Philadelphia chromosome-negative non-Hodgkin's lymphoma occurring in Philadelphia chromosome-positive chronic myeloid leukemia: A case report and literature review

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Abstract. The current study reports the case of a patient with Philadelphia chromosome-negative (Ph^-) non-Hodgkin's lymphoma (NHL) and chronic phase (CP) Philadelphia chromosome-positive (Ph^+) chronic myeloid leukemia (CML) that also possessed characteristic enlarged lymph nodes. A lymph node biopsy resulted in the diagnosis of CP-CML, in addition to T-lymphoblastic cell NHL with negative break point cluster/Abelson tyrosine kinase fusion genes in the lymph node of the patient, which was diagnosed as Ph^- NHL. A review of the literature was performed in the present study to investigate the genetic differences between Ph^- NHL and Ph^+ NHL in patients with CML. The median age of patients with NHL and CML was 41 years. The follow-up time of patients with Ph^+ NHL was significantly shorter (mean, <6 months) compared to the follow-up time of patients with Ph^- NHL (mean, >15 months). Therefore the present study concludes that Ph^+ NHL may be more aggressive compared with Ph^+ NHL. The present study suggests that additional studies are required to assess the clinical and genetic characteristics of NHL patients with CML.

Introduction

Chronic myeloid leukemia (CML) is a clonal proliferative disorder of hematopoietic stem cells that is characterized by the presence of the Philadelphia chromosome (Ph) and break point cluster/Abelson tyrosine kinase (BCR/ABL) fusion genes (1). According to the 2008 World Health Organization classification of hematopoietic tumors (2), CML has a triphasic clinical presentation, consisting of chronic phase (CP), accelerated phase (AP) and blast crisis (BC) (3).

Extramedullary BC Ph^+ CML is infrequent (4) and there are extremely few cases described in the literature (5). At present, it is simple to detect the origin of blast cells using standard cytogenetic analysis, reverse transcription polymerase chain reaction (RT-PCR) and fluorescence *in situ* hybridization (FISH). However, due to the rarity of patients with extramedullary BC Ph^+ CML, little is known concerning the clinical and genetic characteristics of T-lymphoblastic non-Hodgkin's lymphoma (NHL) (T-LBL) with CML. The present study reports the case of a patient with Ph^- NHL and CML, and reviewed the literature review on the clinical and genetic features of similar patients.

Case report

A 28-year-old man presented to the Department of Hematology of the Yunnan Tumor Hospital (Kunming, Yunnan, China) in November 2012 with bilateral axillary and neck swellings that had been present for the past month, and a low fever, slight weight loss and night sweats that had been present for the previous 2 weeks. The patient possessed no history of bone or abdominal pains and had received no treatment prior to the onset of the symptoms. Physical examination revealed that the patient had multiple enlarged lymph nodes on the bilateral cervical, axilla, inguinal and epitrochlear regions (≤10 cm in diameter), slight splenomegaly and no hepatomegaly.

Routine blood tests revealed a white blood cell count of $23.0x10^3$ cells/μl (normal range, 4.0-10.0x10^3 cells/μl) with leukoerythroblastosis: band neutrophils, 17.0% (normal range, 16.4-32.1%); segmented neutrophils, 36.0% (normal range, 4.2-21.2%); basophils, 2.0% (normal range, 0.0-1.0%); lymphocytes, 44% (normal range, 0.0-40.0%); myeloblasts, 0.0% (normal range, 0.0-1.8%); metamyelocytes, 1.0% (normal range, 0.4-3.9%). Furthermore, an erythrocyte count of $4.6x10^6$ cells/μl (normal range, 3.5-5.0x10^6 cells/μl), a platelet count of $3.4x10^6$ platelets/μl (normal range, 1.0-3.0x10^5 platelets/μl), a hemoglobin level of 12.7 g/dl (normal range, 11.0-16.0 g/dl) and a hematocrit level of 47.0% (normal range,

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40.0-50.0%) were observed. A bone marrow smear identified serious granulopoiesis (granulocytes, 95%; blast cells, 1.5%) and extremely reduced activity of neutrophil alkaline phosphatase. Peripheral blood and bone marrow investigations demonstrated that the patient possessed typical CML-CP. Cytogenetic analysis of peripheral blood cells revealed the presence of a Ph chromosome in all 20 metaphase cells of a standard type that were analyzed. In total, 16 of the metaphase cells appeared to possess a double Ph chromosome and chromosomes 8 and 19.

RT-PCR (using a ready-to-use Genequality BCR-ABL kit (AB ANALITICA s.r.l, Padova, Italy) of the RNA obtained from the bone marrow cells of the patient revealed the presence of BCR/ABL gene rearrangements. The BCR and ABL genes were identified in the bone marrow cells by FISH [using a Vysis LSI BCR/ABL dual color dual fusion translocation probe (Abbott Molecular, Inc., Des Plaines, IL, USA) and a 4',6-diamidino-2-phenylindole counterstain (Sigma-Aldrich, St. Louis, MO, USA)], which revealed the presence of the transcript for BCR/ABL p210 (positive rate, 98%) and no argininosuccinate synthetase fusion signal. Immunophenotyping was performed using immunohistochemistry on biopsy slides, and the results revealed that the blast cells were positive for cluster of differentiation (CD)3, CD7 and terminal deoxynucleotidyl transferase (TDT), and did not express myeloperoxidase, indicating that the T cell phenotypic lineage was typical of lymphoma. RT-PCR was performed from the aspirate of the lymph node, and the results revealed a transcript that was negative for BCR/ABL p210. Therefore, a final diagnosis of Ph- NHL non-extramedullary phenotypic T-blast cell lymphoma and CML-CP was established.

The patient was treated daily with intramuscular human lymphoblastoid interferon-α at a dose of 6 million IU. Hydroxyurea for microantibody treatment or stem cell transplantation was not economically feasible for the patient. Subsequent to chemotherapy, partial remission was obtained and the condition of the patient remained stable in CML-CP. The etoposide (100 mg/d; days 3-5), cyclophosphamide (750 mg/m^2; day 1), doxorubicin (50 mg/m2; day 1), vincristine (1.4 mg/m^2; day 1) and predonisone [60 mg/m^2; days 1-5] regimen was administered 2 months later for the enlarged lymph nodes of the patient.. Complete remission was not obtained. In total, 4 weeks later, the patient demonstrated progressive disease with organomegaly and left the hospital, and was lost to follow-up.

Discussion

The present study described the case of a young male patient with CML that developed an extramedullary BC in bilateral axillary and lymph node swellings. The bone marrow of the patient demonstrated CML-CP and a biopsy of the lymph node of the neck indicated that the patient developed an extramedullary BC derived from T blast cell clones.

Partially due to the rarity of this condition, there is little information on the cellular origins, pathogenesis or clinical behavior of Ph- NHL with CML-CP (6). Lymph node enlargement in patients with CML may be due to blast cells originating from the lymphoid or myelo-monocytoid lineages (4). There are patients with NHL that exhibit the same genotype in the lymphoid neoplasms and CML, but there are also patients that exhibit different genotypes in the lymphoid neoplasms and CML. The present study reports the case of a patient belonging to the latter group. To the best of our knowledge, the present study is one of few clearly diagnosed cases of CML combined with Ph- NHL reported between 1980 and the present time (3,7,8). A literature search of the electronic PubMed database (www.ncbi.nlm.nih.gov/pubmed; up to February 2015) was conducted using the terms 'chronic myelogenous leukemia', 'non-Hodgkin lymphoma', 'BCR/ABL' and 'Philadelphia chromosome'. This search reviewed the literature for cases of CML combined with NHL to investigate the genetic differences between patients with Ph- NHL and CML and those with Ph+ NHL and CML (Table I) (4,6-25). The present study concluded that, out of the 24 patients that were diagnosed with NHL and CML, 19 patients possessed Ph+ NHL and 5 patients possessed Ph- NHL. The median age of patients with NHL and CML was 41 years.

Hashimoto *et al* (24) investigated the phenotype in patients with T-LBL and revealed that ~52% T-LBL tumor cells expressed CD79a, and TDT was expressed in 95% of T-LBL cells. It was concluded that these findings were associated with the origin of T-LBL from immature or precursor lymphocytes. However, no studies have reported the origin of tumor cells in T-LBL. Notably, CML is a myeloproliferative stem cell disorder, which has the potential to proliferate into numerous lineages, including myeloid, lymphoid, erythroid, megakaryocytic, undifferentiated or multi-lineage (4,9,26). The BCR/ABL fusion gene, which is present in CML, was also detected in the endothelial progenitor cells of CML patients in China in 2014, which suggests that CML may originate from hemangioblastic progenitor cells that may proliferate into blood and endothelial cells (27). In addition, it was demonstrated that the rearrangement of the BCR/ABL gene may occur at or even prior to the level of hemangioblastic progenitor cells. By contrast, Dorfman *et al* demonstrated that the median time of survival was 7 months for patients that developed an extramedullary BC following a diagnosis of CML (8).

The literature review in the present study revealed that the follow-up time of patients with Ph+ NHL was significantly shorter (mean, <6 months) compared with the follow-up time of patients with Ph- NHL (mean, >15 months) (Table I), which suggests that Ph+ NHL may be a more aggressive disease compared with Ph- NHL. This finding suggests that all cases of NHL with CML may be one disease, without one being an accompanying or secondary cancer, and there may be a key factor, in addition to the BCR/ABL gene, that remains unidentified. In addition, a tumor cell may alter genetically between Ph+ NHL and Ph- NHL during the progression of the disease.

It is challenging to achieve complete remission in patients with Ph+ or Ph- NHL and CML (8). The efficacy of imatinib mesylate treatment in CML-CP patients is clear (26); however, in AP or BC CML phases, treatment remains controversial and is limited. Therefore, a more appropriate treatment, including allogeneic stem cell transplantation, should be offered to such patients. To the best of our knowledge, there has been one study of a patient that achieved complete remission by unmanipulated HLA-haploidentical blood and marrow hematopoietic stem cell transplantation in China (11).

Table I. Review of patients with CML and T-lymphoblastic cell non-Hodgkin's lymphoma in the lymph node between 1980 and the present.

First author, year	Age, years	Gender	Disease (duration, months)	BM phase	Histology	Phenotype	BCR/ABL, BM/LN	Follow-up, months	Ref.
Ichinohasama *et al*, 2000	80	M	CML-LN (32)	CP	CD30 positive anaplastic large cell type	Null	+/-	12	(4)
Krishnan *et al*, 2014	49	F	CML-LN (ND)	CP	Lymphoblastic	T	+/+	>6	(6)
Jacobs *et al*, 1984[a]	21	M	CML-LN (36)	CP		T	+/+	ND	(7)
Ganessan *et al*, 1996	14	M	CML-LN (ND)	CP	Myeloid	T	+/+	2	(9)
Dorfman *et al*, 1997	72	M	CML-LN (36)	CP	Lymphoblastic	T	+/+	5	(10)
Dorfman *et al*, 1997	35	M	CML-LN (29)	CP	Lymphoblastic	T	+/+	4	(10)
Dorfman *et al*, 1997	68	M	CML-LN (11)	CP	Lymphoblastic	T	+/+	4	(10)
Wan *et al*, 2012	43	M	CML-LN (ND)	CP	Lymphoblastic	T	+/-	>24	(11)
Palutke *et al*, 1982[a]	25	M	CML-LN (8)	CP	Blastic	T	+/+	3	(12)
Hogge *et al*, 1984[a]	24	M	CML-LN (40)	CP	Undifferentiated blast, myeloid	T	+/+	2	(13)
Hirose *et al*, 1990[a]	62	ND	CML-LN (26)	CP	Medium-sized, cleaved cell, myeloid	T	+/+	4	(14)
Montefusco *et al*, 1990[a]	38	M	CML+LN (ND)	BP	Lymphoblastic	T	+/+	6	(15)
Montefusco *et al*, 1990[a]	58	M	CML-LN (43)	CP	CD30 positive	T	+/-	ND	(15)
Leone *et al*, 1992[a]	49	M	CML-LN (34)	CP	Immunoblastic monomorphic	T	+/+	5	(16)
González *et al*, 1993[a]	ND	ND	CML-LN (51)	CP	Lymphoblastic	T	+/+	ND	(17)
Tittley *et al*, 1993[a]	40	F	CML-LN (43)	CP	Large cell	T	+/+	ND	(18)
Jacob *et al*, 1994[a]	33	M	CML-LN (ND)	BP	Lymphoblastic	T	+/+	ND	(19)
Van Dorpe *et al*, 1995[a]	66	M	CML-LN (29)	CP	Medium-sized blast	T	+/+	5	(20)
Lucero *et al*, 2000	54	M	CML-LN (ND)	CP	Lymphoblastic	T	+/+	ND	(21)
Chen *et al*, 2013	14	M	CML-LN (3)	BP	Lymphoblastic	T	+/+	>10	(22)
Chen *et al*, 2007	41	F	CML-LN (ND)	ND	Blast crisis	T	+/+	>24	(23)
Vannier *et al*, 1984[a]	13	F	CML-LN (ND)	ND	Small-sized lymphoid blast	T	-/-	ND	(24)
Burger *et al*, 2006	49	M	CML-LN (84)	CP	ND	T	+/+	4	(25)
Present study	27	M	CML-LN (ND)	CP	Lymphoblastic	T	+/-	10	

[a]Previously reviewed in Ichinohasama *et al* (3). CML, chronic myeloid leukemia; M, male; F, female; LN, lymph node; BM, bone marrow; CP, chronic phase; BP, blast phase (blast crisis); CD, cluster of differentiation; ND, not described; T, T cell; BCR/ABL, break point cluster/Abelson tyrosine kinase; +, positive; -, negative.

In conclusion, the present study suggests that additional studies are required to assess the clinical and genetic characteristics of NHL with CML.

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