

T-Cell Blast Crisis in Chronic Myelogenous Leukemia

Immunophenotypic and Molecular Biologic Findings

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T-cell blast crisis in chronic myelogenous leukemia is rare. We examined three patients (ages 35 to 72 years) in whom T-cell blast crisis developed 11 to 36 months (mean, 25 months) after diagnosis of chronic myelogenous leukemia and who died 4 to 12 months (mean, 7 months) thereafter. Two patients had diffuse lymphadenopathy, and the third had marked lymphocytosis (white blood cell count 217,000/ μ L, with 90% circulating blasts). In all three patients, neoplastic cells had the appearance of lymphoblasts and were immunoreactive for T-cell markers by immunohistochemical or flow cytometric analysis or both.

Molecular diagnostic studies revealed the presence of a *bcr-abl* oncogene rearrangement in all three cases, but none exhibited a clonal T-cell receptor δ , β , or γ chain gene rearrangement. One case exhibited deletion of the J δ 1 region of both δ chain genes. The significance of these findings is discussed, and they are compared with those of other reported cases of T-cell blast crisis in chronic myelogenous leukemia. (Key words: Oncogene *bcr-abl*; T-cell receptor gene rearrangement; T lymphocyte) *Am J Clin Pathol* 1997;107:168-176.

Chronic myelogenous leukemia (CML), one of the chronic myeloproliferative disorders, typically is diagnosed in an indolent phase of disease of 3 to 4 years' duration, which, after conventional therapy, is followed by an accelerated phase of 12 to 18 months' duration and a fatal, blast phase (blast crisis) of 3 to 6 months' duration.^{1,2} Blast crisis is defined as the presence of 30% or more blast cells in the blood or bone marrow or a focus of blast cells at an extramedullary site.^{3,4} Blast cells in CML exhibit a myeloid phenotype in 70% of cases and a lymphoid phenotype in 30%.⁴ In most lymphoid blast crises, the blast cells have L1 or L2 lymphoblast morphologic features, are positive for terminal deoxynucleotidyl transferase (TdT), and have the immunophenotypic profile of pre-B cells (CD19 [+], CD20 [\pm], CD10 [+]); surface immunoglobulin [-]; cytoplasmic immunoglobulin [\pm].⁴ Only rare cases of CML blast crisis with a T-lymphoblast immunophenotype have been reported.⁵⁻¹⁸

The characteristic cytogenetic finding in CML, observed in 90% to 95% of cases, is the Ph' chromosome, representing t(9;22)(q34;q11) translocation of the *abl* oncogene on chromosome 9 to the breakpoint cluster region (*bcr*) on chromosome 22.^{1,4,19} Ph chromosome-negative cases of CML are typically positive for the *bcr-abl* translocation by molecular diagnostic methods, including Southern blot testing and polymerase chain reaction (PCR).⁴ Additional cytogenetic abnormalities may appear in CML in the evolution to blast crisis in 70% to 80% of patients, including development of an additional Ph' chromosome, trisomy 8, isochromosome 17q,+19, and additional aneuploidy.^{1,4} Immunoglobulin gene rearrangements may also be detected in B-cell lymphoid blast crisis,²⁰ and T-cell receptor gene rearrangements have been reported in T-cell lymphoid blast crisis.^{13-16,18}

This report describes the histologic, immunophenotypic, and molecular biologic findings in three patients with CML in T-cell blast crisis, discusses the significance of these findings, and compares them with those of other reported cases of this rare phenomenon.

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MATERIALS AND METHODS

Case files of T-cell blast crisis in CML were retrieved from the surgical pathology files of Brigham and Women's Hospital, Boston. Biopsy specimens were

fixed in 10% buffered formalin or B5 fixative (lymph nodes) or Zenker's fixative (bone marrow) before conventional tissue processing, paraffin embedding, and preparation of histologic sections for light microscopic examination or of paraffin sections for immunoperoxidase analysis. Lymph node tissue was also snap-frozen in dry ice-isopentane and used for the preparation of frozen sections for immunoperoxidase analysis.

Frozen sections and deparaffinized paraffin sections were used for immunoperoxidase analysis using sequential peroxidase-conjugated reagents.^{21,22} Monoclonal antibodies used included CD5, CD7, CD43 (Leu-1, Leu-9, and Leu-22, respectively; Becton Dickinson, Mountain View, Calif), CD10, CD13, CD33, CD34 (ALB2, SJ1D1, D3HL60.251, and QBEND10, respectively; Immunotech, Westbrook, ME), CD20, CD22, CD45, CD45RO, myeloperoxidase, TdT (L26, To15, PD7/26, UCHL-1, MPO-7, and HT1-3, respectively; Dako, Carpinteria, Calif), CD2, CD3, CD4, CD8, CD19, CD20 (B1), and antibodies to immunoglobulin κ and λ light chains (provided by Dr Lee Nadler, Dana Farber Cancer Institute, Boston). O13 (anti-CD99) monoclonal antibody was obtained from Signet Laboratories (Dedham, Mass). Studies for immunoglobulin light chains were also performed using polyclonal (rabbit) antibodies and polyclonal anti-lysozyme antibody (A099) (Dako). Staining of specimens was compared with staining of known positive control specimens. A result was considered positive if a majority of neoplastic cells were immunoreactive for the marker being studied.

Flow cytometric immunophenotypic analysis was performed on mononuclear cells obtained from centrifugation of bone marrow with Ficoll-Hypaque using a panel of paired antibodies directly conjugated to fluorescein isothiocyanate (FITC) or phycoerythrin (PE). These included CD45(FITC)-CD14(PE), CD5(FITC)-CD20(PE), CD3(FITC)-CD16(PE), CD10(FITC)-CD20(PE), CD19(FITC)-HLA-DR(PE), CD14(FITC)-CD13(PE), CD11b(FITC)-CD14(PE), and CD34(FITC)-CD33(PE) (Immunotech). Analysis was performed on a fluorescence-activated cell sorter (FACS analyzer; Becton Dickinson Immunocytometry Systems, San Jose, Calif), with data collected as two-parameter correlated histograms and displayed using Consort 30 software (Becton Dickinson). Isotype-matched control antibodies were used to establish positive staining thresholds.

RNA isolation and the reverse transcriptase-polymerase chain reaction (RT-PCR) were performed.²³ The K562 cell line (obtained from the American Type Culture Collection) was used as a source of control b3/a2 fusion *bcr/abl* messenger RNA (mRNA). The

Sup B13 cell line (provided by Dr Stephen Smith, University of Chicago Medical Center) was used as a source of control e1/a2 fusion *bcr/abl* mRNA. Control b2/a2 fusion *bcr/abl* mRNA was obtained from leukocytes isolated from the blood of a patient with CML.

DNA was extracted from frozen tissue using standard techniques. Ten-microgram samples of DNA were digested with *Bam*HI, *Eco*RI, *Bgl* II, or *Hind*III restriction endonucleases (Gibco BRL, Gaithersburg, Md) and size fractionated on 0.8% agarose gel. Details of the methods of Southern blot testing, hybridization, and autoradiography have been described.²³ The probes for the T-cell receptor δ chain (provided by Mark Krangel, PhD, Duke University Medical Center, Durham, NC) consisted of a 1.7-kb *Xba* I restriction fragment containing the J δ 1 region and a 1.1-kb *Bam*HI-*Xba* I restriction fragment containing the J δ 3 region.²⁴ The probe for the T-cell receptor γ chain consisted of a 2.1-kb *Hind*III restriction fragment containing the J γ 1 region.²⁵ The probe for the T-cell receptor β chain is a mix of a 550-bp *Xba* I restriction fragment (J β 1 region) and a 4.3-kb *Eco*RI restriction fragment (J β 2 region).²⁶ For analysis of the breakpoint on chromosome 22, a 1.2-kb *Hind*III-*Bgl* II probe from the 3' end of the *bcr* oncogene (Oncogene Science, Mineola, NY) was used.

RESULTS

Clinical Findings

Patient 1 was a 72-year-old man with a 3-year history of CML that had been treated with hydroxyurea. Fever and diffuse lymphadenopathy developed, and a peripheral blood smear revealed the presence of blast cells. Findings at biopsy and study of a cervical lymph node were consistent with T-cell blast crisis, although in the absence of the above clinical history the findings were initially interpreted as consistent with high-grade T-cell non-Hodgkin's lymphoma. Treatment with six cycles of CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine sulfate], and prednisone) chemotherapy resulted in resolution of the blast crisis. Hydroxyurea therapy was resumed, but myeloid blast crisis developed 5 months later. After a single cycle of CHOP chemotherapy produced no response, treatment was discontinued, and the patient died 2 months later.

Patient 2 was a 35-year-old woman who had a 29-month history of CML that had been treated with hydroxyurea. Painful cervical lymphadenopathy developed, with 18% circulating blast cells. Biopsy and analysis of a cervical lymph node revealed findings consistent with T-cell blast crisis. High-dose chemotherapy

(mitoxantrone, cytosine arabinoside, and etoposide) and subsequent allogeneic bone marrow transplantation resulted in resolution of the blast crisis. Painful cervical lymphadenopathy recurred, however, 8 months after the original diagnosis of blast crisis, and analysis of a biopsied lymph node revealed relapsed T-cell blast crisis. Examination of the peripheral blood and a bone marrow biopsy specimen revealed no evidence of leukemia. Additional high-dose chemotherapy was administered without resolution of the lymphadenopathy, and the patient died 4 months later, after development of pancytopenia, then fever and hypotension.

Patient 3 was a 68-year-old man with an 11-month history of CML treated with hydroxyurea. A productive cough developed, and examination of the peripheral blood revealed a white blood cell count of 217,000/ μ L, with 90% circulating blast cells. This finding, along with examination of the bone marrow, was consistent with T-cell blast crisis, although findings at flow cytometric immunophenotyping were originally misinterpreted as consistent with myeloid blast crisis. Doxorubicin, vincristine, and prednisone chemotherapy was administered. Persistent pancytopenia and recurrent pneumonia developed. Four months after diagnosis, blast crisis recurred, along with bilateral pneumonia with sepsis, and the patient died. At

autopsy, there was widespread evidence of blast crisis, including diffuse lymphadenopathy, massive splenomegaly, and involvement of bone marrow, heart, liver, kidneys, lungs, and one testis. Autopsy findings confirmed that acute bronchopneumonia complicated by sepsis was the immediate cause of death.

Histologic Findings

Histologic examination of the lymph node biopsy specimens diagnostic for T-cell blast crisis in patients 1 and 2 revealed architectural effacement of the lymph nodes by diffuse neoplastic infiltrates. The neoplastic cells from both patients were of intermediate to large size, with oval to irregular vesicular nuclei with dispersed chromatin and distinct nucleoli (Fig 1, A and B). The mitotic rate was high in the lymph node from patient 1. Rare immature eosinophilic myeloid elements were also present in both biopsy specimens.

Histologic examination of the bone marrow biopsy specimen diagnostic for T-cell blast crisis in patient 3 revealed markedly hypercellular marrow, with small to medium-sized cells with scant cytoplasm, round to irregular nuclei, with fine chromatin and small nucleoli constituting 80% of the marrow cellularity (see Fig 1, C). Numerous eosinophilic myeloid forms also were seen.

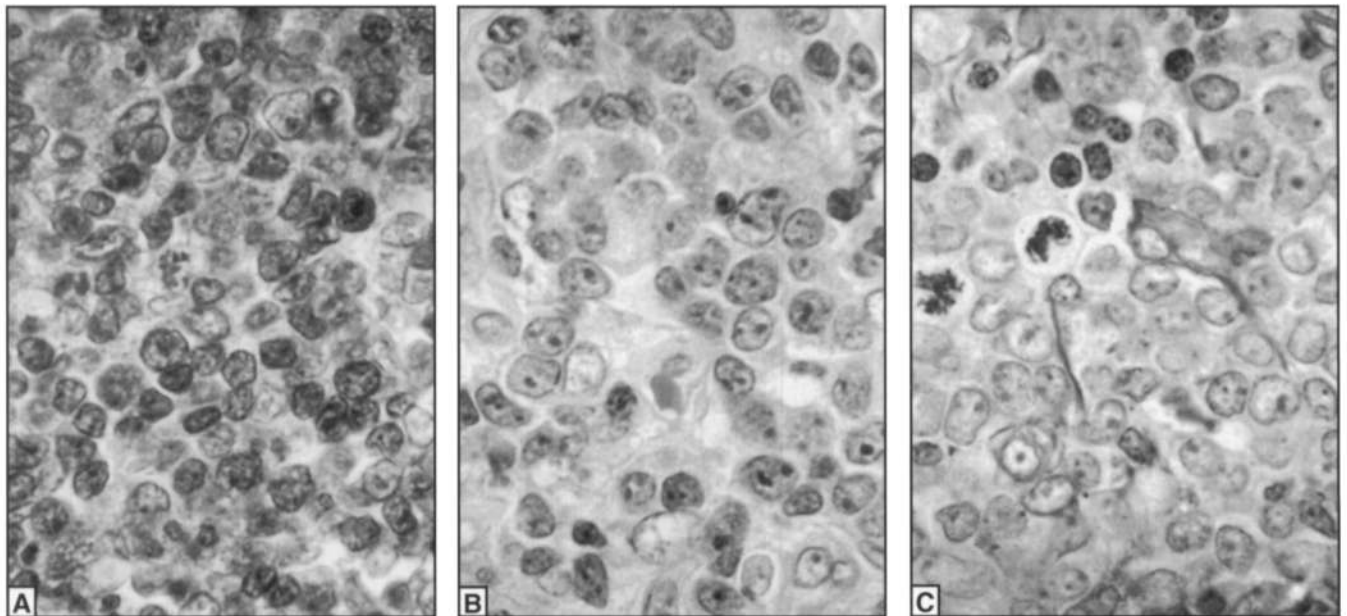


FIG 1. T-cell blast crisis in chronic myelogenous leukemia. A and B (patients 1 and 2, respectively), Lymph node biopsy specimens demonstrate architectural effacement by a diffuse neoplastic infiltrate of intermediate-sized to large cells with oval to irregular vesicular nuclei, with dispersed chromatin and distinct nucleoli (hematoxylin-eosin, original magnification $\times 1000$). C (patient 3), Bone marrow is markedly hypercellular and contains a diffuse infiltrate of small to medium-sized cells with scant cytoplasm and round to irregular nuclei with fine chromatin and small nucleoli. Numerous eosinophilic myeloid forms are also present (hematoxylin-eosin, original magnification, $\times 1000$).

Immunophenotypic Findings

The immunophenotypic findings (Table 1) include data from immunohistochemical analysis of the lymph node biopsy specimens from patients 1 and 2 and cyto-centrifuge preparations as well as flow cytometric immunophenotypic analysis of cells from the bone marrow biopsy specimen from patient 3. The neoplastic cells from all three patients were nonreactive for B-cell markers (CD20 in all three patients, CD19 in patients 2 and 3, CD22 in patients 1 and 2, and surface immunoglobulin light chains in patients 1 and 3). The neoplastic cells in patients 2 and 3 were reactive for CD10 (common acute lymphoblastic leukemia antigen [CALLA]), typically a marker of B-cell blasts but which also has been observed in T-cell blasts in 10% to 40% of cases of T-cell acute lymphoblastic leukemia (ALL)²⁷⁻²⁹ and in T-cell lymphoblastic lymphoma.³⁰

Neoplastic cells from all three specimens were immunoreactive for CD45 (leukocyte common antigen [LCA]), which is observed early in T- and B-cell differentiation,³¹ and TdT, a marker of early T- and B-cell lymphoblasts that also may be observed in a minority of patients with acute myeloblastic leukemia (AML).³² Neoplastic cells from all three specimens were also immunoreactive for CD99 (p30/32^{MIC2}), a surface glycoprotein expressed by immature T cells, 100% of cases of T-cell lymphoblastic lymphoma and ALL, and approximately 75% of cases of B-cell lymphoblastic lymphoma and ALL (but virtually no cases of small noncleaved cell lymphoma and L3 (B-cell) ALL).^{33,34}

Neoplastic cells from all three specimens were positive for T-cell marker CD7, the earliest marker of T-cell differentiation,³⁵ although CD7 expression has been observed in 5% to 10% of cases of AML.^{36,37} All three specimens were positive, however, for additional T-cell markers. Cytoplasmic CD3 (cCD3), a marker first seen early in T-cell differentiation, was present in cases 1 and 2. CD2, another marker seen early in T-cell differentiation, was present in case 3, CD5 in cases 2 and 3, CD43 in cases 1 and 2, and CD45RO in all three cases. In all three cases, the neoplastic cells were nonreactive for T-cell antigen CD3 surface staining (sCD3). Neoplastic cells in cases 1 and 2 were nonreactive for CD4 and CD8, markers that appear relatively late during T-cell differentiation.^{31,38} CD43 has been detected in 9 of 10 cases of T-cell lymphoblastic lymphoma,³⁹ and CD45RO has been detected in T-cell ALL,³⁸ suggesting that both markers may be positive in neoplastic cells with an immature T-cell phenotype. CD43 may also be observed in neoplasms of B-cell and myeloid lineage.

Focal immunoreactivity for myeloid antigens was observed in occasional neoplastic cells from biopsy specimens from patients 1 and 2 (CD13 and myeloperoxidase in both cases, CD 33 and lysozyme in case 2), which has been reported in occasional cases of B- and T-cell ALL.^{29,40} Neoplastic cells from patient 3 were initially thought to be reactive for CD13 and interpreted as myeloblasts because of high background staining. Blast cells from patient 3 were nonreactive for HLA-DR, a marker present during early T-cell differentiation but absent in 60% to 90% of cases of T-cell ALL.²⁸ Blast cells from patients 1 and 3 were immunoreactive for CD34, a hematopoietic progenitor-stem cell marker observed in 10% to 20% of T-cell ALL and 50% to 60% of B-cell ALL.³¹

Molecular Biologic Findings

In all three patients, molecular diagnostic methods were used to detect the *bcr-abl* translocation. The Southern blot technique showed rearrangement of the major *bcr* oncogene in DNA isolated from a diagnostic lymph node from patient 2 (Fig 2, A) and in neoplastic tissue from patients 1 and 3 (data not shown). In patients 1 and 3, *bcr-abl* rearrangement was analyzed by the RT-PCR method. Both patients exhibited a *bcr-abl* PCR product (see Fig 2, B, lanes 1 and 2) of the b3/a2 type, indicating a breakpoint in the *bcr* gene, as is described in CML.⁴¹

Neoplastic cells from all three patients were analyzed for T-cell receptor gene rearrangements by the Southern blot technique. No clonal rearrangements of the δ , β , or γ T-cell receptor genes were identified using several probe-enzyme combinations (J δ 1: *Xba* I, *Bam*HI, *Bgl* II, *Eco*RI, *Hind*III; J δ 3: *Xba* I; J γ : *Bam*HI, *Bgl* II, *Hind*III; J β 1/ β 2: *Bgl* II, *Hind*III). Patient 1 exhibited deletion of the J δ 1 region of both δ chain genes, as may be observed in most cells of T-cell origin (Fig 3) and in T-cell lymphoproliferative disorders.⁴² Representative β and γ chain results are illustrated in Figure 4 for patients 1 and 3; similar results were obtained for patient 2 (data not shown).

DISCUSSION

This report describes the histologic, immunophenotypic, and molecular biologic findings in three patients with T-cell blast crisis, a rare, terminal outcome in CML. In our study of patients with CML (ages 35 to 72 years), T-cell blast crisis developed 11 to 36 months after the initial diagnosis, and all three patients died 4 to 12 months later. An unusual clinical

feature was the development of lymphadenopathy in all three patients. Patients were treated with three different chemotherapeutic regimens; in two patients, the blast crisis resolved initially but recurred rapidly 5 to 8 months later. These clinical findings are similar to those reported in 17 previously described cases of T-cell blast crisis.⁵⁻¹⁸ Patients ranged in age from 19 to 66 years (mean, 41 years). T-cell blast crisis developed after approximately 29 months, based on stated out-

comes in 15 cases, and the patients died 2 months later, based on stated outcomes in 9 cases, after undergoing various treatment regimens.⁵⁻¹⁸ A number of these patients had lymphadenopathy at the time of blast crisis.^{7,8,10,12,14,15,17}

In our three patients, the T-cell blasts had an imma-

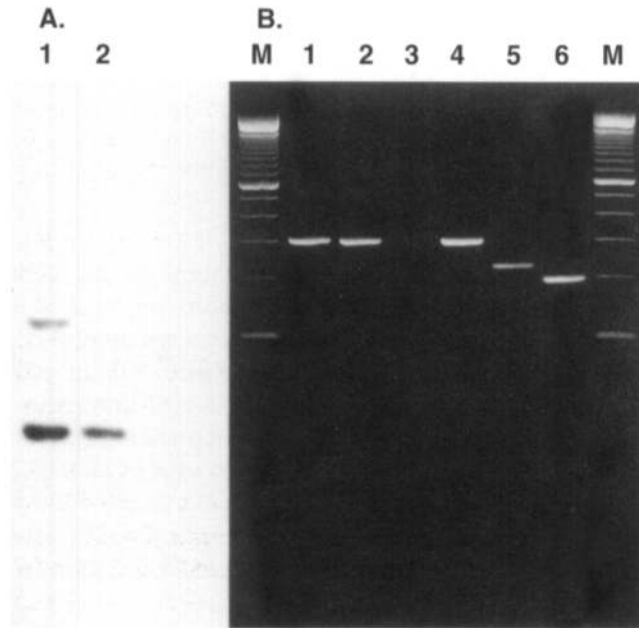


FIG 2. A (patient 2). Autoradiogram of Southern blot of genomic DNA prepared from a biopsied neoplastic lymph node. DNA was digested with Bgl II and hybridized with the *bcr* DNA probe. Lane 1, patient DNA; lane 2, DNA from normal peripheral blood. Upper band represents a rearranged 8.4-kb *bcr* oncogene fragment, representing a *bcr-abl* rearrangement. Lower band is a 4.8-kb germline *bcr* locus restriction fragment. B, Reverse transcriptase-polymerase chain reaction analysis for *bcr-abl* messenger RNA (mRNA). Lane 1, patient 1; lane 2, patient 3; lane 3, water control; lane 4, b3/a2 *bcr-abl* mRNA; lane 5, b2/a2 *bcr-abl* mRNA; lane 6, e1/a2 *bcr-abl* mRNA. All samples underwent electrophoresis on 2.0% agarose gel stained with ethidium bromide and photographed under ultraviolet light. A 100-bp molecular weight ladder is shown at both ends of the gel.

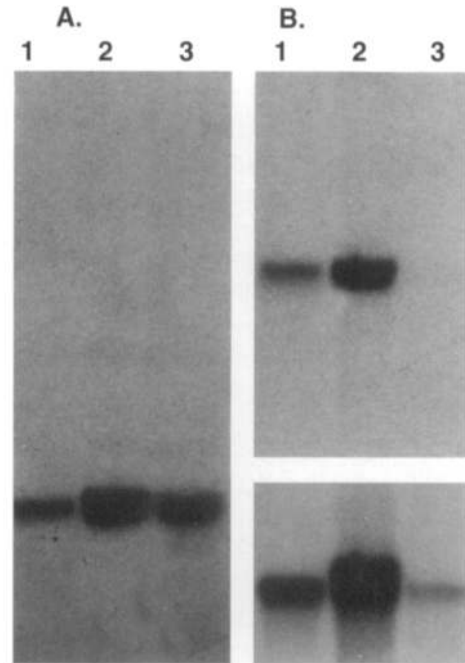


FIG 3. Autoradiograms of representative Southern blots of genomic DNA prepared from normal human tissue (lanes A1 and B1) and neoplastic tissue from patient 1 (lane B3), patient 2 (lane A3), and patient 3 (lanes A2 and B2), digested with Xba I (A) or Bgl II (B), electrophoresed on 0.8% agarose gel, Southern blotted, and probed for rearrangements of the T-cell receptor β locus (A) or δ locus (B). A, Autoradiogram reveals presence of 5.0-kb germline T-cell receptor β locus Xba I restriction fragments in control genomic DNA and DNA from patients 2 and 3 hybridizing to the T-cell receptor β locus probe. B, Autoradiogram reveals presence of 4.9-kb germline T-cell receptor δ locus restriction fragments in control genomic DNA and DNA from case 3. Case 1 exhibits deletion of δ chain genomic material at this locus; no autoradiographic signal is evident even with prolonged exposure (not shown). Bottom panel shows the same Southern blot stripped and rehybridized with a *bcr* probe, showing presence of *bcr* hybridizing genomic DNA in all three lanes.

TABLE 1. IMMUNOPHENOTYPIC FINDINGS IN T-CELL BLAST CRISIS IN CHRONIC MYELOGENOUS LEUKEMIA

Patient	Age (yr)	Sex	Tissue	CD45	HLA-DR	CD34	CD19	CD20	CD22	CD10	sIg	CD2	cCD3	sCD3
1	72	M	Lymph node	+(fr)		+(p)	-(fr)	-(fr,p)	-(fr)	-(fr)	-(fr)	-(fr)	+(p)	
2	36	F	Lymph node	+(p)		+(p)		-(fr,p)	-(fr)	foc+(fr)	-(fr)		+(p)	-(fr)
3	67	M	Bone marrow	+(fl)	-(fl)	-(fl)	-(fl)	-(fl)		+(fl)		+(fl)		-(fl)

sIg = monotypic surface immunoglobulin light chain staining; cCD = cytoplasmic CD3 staining; sCD3 = surface CD3 staining; TdT = terminal deoxynucleotidyl transferase; MPO = myeloperoxidase; + = staining of neoplastic cells; - = absence of staining of neoplastic cells; foc+ = focal staining of neoplastic cells; fr = immunoperoxidase studies on frozen sections; p = immunoperoxidase studies on paraffin sections; cy = immunoperoxidase studies on cytocentrifuge preparations; fl = flow cytometric immunophenotypic analysis.

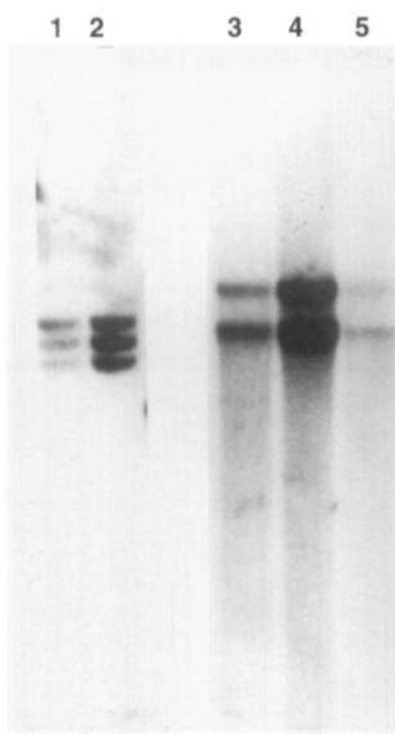


FIG 4. Autoradiograms of a representative Southern blot of genomic DNA prepared from normal human tissue (lanes 1 and 3) and from neoplastic tissue from patient 1 (lanes 2 and 5) and patient 3 (lane 4), digested with *Bgl* II restriction enzyme, electrophoresed on 0.8% agarose gel, Southern blotted, and probed for rearrangement of the T-cell receptor $\beta 1/\beta 2$ locus (lanes 1 and 2) or the T-cell receptor δ locus (lanes 3 to 5). Lanes 1 and 2 reveal presence of normal 11-, 10-, and 9.3-kb genomic bands hybridizing to the T-cell receptor $\beta 1/\beta 2$ probe, with no additional, rearranged bands seen in the patient sample (lane 2). Similar results were obtained with specimens from patients 2 and 3 (data not shown). Lanes 3 to 5 reveal the presence of normal 12.6- and 9.5-kb genomic bands hybridizing to the T-cell receptor γ probe, with no additional, rearranged bands seen in the patient samples (lanes 4 and 5), even with prolonged exposure (data not shown). Similar results were obtained with a specimen from patient 2 (data not shown).

marker CD34 in two of the three patients. Cells in all three patients were positive for the pan-T-cell marker CD7, and, where studied, were negative for late T-cell markers CD4, CD8, and sCD3. Cells in two of the three patients were positive for additional pan-T-cell markers present early in T-cell differentiation: cCD3, CD2, and CD5. Similarly, the cells in most cases of B-cell lymphoid blast crisis exhibit immunophenotypes characteristic of early B-cell differentiation.²⁰

All three patients with T-cell blast crisis in our study were positive for the t(9;22) translocation by Southern blot analysis for *bcr-abl* t(9;22) translocation, a defining characteristic of CML, including the blast crisis stage.^{1,4,19} In reported cases of T-cell blast crisis, 17 of 17 exhibited t(9;22) by the presence of the Ph chromosome,⁵⁻¹⁸ and 3 cases by molecular biologic analysis for the *bcr-abl* translocation.^{13,16,18}

All three patients with T-cell blast crisis in our study were negative for T-cell receptor δ , β , and γ chain gene rearrangements by Southern blot analysis, although one exhibited deletion of the $J\delta 1$ region of both δ chain genes. Gene rearrangement at the T-cell receptor δ chain locus appears to be the earliest genotypic event in T-cell differentiation and has been observed in T-cell ALL,⁴³ although examples of T-cell ALL without δ chain gene rearrangements have been described.⁴³ Furthermore, post-thymic T-cell non-Hodgkin's lymphomas have been described with partial deletion of the δ chain locus and absence of clonal T-cell receptor δ , β , or γ chain gene rearrangements.⁴² T-cell receptor γ chain gene rearrangements are observed beginning at the prothymocyte to immature thymocyte stage of T-cell development, and precede β chain gene rearrangements, which are first observed at the immature thymocyte stage of development (reviewed in references 38 and 44). A number of cases of T-cell ALL have been reported with an early T-cell immunophenotype (positive for CD7 \pm CD2 and CD5) but lacking T-cell receptor δ , β , or γ chain gene rearrangements,^{43,45-48} suggesting that the expression

ture phenotype, including positivity for TdT and CD99, and for the hematopoietic progenitor cell

CD4	CD5	CD7	CD8	CD43	CD45RO	TdT	CD11b	CD13	CD14	CD33	MPO	Lysozyme	CD99
-(fr)	-(fr)	+(fr)	-(fr)	+(p)	+(p)	+(fr)		foc+(fr)			foc+(p)		+(p)
-(fr)	+(fr)	+(fr)	-(fr)	+(p)	foc+(p)	+(fr)		foc+(fr)		foc+fr	foc+(p)	foc+(p)	+(p)
	+(fl)	+(fl)			foc+(p)	+(cy)	-(fl)	-(fl,cy)	-(fl)	-(fl)	-(p)	-(p)	+(p)

TABLE 2. COMPARISON OF CLINICAL, IMMUNOPHENOTYPIC, AND MOLECULAR BIOLOGIC FINDINGS IN T-CELL BLAST CRISIS

Reference	Age (y)	Sex	T-cell Phenotype	TdT	HLA-DR	Cyto-genetics	bcr-abl	TCR Rearrangement	Treatment	Follow-up
13	66	M	CD2, 7, 10 +; CD1, 4, 8 -	+		+	+	TCR β		
14	59	F	CD 4, 5, 10, 26 +	+		+		TCR β		
15	19	F	CD1, 2, 4, 5, 8 +; CD3, 10 -		-	+		TCR α, β	Prednisone, vincristine, asparaginase, doxorubicin, cyclophosphamide	DOD after a short time
16	33	F	CD2, 4, 5, 7, 8 +; CD1, 3, 10 -	-	-	-	+	TCR β		DOD at 2 months
18	63	F	CD2, 3, 43 +; CD45RO-			+	+	TCR β	Local irradiation	DOD at 10 days
Current study										
Patient 1	72	M	CD7, 43, 45RO +; CD2, 4, 5, 8, 10 -	+			+	Absent	Cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), prednisone	Resolution of blast crisis; myeloid blast crisis at 5 months; DOD 2 months later
Patient 2	35	F	CD5, 7, 10, 43, 45RO +; CD3, 4, 8 -	+			+	Absent	Mitoxantrone, cytosine arabinoside, etoposide	Resolution of blast crisis; recurrence at 8 months; DOD 4 months later
Patient 3	68	M	CD2, 5, 7, 10, 45RO +; CD3 -	+	-		+	Absent	Daunorubicin, vincristine, prednisone	DOD at 4 months

DOD = dead of disease.

of these early T-cell markers may occur without rearrangements of the T-cell receptor gene loci. For example, Griesinger et al⁴⁵ reported two cases of T-cell ALL (one expressing CD7 and CD2, and one expressing CD7, CD2, and CD5) that lacked T-cell receptor δ and γ chain rearrangements. Pittaluga et al⁴⁸ reported two cases of T-cell ALL (one expressing CD7 and CD2, and one expressing CD7 and CD5) that lacked gene rearrangements at the T-cell receptor β locus.

T-cell lymphoproliferative disorders may aberrantly lack clonal β and γ chain gene rearrangements, even in cases with a mature T-cell immunophenotype (eg, positive for CD4, CD8, or both).^{44,49} Weiss et al⁴⁹ raise the possibility of T-cell receptor gene rearrangements and subsequent deletion, or the occurrence of polyclonal T-cell receptor gene rearrangements after malignant transformation in some T-cell lymphoproliferative processes. Alternatively, it appears possible that neoplastic T cells may simply fail to undergo rearrangement at some or all T-cell receptor gene loci.

Five reported cases of T-cell blast crisis with T-cell receptor gene rearrangement studies are summarized in Table 2. All five cases exhibited T-cell receptor β chain gene rearrangements. In one case a T-cell receptor α chain gene rearrangement, typically first seen

later in T-cell development than β chain rearrangements,^{38,44} was observed. The presence of T-cell receptor gene rearrangement correlated with the immunophenotypic findings. Three of five cases were positive for CD4 or CD8 expression, or both; a fourth case was positive for CD3 expression. These findings are consistent with a more mature stage of T-cell development than observed in our three cases. The fifth case was positive for CD7 and CD2, and negative for CD1, CD4, and CD8, consistent with the immature thymocyte stage of T-cell development, during which T-cell receptor β chain gene rearrangements have been observed.^{38,44} On the basis of these findings, we conclude that our cases of T-cell blast crisis represent a subtype not previously described, in which immunophenotypic evidence of early T-cell differentiation is present, yet genotypic evidence of T-cell differentiation at the T-cell receptor gene loci is absent.

In summary, we describe three cases of CML in T-cell blast crisis, characterized by T-cell blasts that exhibit the t(9;22) *bcr-abl* oncogene rearrangement, immature T-cell immunophenotypes, and the absence of T-cell receptor δ , β , and γ locus gene rearrangements. Although T-cell blast crisis is rare, it is important to recognize this complication of CML.

Findings such as those in our study (ie, T-cell blasts with a T-cell immunophenotype but lacking evidence of a T-cell genotype) may be confusing in clinical practice, and in the absence of adequate clinical information may be misinterpreted. Furthermore, the presence of lymphadenopathy at presentation with blast crisis, an unusual finding that has been observed in a number of cases of T-cell blast crisis, may be misinterpreted as evidence of a primary T-cell lymphoproliferative disorder.

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