A case of myelodysplastic syndrome developed blastic crisis of chronic myelogenous leukemia with acquisition of major *BCR/ABL*.

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Abstract

We describe a rare case of myelodysplastic syndrome that developed chronic myelogeneous leukemia with acquisition of Philadelphia chromosome. The major *BCR/ABL* transcript was confirmed by molecular analysis. The patient shortly showed transformation to blastic crisis. Hematological remission was achieved after 3 months treatment with imatinib mesylate. The patient relapsed with additional chromosomal abnormalities and the disease became refractory to the treatment. Acquisition of the Philadelphia chromosome is an infrequent event in myelodysplastic syndrome, and the addition of this change to the initial genetic abnormality that caused MDS may have been associated with the accelerated clinical course of this patient.

Key words:

Myelodysplastic syndrome, Philadelphia chromosome, major *BCR/ABL*, blastic crisis, imatinib mesylate

Introduction

The Philadelphia (Ph) chromosome is a hallmark of chronic myeloid leukemia (CML), that is considered closely associated with leukemogenesis in this disease. Recent advances in molecular biology has demonstrated that the Ph chromosome is produced by reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 22, resulting in the formation of a novel *BCR/ABL* gene. The products of this chimeric gene (p210) have strong tyrosine kinase activity, which is assumed to stimulate cell proliferation and contribute to leukemogenesis. Recently, an abl-specific tyrosine kinase inhibitor, imatinib mesylate, has been designed and developed as a therapeutic drug for CML and has already shown strong potency in clinical settings.

The Ph chromosome is found in the majority of CML cases, in approximately 20 % adult cases and 5 % pediatric cases demonstrating acute lymphoblastic leukemia (ALL), and in 3 % acute myeloblastic leukemia (AML) cases. In myelodysplastic syndrome (MDS), however, the Ph chromosome is rarely involved. We present a rare case of MDS showing a normal karyotype that later evolved into chronic phase CML, and shortly after developed blastic phase CML with acquisition of the Ph chromosome.

Case report

The patient was a 73-year-old male who was initially diagnosed as refractory anemia with excess blasts (RAEB) subclass of MDS with normal karyotype [15/15] in March 1999. The bone marrow film showed 8% blast cells at that time. Absence of the fusion signal of bcr and abl gene was retrospectively confirmed by fluorescence in-situ hybridization (FISH). The clinical course and genetic events in this patient are summarized in Table 1. The patient remained stable until September 2001, when

hematological features suddenly changed with an increase in peripheral white blood cell count and a series of immature neutrophils similar to those in CML were observed. The bone marrow film showed increased numbers of blast cells (12%) and cytogenetic examination demonstrated the Ph chromosome [20/20]. RT-PCR was positive for major *BCR/ABL* transcript. The percentage of blast cells rapidly increased to 60% in the bone marrow three months later. The blast cells expressed B-cell antigen including CD10,CD19 and CD20 and lacked myeloperoxidase reaction. Thus, we concluded that this patient with MDS developed chronic phase CML, which shortly progressed to lymphoblastic crisis. The patient had never been exposed to any mutagenic agent or radiation. We carefully observed the patient without any cytotoxic drugs until April 2002, when the peripheral white blood cell counts rapidly increased and the bone marrow showed proliferation of immature cells featuring both myeloid and lymphoid phenotypes. Hepatosplenomegaly and extra nodal chloroma emerged. The karyotype was still 46,XY,t(9;22). FISH detected 87% *BCR/ABL* fusion positive cells in the bone marrow. Complete hematological remission was achieved after 3 months of treatment with imatinib mesylate. Hepatosplenomegaly vanished soon after administration of imatinib mesylate. In October 2002, blast cells were increased again in the peripheral blood. The bone marrow film showed 56% blast cells. Cytogenetic examination at this point demonstrated a mixed karyotypic pattern consisting of 46,XY, 46,XY,t(9;22) and 49,XY,+8,+9t(9;22),+19,-21,+der(22)t(9;22). FISH analysis demonstrated 20% cells with single Ph, 56% cells with double Ph. The patient was thought to have become resistant to imatinib mesylate. Despite optimal supportive therapy, the patient died of pneumonia one year after developing CML blast crisis. Autopsy was not permitted.

Discussion

Transformation to AML is a frequent event in MDS, in which cytogenetic evolution is assumed to play a role [1, 3, 12]. We describe a patient who presented with MDS (RAEB) and subsequently developed Ph positive CML in the chronic phase then evolved rapidly to the blastic phase. In the literature, nineteen cases of MDS were reported to have Ph chromosome in their clinical courses. Among these, ten MDS cases demonstrated a transformation to leukemias with acquisition of Ph chromosome (Table 2) [2, 4-11, 13]. Types of leukemia in these cases included AML in eight cases and ALL in one case. Only one case was reported to have CML in the accelerated phase [13]. In only four cases, molecular analysis was performed: one case demonstrated major *BCR/ABL* transcript [9], two showed minor *BCR/ABL* transcript [6, 8], and one case had both major and minor *BCR/ABL* transcript [4]. Because there was no description of the differential determination between major and minor translocation of the *BCR/ABL* gene in the majority of case reports, it is not clear how often the major *BCR/ABL* was acquired in these cases of MDS. It is also unclear whether the cases showing transformation to AML or ALL were de novo acute leukemia or blastic crisis of CML. Thus, this report will provide precise information about such issues. Our patient was definitively diagnosed with MDS, then showed progression to CML with major *BCR/ABL* transcript that was molecularly confirmed.

The pattern in which Ph chromosome emerged in cases of MDS can be classified in two forms (Table 2). In five cases, a Ph positive clone already existed at time of MDS and expanded in leukemic phase. Whereas, the rest of six cases including ours showed absence of Ph chromosome at time of MDS and acquisition of Ph chromosome at transformation. Several issues are addressed from these observations; when and how Ph chromosome is acquired and how it is associated with clonal evolution. It seems that

no pre-existing chromosomal abnormality was specifically associated with acquisition of Ph chromosome. Hematological changes in our patient are thought to reflect the accumulation of chromosomal abnormality including Ph chromosome, +8,+9,+19 and -21. Because the patient showed normal karyotype in the MDS phase, it cannot be determined whether the CML clone in this patient developed from the existing MDS clone or emerged independently. Thus, there are several possibilities in the pathogenesis of the disease in such cases. It is thought reasonable that an additional genetic event that works synergistically with the initial genetic event occurred in the existing MDS clone to develop an aggressive abnormal clone. Kohn *et al.* reported a case of MDS that transformed to AML with acquisition of Ph chromosome in addition to the original abnormality of monosomy 6 [5]. This clearly showed that chromosomal evolution can result in a transformation of disease. It is, however, possible that a 'de novo' abnormal clone emerged with a single genomic change such as Ph chromosome.

We described a patient with MDS who developed CML blastic crisis with Ph chromosome and major *BCR/ABL* transcript. It is strongly suggested that acquisition of Ph chromosome is an infrequent but important genetic change triggering leukemogenesis in MDS. Future studies will elucidate the mechanism of Ph acquisition in MDS.

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Table 1. Morphological changes and chromosomal evolution.

Date	Bone marrow morphology	Karyotype	FISH(*BCR/ABL*)	RT-PCR(*BCR/ABL*)
2001.3	MDS-RAEB	46,XY [15]	negative	
2001.9	CML-CP	46,XY,t(9;22) [14]	single Ph 98.0%	Major(b2a2)
2001.12	CML-lymphoid crisis	46,XY,t(9;22) [20]		Major(b2a2)
2002.4	CML-mixed lineage crisis	46,XY,t(9;22) [20]	single Ph 87.3%	
2002.7	CHR* by imatinib mesylate		single Ph 42.2%	
2002.10	relapse of CML-BC	46,XY [3]/	single Ph 20.0%	
		46,XY,t(9;22)(q34;q11) [7]/	double Ph 56.4%	
		49,XY,+8,+9t(9;22)(q34;q11),+19,-21,+der(22)t(9;22) [6]		

*CHR:complete hematological response

Table 2. Review of patients with MDS which transformed to leukemias with acquisition of Ph chromosome

No	Age	SEX	FAB	initial karyotype at MDS phase	Ph%	bcr/abl	Author	Year
1	43	M	MDS→AML	N.D.*	10→100		Canellos et al.	1972
2	38	F	RAEB→AML	45,XX,-6	0→29		Kohn et al.	1975
3	49	F	RA→AML RAEB →	N.D.*	38→50		Roth et al.	1980
4	62	M	AML(M2) RAEBt →	46,XY	0→100		Smadja et al.	1985
5	3	M	AML(M7)	46,XY 45,XY,-1,-2,-12,+der(1)t(1;12)(p32;q13),der(11)(9?;11)(q22?;p15),+der(X)t(X;1)(q22;p13)[15/30] / 45,XY,-1,-2,-12,+der(1)t(1;12)(p32;q13),t(9;22)(q34;q11),der(11)(9?;11)(q22?;p15),+der(X)t(X;1)(q22;p13)[15/30]	0→100	Major	Nakamura et al.	1991
6	56	M	RA→AML		50→100	(+)	Larripa et al.	1992
7	63	M	RA→CML(AP)	46,XY	0→100		Verhoef et al.	1992
8	39	M	RAEB→AML	46,XY,t(3;3)(q21;q26)[19/20] /	0→5	M+m	Katsuno et al.	1994
9	54	M	RA→ALL	46,XY 46,XY[7/13] /	0→90	minor	Kohno et al.	1996
10	64	M	RAEB→AML RAEB →	47,XY,+8,t(9;22)(q34;q11)[6/13]	46→81	minor	Lesesve et al.	1996
our case	75	M	CML(BC)	46,XY	0→100	Major		

*No Data