) roughly correspond to the centrocytes and centroblasts, respectively, in the Kiel classification (Lennert et al. 1985), most of the tumours described may originate from follicular center cells. The "pleomorphic variant" described in the above mentioned study (Dosoretz et al. 1982) seems roughly to correspond to malignant lymphoma, multilobated type, which is, in contrast to the original description (Pinkus et al. 1979), in a high percentage a B-cell lymphoma of germinal center cell origin.

A second series (Bacci et al. 1986) included also only small cleaved, large cleaved and large non-cleaved malignant lymphomas of the bone. It therefore seems likely that the majority of primary lymphomas of the bone may be B-cell tumours, probably of follicle center cell origin with a large spectrum of morphologic variants.

The differentiation of primary NHL of the bone from other primary round cell tumours is important because of the different therapies required. The prognosis in retrospective series (Dahlin 1978; Schajowicz 1981; Vassallo et al. 1987) is reported to be more favourable than in other malignant primary bone tumors.

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