Case Report

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Differential Diagnosis from Isolated Lymphoid Extramedullary Blast Crisis from Secondary Non-Hodgkin Lymphoma in Chronic Myelogenous Leukemia: A Case Report and Literature Review

Tingting Wang[1], Li Fu[1], Na Wei[2], Xiaoge Zhou[3], Xiaodan Zheng[3], Li Li[1*], Zhao Wang[2*]

[1]Department of International Medical Center, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China; [2]Department of Hematology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China; [3]Department of Pathology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

ABSTRACT

Extramedullary blast crisis (EBC) is a special kind of blast crisis of chronic myelogenous leukemia (CML). It is more likely to be misdiagnosed as lymphoma when EBC cells are of lymphoid cell lineage and lymphadenopathy is the only symptom before the final diagnosis. In this study, we presented a patient with an unusual presentation of CML transformation as a rapid growth of generalized lymphadenopathy that appeared 5 months after the initial diagnosis of CML. The patient underwent the left supraclavicular lymph node biopsy and repeat bone marrow aspiration. The revealed CD3+, terminal deoxynucleotidyl transferase (TdT)+, CD5+, CD23+, myeloperoxidase (MPO)-, CD20-, cyclin D1-, CD10-, which was consistent with the diagnosis of T-cell lymphoblastic lymphoma (T-LBL). Fluorescence in situ hybridization (FISH) verified the BCR-ABL rearrangement, and T-cell EBC of CML was finally diagnosed. Our report suggested that the FISH was necessary to distinguish isolated lymphoid extramedullary blast crisis from secondary NHL in CML.

Keywords: Chronic myelogenous leukemia, Extramedullary blast crisis, Secondary non-Hodgkin lymphoma

*Corresponding author:
Li Li,
Department of International Medical Center, Beijing Friendship Hospital, Capital Medical University, 95 Yong An Road, Xicheng Distract, Beijing 100050, China
Email: lili_l@aliyun.com
Zhao Wang,
Department of Hematology, Beijing Friendship Hospital, Capital Medical University, 95 Yong An Road, Xicheng Distract, Beijing 100050, China
Tel: +86 10 63139760
Fax: +86 10 63138606
Email: zhao_wz@aliyun.com

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INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder, which is caused by the neoplastic transformation of primitive multipotent hematopoietic stem cells. The t(9;22) (q34;q11) reciprocal translocation of the Philadelphia (Ph) chromosome can

be observed in more than 95% of patients with CML generating BCR-ABL, a fusion gene (1). The clinical manifestation of CML is usually characterized by a chronic phase (CP) followed by an accelerated phase (AP) or blast crisis (BC). According to the World Health Organization (WHO) classification of hematopoietic tumors in 2008, CML-BC could be diagnosed if patients have one or more symptom of the following symptoms, (1) 20% or more blasts presented in peripheral white blood cells or bone marrow cells; (2) having extramedullary blast proliferation (EBC); (3) large focus or clusters of blasts presented in bone marrow biopsy (2).

Here, we described a CML patient with a Ph-positive T cell EBC in lymph nodes. The clinical manifestation was similar to non-Hodgkin's lymphoma (NHL), and we reviewed the related literature.

CASE REPORT

A 45-year-old male was diagnosed with Ph-positive CML in CP in May 2011. There was leukocytosis confirmed by a routine examination. No other symptoms were accompanied. Laboratory examination showed that white blood cell count was 178.96×10^9/L (myelocytes 11%, metamyelocytes 6%, stab forms 14%, segmented forms 52%, eosinophils 1%, basophils 2%, lymphocytes 8%, and monocytes 6%), hemoglobin was 120 g/L, and platelets were 339×109 /L. The liver and kidney functions were normal. Karyotypic analysis revealed t (9;22), and reverse transcriptase-polymerase chain reaction (RT-PCR) reported the BCR-ABL p210 rearrangement. After the patient receives cytoreductive therapy with hydroxyurea followed by α-interferon, he achieved a partial hematological response, but no cytogenetic response. In October 2011, he was admitted to our hospital again and presented indolent generalized lymphadenopathy (0.5-5 cm) and splenomegaly (6 cm below the left costal margin). The white cell count was 15.7×10^9/L, the hemoglobin was 11.1 g/dl, and the platelet count 346×10^9/L.

The patient underwent the left supraclavicular lymph node biopsy as well as another bone marrow aspiration. Bone marrow aspiration showed myeloid hyperplasia with a myeloid/erythroid ratio of 16.55:1. At all stages of maturation, bone marrow components increased. The morphological features of peripheral blood and bone marrow were consistent with CP of CML. The karyotype analysis of the bone marrow reported a complex abnormality with 46,XY,t(9;22)(q34;q11) [17]/ 50,XY,t(9;22)(q34;q11)+6,+19,+10,+der(22) t(9;22)(q34;q11) (1). Lymph node the biopsy revealed diffuse infiltration by monomorphic lymphoid cells with an immature T-cell immunophenotype, including CD3+, terminal deoxynucleotidyl transferase (TdT)+, CD5+, CD23+, myeloperoxidase (MPO)-, CD20-, cyclin D1- and CD10- (Figure 1).

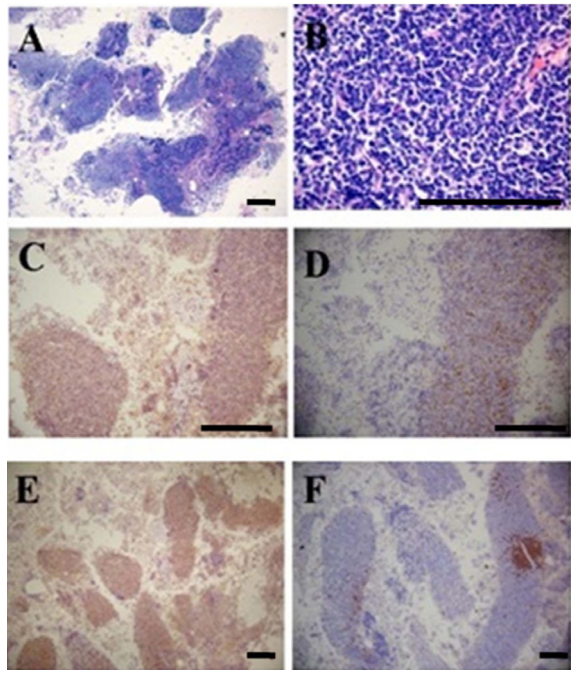

Figure 1. Extramedullary blast crisis of CML mimicking a T-LBL. Hematoxylin/eosin (HE) staining (A) showed The lymphoid follicles were effaced. The lymph nodes were diffusely or focally infiltrated by the neoplastic cells. Medium- to large-sized lymphoid cells who have irregular nuclear contours were reported by a higher magnification (B). Immunohistochemical staining revealed strong reactivity of the lymphoid cells with antibodies against the antigens CD3 (C), TdT (D), and CD5 (E). CD20 (F) was negative. Bar=1 μm. T-LBL: T-cell lymphoblastic lymphoma.

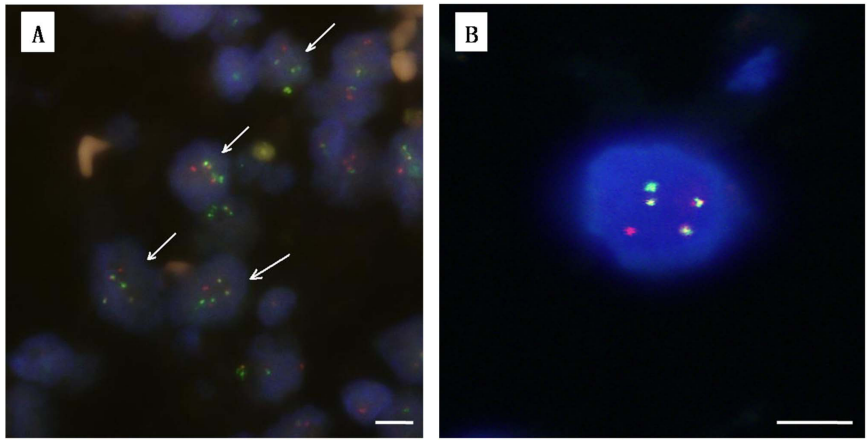

Figure 2. The FISH analysis for the detection of the BCR-ABL fusion gene in interphase cells from the lymph node. The red signals are for the ABL gene as well as the green signals for the BCR gene. The yellow signals represent the BCR-ABL fusion. (a) Gene fusion signals are found in most tumor cells of the lymph node. (b) A cell showing 3 BCR fusion signals, 1 isolated ABL copy, and 1 isolated BCR copy. Bar=0.1 μm

It was consistent with the diagnosis of T-cell lymphoblastic lymphoma (T-LBL).

The BCR-ABL p210 fusion transcript was detected in the bone marrow and lymph node with positive rates of 100% and 42.13%, respectively. Two-color fluorescence in situ hybridization (FISH) analysis of lymph node sections showed diffuse gene fusion signals in most tumor cells of the lymph node. In addition, three yellow fusion signals were found in some tumor cells, which indicated the presence of three Ph chromosomes (Figure 2).

DISCUSSION

BC phase is the terminal stage of CML. EBC is a special kind of blast crisis that occurs in about 4-6.4% of patients with CML and commonly involves bone, skin, lymph nodes, and other soft tissues (3-5). Specchia *et al.* reported that 20% of EBC occurs while the bone marrow still shows CP features (4). If the EBC cells are lymphoid cell lineage and lymphadenopathy is the only symptom before the final diagnosis, it may be usually misdiagnosed as lymphoma.

In the current article, we have summarized a case of a patient with an unusual presentation of CML transformation as a rapidly growing generalized lymphadenopathy that appeared 5 months after an initial diagnosis of CML. A lymph node biopsy showed diffuse infiltration by monomorphic lymphoid cells with an immature T-cell immunophenotype, which was consistent with a diagnosis of T-LBL. T-cell EBC of CML was finally diagnosed when the FISH analysis of the lymph node biopsy verified the BCR/ABL rearrangement.

In previous literature, there were 29 cases reported since 1990 and patients had CML with isolated lymphoid lineage EBC while the bone marrow remained in CP (5) (Table 1).

Secondary malignancies in CML are rare and usually consist of solid tumors (5).

Chronic myeloid leukemia (CML) is a rare entity that develops into NHL.

It may be underreported in cases where lymphadenopathy is considered to be a blast of CML, or in cases based on the conventional cytogenetic diagnosis. There have been 10 cases of secondary NHL developed in CML reported since 1990 (Table 2).

It is important to distinguish lymphoid EBC from secondary NHL occurring in Ph-positive CML for the prognosis and treatments. The crucial point is to discover the origin of the extramedullary tumor. A combination of morphological findings and immunophenotypic analysis by flow cytometry and/or immunohistochemical

Table 1. CML cases presenting with an isolated lymphoid EBC mimicking lymphoma.

Author/publish year	A/G	Biopsy sites	Time (mo)	Tx before EBC	Phenotype	Positive antigens in neoplastic cells	Ph[1]	Bcr RE[2]	bcr/abl mRNA[3]	FISH [4]	Tx after EBC	Outcome (month)
Blonk[6]1990	27/M	LN	55	Bu	T	MT-1,CD7,OKT9	NA	NA	NA	NA	C	D(9M)
Sun[7] 1991	63/F	Bone, Soft tissue	59	Bu	T	MT-1,CD2,CD3	NA	P	NA	NA	R	D(<1M)
Advani[8]1991	35/M	LN, kidney	28	Bu	T	CD2,CD7,CD8	P	NA	NA	NA	NA	D(9d)
Leone[9] 1992	49/M	LN	35	IFN-α	T	TDT,CD2,CD7,CD45	P	P	NA	NA	C+R	D (8M)
González[10] 1993	NA	LN	51	NA	T	CD1,CD2,CD5,CD7	NA	P	NA	NA	NA	NA
Tittley[11]1993	41/F	LN	8	Hu, IFN-α	T	CD5,CD8, TDT	NA	P	NA	NA	NA	NA
Van Dorpe[12] 1995	66/M	LN	29	NA	T	CD2,CD3,CD5,CD7,CD38,TDT	P	P	NA	NA	NA	NA
Dorfman[13] 1997	35/F	LN	29	Hu,HSCT	T	cCD3,CD5,CD43	NA	P	NA	NA	C	D(4M)
Kell[14]1998	38/M	Chest mass	>16	Hu, IFN-α, HSCT	T	CD3, MT1, UCHL-1	P	NA	NA	P	NA	NA
Au[15] 1999	50/M	LN	29	IFN-α	T	CD2,CD3,CD5,CD7 ,TDT,	NA	NA	NA	NA	C+IFN-α	CR(25M)
Apfelbeck[16] 2000	48/F	LN	11	Hu, IFN-α	T	CD3	NA	P	NA	P	C+ HSCT	CR(30M)
Lucero[17]2000	54/M	LN	20	Hu, IFN-α	T	cCD3,CD5,CD7	P	NA	NA	NA	C+ IFN-α	D(15M)
Beedassy[18]2000	29/M	Testis,CSF	32	IFN-α	B	CD20 , TdT	NA	NA	P(csf)	NA	R, IT, C, HSCT	Relapse (9M after HSCT)
Okazuka[19]2001	45/M	LN	40	Hu, IFN-α	T	MT1, UCHL1, CD3	P	P	NA	P	C+R+HSCT	CR
Ye[20] 2002	32/M	Mediastinal mass	20	Hu, IFN-α, HSCT	T	CD2,CD3,CD4,CD5,CD7,CD8, CD10	NA	NA	P	P	C	D(soon)
Kroschinsky[21]2003	38/M	First rib	55	Hu, IFN-α, HSCT	B	CD34, CD79a, CD43, CD30, TdT,CD20	NA	NA	NA	P	R,C, Imatinib	D(6M)
Yashima-Abo[22] 2005	50/M	LN	NA	None	T	TdT.cCD3, CD7, CD34,	NA	N	P	P	NA	NA
	53/M	LN	NA	Hu, IFN-α	T	CD45,MPO,CD99	P	P	P	P	NA	NA
	20/M	LN	NA	Hu, IFN-α	T	TdT,cCD3, CD7, CD34, CD45,MPO,CD99 TdT, cCD3, CD34, CD45,CD99	P	P	P	P	NA	NA
Maloisel[5]2005	66/M	Cervical spine (C1)	13	IFN-α	L	NA	NA	NA	NA	NA	R +C	D(7M)
Burger[23]2006	49/M	LN	80	Hu, IFN-α	T	CD7,c CD3, CD5, TdT, CD34, CD38,CD45	P	NA	NA	P	Imatinib	CR(51M)

Kim[24] 2008	72/M	LN	5	Imatinib	T	CD1a, CD4, CD5, CD7,CD34, TdT	NR	NA	P	NA	C	CR(9M)
	32/F	LN	4	Imatinib	T	CD1a, CD3, CD2, CD4, CD5, CD7, TDT	N	NA	P	NA	C+ HSCT	D(4M)
Jin[25] 2013	40/M	LN	0	None	T	CD3, CD5, CD7, TdT, CD79a	NA	NA	NA	P	Hu	D(27M)
Wei[26]2013	35/M	LN	2	Hu	T	TdT, CD99,CD3, CD43, CD5, Bcl-2	NA	NA	NA	P	Dasatinib+C	CR
Zhang[27]2013	12/M	LN	0	None	T	CD3, CD5,CD34,TDT	NA	NA	P	NA	imatinib	CR(12M)
Xu[28]2014	66/M	LN	0	None	T	CD1a, CD3,CD5, CD7, TdT	P	NA	NA	NA	C	NA
Yuceturk[29]2014	21/M	Testis	120	HSCT	B	CD10,CD20,CD99,CD79a,TDT	NA	NA	NA	NA	NA	NA
Zeng[30]2015	44/M	LN	0	None	T	CD7, CD3, PAX5, Bcl-2, TdT	NA	NA	NA	P	C+HSCT	CR(51M)
Our case2017	45/M	LN	5	HU	T	CD3,CD5, CD7, CD56, TDT,CD99	NA	NA	P	P	NA	NA

A/G: Age/Gender; LN: lymph node; BM: bone marrow; CSF: Cerebrospinal Fluid; Time(mo):Months between initial disease and EBC; Tx: Treatment; BU: Melphalan; HU: Hydroxyurea; C: Chemotherapy; R: Radiotherapy; HSCT: Hematopoietic Stem Cell Transplantation; IT: Intrathecal Infusion; NA: not done or not described; P: positive findings by the examination; N: negative positive findings by the examination; TdT:Terminal deoxynucleotidyl transferase; D:Died. Ph^1: detected in the extramedullary biopsy tissue. BCR RE^2: BCR gene rearrangement by southern blot analysis in the extramedullary biopsy tissue. Bcr/abl mRNA[3]: Bcr/abl fusion transcript detected by reverse transcription polymerase chain reaction (RT-PCR) in the extramedullary biopsy tissue.$FISH^4$: detected in the extramedullary biopsy tissue.

stains can provide some evidence for the origin, lineage differentiation, and maturation of the blasts. EBC tumor cells are usually admixed with abundant leukocytes, and in some cases, they may express unusual myeloid lineage markers (6) and even show a mixed phenotype of myeloid and lymphoid (7-11). Thus, the markers used to identify the immunophenotype of the neoplasms also need to identify stem cells and myeloid cells, including CD34, CD117, MPO, CD33, glycophorin C, CD68, CD42b/CD61, etc., in addition to lymphoid lineage marker (6). Karyotypic analysis, RT-PCR, and Southern blotting cannot be applied to single cells, limiting the accuracy of these techniques. These techniques cannot reliably distinguish two independent malignant clones, one with two abnormal clones, or the presence of mixed hematopoietic (non-tumor) contaminated cells. The FISH analysis is a simple and sensitive tool for the detection of the BCR-ABL fusion gene in a single cell, and the morphological and phenotypic evaluation is performed using the BCR-ABL fusion probe (11, 12).

In conclusion, through the comprehensive analysis of morphology, immunophenotype, RT-PCR, and the FISH results, the patient was diagnosed as lymph node type EBC. Our report demonstrates the importance of the FISH analysis for determining whether the neoplasm is either EBC of CML or a genetically distinct neoplasm.

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ETHIC APPROVAL

This study is approved by relevant Ethics

Table 2. Ph-negative NHL developing in CML.

Author/publish year	A/G	Time (mo)	Tx before	BM status	Biopsy sites	Phenotype	Positive antigens in neoplastic cells	Ph[1]	bcr RE[2]	bcr/abl mRNA[3]	FISH[4]	Tx after	Outcome (month)
Djulbegovic[32] 1991	35/M	31	HU	CP	Femoral and cervical masses	High-grade T-cell lymphoma	CD7, TDT	NA	NA	NA	NA	C+R	NR
Montefusco[33] 1993	58/M	43	Hu, IFN-α	CP	LN	T-ALCL	Ki-1,CD2, CD3, CD7,	NA	N	NA	NA	C	CR
Acar[34] 1999	38/F	0	None	CP	LN	Large-cell NHL	NA	NA	NA	NA	N	C	CR
DAWSON[35] 1999	34/M	70	Hu+IFN-α+C	BP	BM	T-cell ALL(TcR-γδ type).	CD2,CD3,CD7,TDT,CD45, TcR-γδ	N	NA	N	NA	C	D/2M
Ichinohasama[36] 2000	59/M 80/M	31 10	Hu, IFN-α None	CP CP	LN Pleural	T cell rich B cell-diffuse, large cell) NHL, Anaplastic large cell lymphoma	CD19,CD20. CD22,CD45,HLA-DR, λ light chain restriction, CD30,EMA	N NA	P P	P P	N N	C None	D/20M D/2M
AU[37] 2003	67/F	0	None	CP	Mediastinal mass.	B cell lymphoma	CD20	NA	N	NA	NA	C +HU	Stable
Rodler[38] 2004	65/M	35	Hu, IFN-α ,imatinib	BP	BM and PB	MCL	CD19,CD20, CD5, CD23, k light chain restriction	N	NA	NA	N	C+ R+ IT	D/12M
GĂMAN[39] 2013	79/F	8	HU	AP	Soft palate	Medium B-cell NHL	CD20, CD79a	N	NA	NA	NA	R	CR
Yoo[40] 2017	67/M	0	None	CP	LN	DLBCL	NA	NA	NA	NA	NA	R+ imatinib	CR

A/G: Age/Gender; Time(mo):Month between initial CML and second NHL; Tx : Treatment; HU: hydroxyurea; LN: lymph node; BM:bone marrow; PB: Peripheral blood; CSF: Cerebrospinal Fluid; NA: not done or not described; P: positive findings by the examination; N: negative positive findings by the examination; TdT:Terminal deoxynucleotidyl transferase; EMA: Epithelial membrane antigen; C: Chemotherapy; R: Radiotherapy; IT: Intrathecal Infusion; D:Died. Ph[1]: detected in the extramedullary biopsy tissue. BCR RE[2]: BCR gene rearrangement by southern blot analysis in the extramedullary biopsy tissue. Bcr/abl mRNA[3]: Bcr/abl fusion transcript detected by reverse transcription polymerase chain reaction (RT-PCR) in the extramedullary biopsy tissue. FISH[4]: detected in the extramedullary biopsy tissue.

Committee. This study is also obtained the signed informed consent from all participants/ patient.

Conflicts of Interest: None declared.

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