

Primary Bone Marrow B-Cell Lymphoma:

Report of Four Cases

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Abstract

Bone marrow involvement is infrequent at presentation in cases of diffuse large B-cell lymphoma. We report four adult patients with diffuse large B-cell lymphoma in whom bone marrow involvement with hematologic manifestations was the predominant clinical feature at presentation. Three patients presented with a leukoerythroblastic blood picture and one with pancytopenia. In each case, the unusual hematologic manifestations, with bone marrow replacement and the presence of immature forms in the peripheral blood, led to consideration of alternative hematologic diagnoses, including acute granulocytic leukemia in three cases and a myelodysplastic syndrome in one. The correct diagnoses were established by immunohistochemistry on formalin-fixed, paraffin-embedded bone marrow for two cases and by flow cytometry on aspirated bone marrow or peripheral blood lymphocytes for the other two. Diffuse large B-cell lymphoma should be considered in the differential diagnosis of unusual hematologic presentations, particularly in the elderly.

Key Words: B-cell, non-Hodgkin's, lymphoma, bone marrow.

Introduction

IN CONTRAST TO THE LOW-GRADE, non-Hodgkin's lymphomas, bone marrow involvement in diffuse large B-cell lymphoma is relatively infrequent at presentation, occurring in 10–12% of cases of diffuse large cell lymphoma of large cleaved, large non-cleaved, and immunoblastic cell types in the Working Formulation (1) and 3–17% of cases of diffuse large B-cell lymphoma (DLBCL) in the Revised European-American Lymphoma (REAL) Classification (2, 3). Bone marrow involvement may be more frequent in cases of T-cell-rich, diffuse large B-cell lymphoma (62% vs. 8% in DLBCL) (4). Although bone marrow involvement in non-Hodgkin's lymphoma is generally believed to represent systemic dissemination of disease arising elsewhere, some cases may arise primarily in the bone marrow (5–9). In this study,

we report on four cases of DLBCL which presented with primarily hematologic manifestations due to bone marrow involvement. Three patients presented with leukoerythroblastosis and one with pancytopenia. In each case, the hematologic manifestations suggested alternative hematologic diagnoses, including acute granulocytic leukemia in three and a myelodysplastic syndrome in one.

Materials and Methods

Immunohistochemistry

Tissue was fixed in 10% neutral-buffered formalin and processed for paraffin embedding. Tissue sections for immunohistochemistry were deparaffinized in xylene and rehydrated through graded ethanol to deionized water. Immunohistochemistry was performed on deparaffinized sections using the EnVision+ System (Dako, Carpinteria, CA). Antibodies utilized were: CD45RB (LCA), CD20 (L26), kappa, and lambda (Dako, Carpinteria, CA); and CD5 and CD10 (Novocastra, Newcastle-upon-Tyne, England).

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Flow Cytometry

Flow cytometry was performed on lysed peripheral blood and bone marrow aspirate using the Beckman-Coulter EPICS XL/MCL flow cytometer (Beckman-Coulter, Fullerton, CA) and dual-color staining. Antibodies utilized were: CD5, CD10, CD19, CD20, CD22, CD23, CD45, kappa and lambda (Beckman-Coulter, Fullerton, CA).

Results

Case 1

An 82-year-old man presented with a 4-month history of fevers, night sweats, and hypotension. The history was remarkable for monoclonal gammopathy of undetermined significance. Physical examination revealed hepatosplenomegaly but no lymphadenopathy. Laboratory studies revealed hemoglobin 119 g/L, hematocrit 34.8%, platelets $53 \times 10^9/L$, white blood cells $10.1 \times 10^9/L$ with 34% segmented neutrophils, 17% lymphocytes, 2% atypical lymphocytes, 14% monocytes, 2% eosinophils, 2% basophils, 14% band neutrophils, 4% neutrophilic metamyelocytes, 7% neutrophilic myelocytes, 3% blasts, 1% plasma cells, and 1 nucleated red blood cell per 100 white blood cells. LDH was 695 U/L (normal < 220). Serum immunoglobulins were IgG 18.8 g/L, IgA 1.45 g/L, and IgM 13.5 g/L. IgG kappa and IgM kappa monoclonal proteins were identified on immunofixation and accounted for 40% of the IgG and 70% of the IgM.

Bone marrow biopsy and aspiration were performed. The bone marrow biopsy specimen was hypercellular (80%), diffusely infiltrated by blasts with round-to-ovoid nuclei, one or two inconspicuous nucleoli, and scant cytoplasm (Fig. 1). Leder stain (chloroacetate esterase) was positive in residual granulocytic precursors but negative in the blast cells. The bone marrow aspirate smears showed sheets of blasts with round-to-ovoid nuclei, finely distributed chromatin, one or two nucleoli, a rim of agranular, faintly basophilic cytoplasm, and numerous "lymphoglandular bodies" scattered between the blasts (Fig. 2). Flow cytometry on bone marrow aspirate demonstrated a monoclonal B-cell phenotype (CD5-, CD10+, CD19+, CD20+, CD22+, CD23-, CD45+, surface immunoglobulin lambda light chain). A diagnosis of DLBCL was established. Chemotherapy

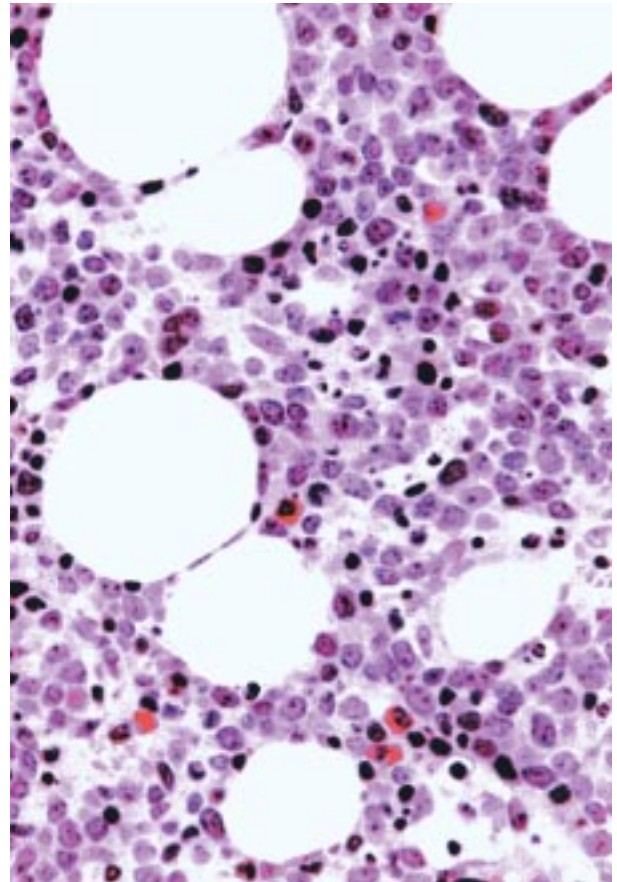


Fig. 1. Bone marrow biopsy specimen from Case 1, showing diffuse infiltration by blasts. A "leukemic" pattern is present with preservation of fat cells and scattered eosinophilic myelocytes (Hematoxylin & Eosin, $\times 200$).

with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) was administered and the patient showed improvement.

Case 2

An 86-year-old man presented with back pain, fever, and leg weakness. The medical history revealed prostatic adenocarcinoma, Gleason's pattern 4+4, score = 8, diagnosed 4 years previously and treated with hormonal therapy. Physical examination revealed no lymphadenopathy. There was bilateral lower-motor-neuron weakness of the lower extremities. Laboratory studies revealed hemoglobin 91 g/L, hematocrit 25.9%, platelets $98 \times 10^9/L$, white blood cells $7.3 \times 10^9/L$ with 47% segmented neutrophils, 7% lymphocytes, 5% atypical lymphocytes, 5% monocytes, 19% band neutrophils, 5% neutrophilic metamyelocytes, 11% neutrophilic myelocytes, 1% promyelocytes, and 6 nucleated red blood cells per 100 white

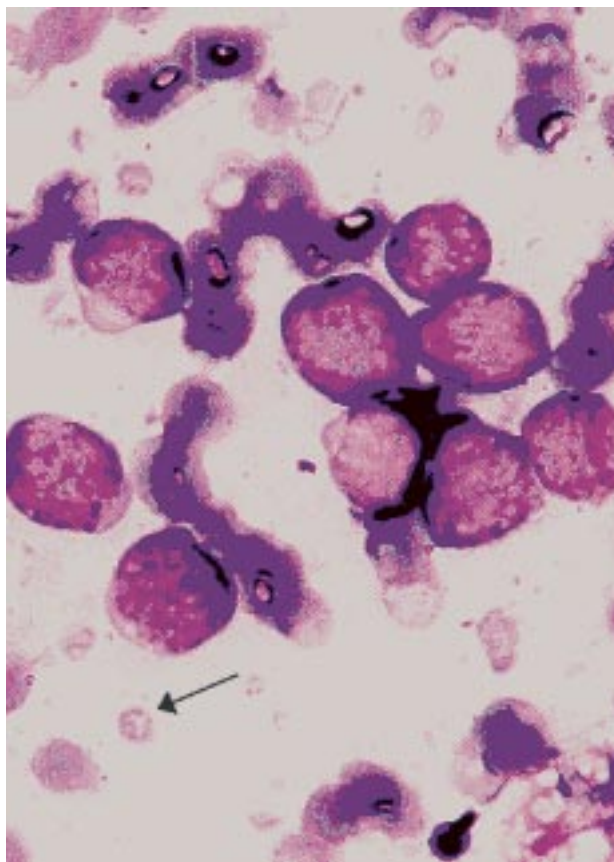


Fig. 2. Bone marrow aspirate smear from Case 1, showing blasts with faintly basophilic agranular cytoplasm. "Lymphoglandular bodies," pale basophilic globules (arrow) of varying size, are present between the cells (Giemsa, $\times 600$).

blood cells. Serum prostate-specific antigen (PSA) was 0.1 ng/mL. CT scan of the abdomen and pelvis showed minimally enlarged para-aortic and presacral lymph nodes. Bone scan was negative. A tentative diagnosis of metastatic prostatic adenocarcinoma with cauda equina syndrome was made and radiotherapy was begun.

Bone marrow biopsy and aspiration were performed. The bone marrow biopsy specimen was hypercellular (80%) with extensive coagulative necrosis. Foci of viable marrow were diffusely replaced by blasts with round-to-ovoid nuclei, one or two inconspicuous nucleoli, and scant cytoplasm. Leder stain (chloroacetate esterase) was negative. The bone marrow aspirate smear showed sheets of cells with pyknotic degenerating nuclei admixed with scattered viable blasts with round-to-ovoid nuclei, one or two nucleoli, and moderately abundant, deeply basophilic cytoplasm with occasional cytoplasmic vacuoles. Flow cytometry on peripheral blood

demonstrated a monoclonal B-cell phenotype (CD5-, CD10+, CD19+, CD20+, CD22+, CD23-, CD45+, surface immunoglobulin lambda light chain). A diagnosis of DLBCL was established. Chemotherapy with cyclophosphamide, vincristine, and methotrexate was administered, but the patient expired due to sepsis and neutropenia 10 days later. Autopsy was not performed.

Case 3

A 76-year-old woman presented with syncope and a 2-month history of malaise and weight loss. Laboratory studies revealed hemoglobin 95 g/L, hematocrit 28.0%, platelets 34×10^9 /L, white blood cells 5.4×10^9 /L with 41% segmented neutrophils, 26% lymphocytes, 11% monocytes, 1% basophils, 17% band neutrophils, 2% neutrophilic metamyelocytes, and 2% neutrophilic myelocytes. Rare nucleated red blood cells (< 1 per 100 white blood cells) were present. Serum calcium was 3.82 mmol/L (normal 2.20–2.60 mmol/L). LDH was 434 U/L (normal < 220) and alkaline phosphatase 213 U/L (normal < 110). Physical examination was unremarkable. There was no lymphadenopathy. Gallium scan revealed an ill-defined area of uptake in the pulmonary hila and posterior mediastinum. CT scan of the chest and abdomen was negative, except for multiple rib fractures.

Bone marrow biopsy and aspiration were performed. Bone marrow could not be aspirated. The bone marrow biopsy was markedly hypercellular (100%), with extensive coagulative necrosis. Areas of viable marrow were replaced by sheets of blasts with irregular, ovoid-to-lobated nuclei, inconspicuous nucleoli and scant cytoplasm. Immunohistochemical staining demonstrated a B-cell phenotype (CD5-, CD10-, CD20+, CD45+, kappa and lambda immunoglobulin light chain negative). A diagnosis of DLBCL was established. The patient was treated with vigorous hydration and forced diuresis with resolution of the hypercalcemia. Chemotherapy with CHOP was administered and the patient showed improvement.

Case 4

A 45-year-old woman presented to her physician with generalized weakness. Physical examination was unrevealing. There was no lymphadenopathy. Laboratory studies revealed hemoglobin 67 g/L, hematocrit 19.4%, platelets

$88 \times 10^9/L$, white blood cells $3.3 \times 10^9/L$ with 32% segmented neutrophils, 56% lymphocytes, and 12% monocytes.

Bone marrow biopsy and aspiration were performed. Bone marrow could not be aspirated. The bone marrow biopsy was hypercellular with reticulin fibrosis, increased immature forms of uncertain lineage, and atypical megakaryocytes. A diagnosis of a myelodysplastic syndrome was entertained. A bone marrow biopsy was repeated six months later. The bone marrow biopsy was markedly hypercellular (100%), with a diffuse infiltrate of large blasts with ovoid-to-lobated nuclei, prominent nucleoli and abundant pale cytoplasm, admixed with small, atypical lymphocytes with irregular, twisted nuclei. Immunohistochemical staining demonstrated a B-cell phenotype (CD5-, CD10-, CD20+, CD45+, kappa and lambda immunoglobulin light chain negative). A diagnosis of DLBCL was established. Chemotherapy with CHOP was administered. There was a complete response, which was followed by bone marrow relapse 14 months later. She subsequently received a bone marrow transplant and is free of disease four years later.

Discussion

Bone marrow involvement is less frequent at presentation in diffuse large B-cell lymphoma than it is in low-grade B-cell lymphomas (chronic lymphocytic leukemia / small lymphocytic lymphoma, follicle center lymphoma, and mantle cell lymphoma) (1–3). However, T-cell-rich DLBCL, characterized by a major component of reactive T cells, is an apparent exception, with marrow involvement in up to 62% of cases (4). In the present series, we report on four cases of diffuse large cell lymphoma which presented primarily as bone marrow disease with hematologic manifestations, including leukoerythroblastosis and pancytopenia (Table 1). Lymphadenopathy in these cases

was absent or inconspicuous. In each case, the prominence of hematologic manifestations led to consideration of alternative diagnoses, including acute granulocytic leukemia and a myelodysplastic syndrome. The presence of circulating immature granulocytes and diffuse marrow replacement by blasts suggested acute granulocytic leukemia in three patients; in the fourth, the presence of pancytopenia and scattered single blasts in the bone marrow suggested a myelodysplastic syndrome. A clue to the correct diagnosis, in the one case in which they were prominent, Case 1, was the presence of numerous “lymphoglandular bodies” in the bone marrow aspirate smear (Fig. 2). These extracellular basophilic bodies, globules of extruded cytoplasm, are well known to cytopathologists to be a feature of malignant lymphoma in fine-needle aspiration smears, but are less familiar to surgical pathologists and hematologists. The presence of “lymphoglandular bodies” in bone marrow aspiration smears has been reported to be a clue to the presence of B-cell malignancy (10).

In three of these cases, additional clinical manifestations associated with lymphoma were present: monoclonal gammopathy in Case 1, sepsis and neutropenia in Case 2, and life-threatening hypercalcemia in Case 3. Monoclonal gammopathy of undetermined significance (defined by a monoclonal serum protein of less than 30 g/L and the absence of anemia, hypercalcemia, lytic bone lesions, or bone marrow plasmacytosis exceeding 10%) is associated with progression to multiple myeloma, lymphoma, amyloidosis, chronic lymphocytic leukemia, or Waldenström’s macroglobulinemia in up to 30% of patients with long-term follow-up, at a rate of approximately 1% per year (11). Although this patient (Case 1) had an IgM paraprotein, he did not meet the criteria for Waldenström’s macroglobulinemia, since his serum IgM paraprotein was less than 30 g/L. Sepsis and neutropenia are recognized complications

TABLE 1
Hematologic Findings

Case	Hgb g/L	Hct %	WBC $\times 10^9/L$	PLT	PMN %	LYM %	MON %	BND %	META %	MYE %	BLAST %	NRBC /100 WBC
1	119	34.8	10.1	53	34	19*	14	14	4	7	3	1
2	91	25.9	7.3	98	47	12*	5	19	5	11	1	6
3	95	28.0	5.4	34	41	26	11	17	2	2		rare
4	67	19.4	3.3	88	32	56	12					

*atypical lymphocytes (2% in Case 1; 5% in Case 2).

TABLE 2
Immunophenotypic Studies

Case	CD45	CD5	CD10	CD19	CD20	CD22	CD23	Sig
1 BM*	+	-	+	+	+	+	-	Lambda
2 PB*	+	-	+	+	+	+	-	Lambda
3 BM**	+	-	-	ND	+	ND	ND	-
4 BM**	+	-	-	ND	+	ND	ND	-

* flow cytometry

**immunohistochemistry

ND = not determined

of cytotoxic chemotherapy for malignant lymphoma and other neoplasms. The extensive marrow replacement by lymphoma in these patients may predispose to neutropenia as a result of limited bone marrow reserve; in one patient (Case 4), mild neutropenia was present at presentation. Life-threatening hypercalcemia is an infrequent complication of malignant lymphoma, which is humorally mediated in most cases (12). Hydration and diuresis are the mainstays of therapy; addition of biphosphonates, calcitonin, mithramycin, or gallium nitrate may be necessary in refractory cases. Bone marrow necrosis was a prominent feature in the biopsies in Case 2 and Case 3. Bone marrow necrosis may be the presenting feature of hematologic malignancies, including acute leukemia (13, 14) and malignant lymphoma (7). The diagnosis of malignant lymphoma in these cases was ultimately established by immunophenotypic studies (Table 2) utilizing immunofluorescence flow cytometry (Cases 1 and 2) or immunohistochemical staining of bone marrow sections (Cases 3 and 4).

The origin of the bone marrow lymphoma in these patients is unclear. Although some evidence of extramedullary involvement was present in three cases (hepatosplenomegaly in Case 1, retroperitoneal lymphadenopathy in Case 2, positive gallium scan in Case 3), extramedullary involvement in these cases was clinically inconspicuous, suggesting the possibility of primary bone marrow lymphoma. Cases of primary bone marrow lymphoma are reported in the literature (5–9); however, the criteria for diagnosis are not well established. It is hypothesized that primary bone marrow lymphoma could arise from lymphoid follicles normally present in the bone marrow, which increase with age (15). Since the criteria for primary bone marrow lymphoma are not well established, these cases could be considered as diffuse large B-cell lymphoma presenting

as bone marrow involvement, rather than as primary bone marrow lymphoma *per se*; however, this distinction seems semantic and a bone marrow origin of these lymphomas seems likely on clinical and pathologic grounds.

Diffuse large B-cell lymphoma may present with bone marrow involvement mimicking a primary hematologic disorder as the major manifestation. Immunophenotypic studies are necessary for diagnosis. DLBCL should be considered in the differential diagnosis of unusual hematologic presentations, particularly in the elderly.

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