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Del(15q) is a recurrent “minor route” cytogenetic abnormality in the clonal evolution of chronic myelogenous leukemia

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Abstract

Del(15q) is known to occur in acute leukemias, but has been described rarely in chronic myelogenous leukemia (CML). We describe five cases of CML associated with del(15q). There were four men and one woman. Bone marrow aspirate smears demonstrated increased blasts in all cases at the time of del(15q) detection, showing accelerated phase in two and myeloid blast phase in three. Conventional cytogenetic analysis showed t(9;22) and del(15q), as well as other inconsistent clonal abnormalities. All patients received imatinib mesylate, four received additional chemotherapy, and two underwent allogeneic stem cell transplantation (ASCT). For the three patients who did not receive ASCT, one died, one was in persistent blast phase, and one was in clinical remission with molecular evidence of residual disease, 16, 6, and 34 months after identification of del(15q), respectively. For the two patients who underwent ASCT, one died and one was in clinical remission with molecular evidence of disease, 15 and 64 months after identification of del(15q), respectively. Our findings indicate that del(15q) is a recurrent cytogenetic abnormality that may be seen either at initial presentation of advanced disease or emerge during disease progression. Del(15q) appears to be associated with a poor prognosis in CML.

Keywords

del(15q); CML; minor route abnormality; clonal evolution

INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of pluripotent hematopoietic stem cells defined by the reciprocal t(9;22)(q34;q11), also known as the Philadelphia chromosome (Ph), which results in the formation of BCR-ABL1 fusion protein, a constitutively-activated tyrosine kinase that plays a central role in CML pathogenesis [1–

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6]. Complex translocations involving chromosomes 9 and 22 with additional chromosomal abnormalities also occur in a small subset of CML cases [7].

In most patients with CML, the clinical course is characterized by an initial chronic phase, followed by an accelerated phase, and a terminal blast phase. The accelerated and blast phases indicate disease progression and are associated with resistance to therapy and a poor prognosis [8]. During this evolution, the neoplastic cells usually acquire additional chromosomal abnormalities, most commonly and extra Ph, der(22), +8, i(17q), and +19, the so-called “major route” changes [9]. Less common “minor route” changes include -7, -17, +17, +21, -Y, t(3;21)(q26;q22), t(8;21)(q22;q22), and inv(16)(p13q22) [9–13].

Deletions in the long arm of chromosome 15, del(15q), have been reported in myeloid and lymphoid malignancies, including acute myeloid leukemia (AML) [14–19] and acute lymphoblastic leukemia (ALL) [20]. Deletion of 15q as a secondary cytogenetic abnormality in CML has been reported rarely, in only six cases in the literature, four as single case reports with limited clinical information [21–25]. We describe in detail the clinical, morphologic, immunophenotypic, and molecular genetic characteristics of five cases of Ph-positive CML with del(15q). Our findings indicate that del(15q) is a recurrent minor route cytogenetic abnormality associated with disease progression.

MATERIALS AND METHODS

Case Selection

We searched the files of the Cytogenetics Laboratory in the Department of Hematopathology at The University of Texas MD Anderson Cancer Center for cases of CML with del(15q) from January 2000 to March 2008. The diagnosis of CML was based on the World Health Organization classification of hematopoietic tumors [26]. The diagnosis of CML-BP requires 20% blasts in the peripheral blood (PB) or bone marrow (BM).

Bone Marrow Examination

We reviewed Wright-Giemsa-stained PB and BM aspirate smears, and H&E-stained sections of BM aspirate clot and core biopsy specimens. Cytochemical stains for myeloperoxidase and butyrate esterase were performed on BM aspirate smears in cases with increased blasts using conventional methods.

Immunophenotypic Analysis by Flow Cytometry

Three- or four-color flow cytometry analysis was performed on PB or BM aspirate specimens as described previously [10]. The panel of monoclonal antibodies included those specific for CD45 (peridin-chlorophyll-a-protein [PerCP]-conjugated), CD2 (fluorescein isothiocyanate [FITC]), CD3 (allophycocyanin [APC]), CD7 (FITC or phycoerythrin [PE]), CD10 (FITC), CD13 (PE), CD14 (APC), CD19 (FITC or APC), CD33 (FITC or PE), CD34 (FITC), CD64 (PE), CD117 (FITC or PE), myeloperoxidase (FITC) and TdT (FITC). All antibodies were purchased from BD Biosciences (San Jose, CA), and the analyses were performed using FACScan or FACSCaliber cytometers (BD). For each antibody, negative staining levels were set by comparison with an isotype-matched control.

Conventional Cytogenetic and Fluorescence In Situ Hybridization (FISH) Analyses

Conventional cytogenetic analysis was performed on metaphase cells prepared from BM aspirates cultured for 24 or 48 hours without mitogens using standard techniques as previously described [27]. Giemsa-banded metaphases were analyzed and the results were reported using the International System for Human Cytogenetic Nomenclature, 2005. Fluorescence in situ hybridization (FISH) for *BCR/ABL1* rearrangement was performed on interphase nuclei using the LSI® *BCR/ABL1* ES dual color translocation probe (Vysis Inc., Downers Grove, IL) as described previously [10]. The cutoff for positive *BCR/ABL1* rearrangement used in our laboratory is 1.5%.

Quantitative Real-time RT-PCR Assay

Levels of *BCR/ABL1* fusion transcripts were quantified in a multiplex real-time reverse transcription polymerase chain reaction (RT-PCR) assay that simultaneously detects b2a2, b3a2 and e1a2 transcript types. RNA was extracted from PB or BM samples using Trizol reagent (Gibco-BRL, Gaithersburg, MD) according to the manufacturer's instructions. Reverse transcription was performed on total RNA (1 µg) using random hexamers and superscript II reverse transcriptase (Gibco-BRL) as described previously [28]. The resulting cDNA was subjected to PCR to amplify *BCR/ABL1* fusion transcripts on an ABI PRISM 7700 Sequence Detector (Perkin Elmer/Applied Biosystems, Foster City, CA) using primers and conditions as described previously [28]. Quantitative *BCR/ABL1* levels were normalized to total *ABL1* transcript levels as described previously [28].

RESULTS

Clinical Findings

We identified five patients with CML and del(15q) out of 1784 CML patients (0.3%), which included 148 patients in blast phase (BP) (3.4%) during the study period. There were four men and one woman, with a median (range) age of 39 (26–58) years. All patients received a diagnosis of CML at another institution, and were referred to our institution for treatment. The patients were followed for a median (range) of 36 (6 – 64) months from the time of initial diagnosis. The clinical and laboratory data at initial presentation to our institution, therapy prior to and post the occurrence of del(15q), as well as the outcome are summarized in Table I.

Morphologic Findings

In all cases, BM specimens showed morphologic features characteristic of CML. The BMs were hypercellular (range 85–100%, median 95%) with left-shifted granulocytic hyperplasia, basophilia, eosinophilia, increased micromegakaryocytes, and reticulin fibrosis. Two patients (cases 4 and 5) were in myeloid BP, with BM blast counts of 20% and 70%, respectively.

At the time the del(15q) was observed, BM aspirate smears demonstrated increased blasts in all cases (range 6–70%, median 20%). Three patients (cases 2, 4, and 5) were in myeloid BP, and two (cases 1 and 3) were in AP. The blasts were of medium to large, with prominent nucleoli and a scant to moderate amount of cytoplasm (Figure 1); most were positive for

myeloperoxidase. In cases 2 and 3, the blasts showed monocytic differentiation and were strongly positive for butyrate esterase. In addition, at the time del(15q) was detected, mild dysgranulopoiesis (cases 4 and 5), dyserythropoiesis (cases 4 and 5), and/or dysmegakaryopoiesis (cases 2–5) were observed.

Immunophenotypic Findings

Flow cytometry immunophenotypic analysis of the BM aspirate samples demonstrated that the blasts in the three BP cases (cases 2, 4 and 5) were of myeloid lineage, positive for CD13, CD33, CD34, CD117, HLA-DR, and myeloperoxidase (subset).

Cytogenetic Findings

The results of conventional cytogenetic analysis are summarized in Table II. The t(9;22) was identified in all cases. Two patients (cases 2 and 3) presented in chronic phase without evidence of del(15q). The del(15q) was identified at disease progression, 16 months (case 2) and 40 months (case 3), respectively, following initial diagnosis of CML, associated with BP in case 2 and AP in case 3. The del(15q) was identified at the initial diagnosis of CML in two cases (cases 1 and 4), one of whom presented in AP (case 1), and the other presented in BP (case 4, Figure 2A). The initial karyotype in case 5 is unknown. However, del(15q) was identified at the time of presentation to our institution, 4 months after initial diagnosis of CML. In addition to the t(9;22) and del(15q), all cases exhibited other clonal abnormalities at the time of clonal evolution; none of which was consistent from case to case (Figure 2B).

Fluorescence in situ hybridization was also performed on interphase nuclei of all 5 cases and *BCR-ABL1* fusion signals were readily detected in all cases.

Although all patients had hematologic response after therapy, only two (cases 1 and 4) obtained sustained cytogenetic remission. One patient (case 3) briefly achieved a complete cytogenetic remission after ASCT, but eventually relapsed, at which time the del(15q) was identified.

Molecular Diagnostic Findings

In all cases, *BCR/ABL1* fusion transcripts were detected by RT-PCR assay, which demonstrated b2a2 transcripts (case 1), or b2a2 and b3a2 transcripts (cases 2–5). Only two patients (cases 1 and 4) achieved a major molecular remission (MMR), with a 3-log reduction of the *BCR/ABL1* to *ABL1* transcripts ratio.

DISCUSSION

Secondary chromosomal aberrations associated with clonal evolution are found in 60–80% of CML cases in AP or BP [29]. Based on their frequency, these secondary changes are classified as “major route” or “minor route” abnormalities [9]. The major route abnormalities are an additional copy of the Ph, +8, i(17q), and +19; they account for 38%, 34%, 20%, and 13% of cases, respectively [9, 30]. The minor route abnormalities include –7, –17, +17, +21, and –Y. Rare CML cases, usually at time of BP, are associated with translocations and inversions that are typically occur in myelodysplastic syndromes or *de*

novo AML, such as t(3;21)(q26;q22), t(8;21)(q22;q22), and inv(16)(p13q22) [10–13]. We describe five CML cases in which the del(15q) was detected at time of AP or myeloid BP. Although previous reports suggest that del(15q) is associated with myelomonocytic or monocytic differentiation [16–19], our findings indicate that this is not a consistent feature. We identified evidence of monocytic differentiation in only two of five cases in this study.

Although the number of cases in this study is small, CML patients with del(15q) appear to have a poor prognosis. Overall, CML patients treated with imatinib-based therapy have 5- to 7-year survival rates of 85% to 90% [31]. With ASCT, the 10-year overall survival ranges from 10% to 70% depending upon disease phase, patient age, and donor type [26]. In this study, two patients died, one patient was in persistent BP, and only two patients were in complete hematologic remission with molecular evidence of residual disease. The poor prognosis did not correlate with therapy in this study, in other words, chemotherapy alone versus ASCT. Although all patients had hematologic response, only two obtained sustained cytogenetic remission and major molecular response, and only one achieved a brief molecular remission prior to the occurrence of del(15q). Cytogenetic and molecular response is known to have prognostic significance in CML. Patients with CML who achieve a major molecular response, particularly within the first year of therapy, are more likely to sustain a durable cytogenetic remission and are less likely to experience disease progression [32]. In our study, the lack of cytogenetic and molecular response in three of five patients is consistent with their aggressive disease course.

Progression to BP in CML is almost always accompanied by additional chromosomal abnormalities [5, 33]. Secondary genetic changes in CML may provide alternative survival or proliferation signals that bypass the *BCR-ABL1* pathway. In four of our five CML patients, detection of the del(15q) heralded myeloid blast transformation. The mechanisms by which del(15q) contributes to CML progression are unknown. However, other studies have suggested that two regions in the long arm of chromosome 15 contain tumor suppressor genes. The *CCNDBP1* gene, which maps to 15q15, is significantly down regulated in a variety of solid tumors [34]. The *THBS1* and *CYP19* genes, which map to 15q21, are putative tumor suppressor genes in sporadic colorectal carcinoma and advanced breast carcinoma, respectively [35, 36]. In four of our five cases, the 15q15 and/or 15q21 regions were deleted. Of the previously reported six cases, two also had deletions in these regions [24, 25]. Two had del(15)(q22) [22, 23]. The deleted regions are not reported for the other two cases [21, 25]. These findings raise the possibility that one or more of these genes, or other as yet unknown genes, in these regions could function as tumor suppressor genes in CML cases with del(15q). Further, the presence of *BCR/ABL1* mutations may also contribute to the development of resistance to tyrosine kinase inhibitors and transformation to a more aggressive disease.

In summary, we describe the clinical, morphologic, immunophenotypic and molecular genetic features of five cases of Ph-positive CML in which del(15q) developed along with other abnormalities at time of accelerated or blast phase. Our findings indicate that del(15q) is a recurrent cytogenetic abnormality that may be seen either at initial presentation or emerge during disease progression. Del(15q) appears to be associated with an unfavorable prognosis when it occurs in the setting of CML.

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Figure 1.
Case 4. The bone marrow aspirate smear reveals numerous medium to large blasts with prominent nucleoli and scant to moderate amount of cytoplasm (Wright-Giemsa, x1000).

Figure 2.

A. Case 4. Conventional cytogenetic analysis demonstrates 46,XX,t(9;22)(q34;q11.2),del(15)(q21),add(19)(p13). B. Composite karyotype (G-banding) showing the

t(9;22)(q34;q11.2) and the del(15q), as well as the other random abnormalities for all the five cases as listed in Table II.

Table 1

Clinical findings at initial presentation to our institution, treatment and outcome

Case	Age*/Sex	Stage/del(15q)	WBC (x10 ⁹ /L)	Hb (g/dL)	Plt (x10 ⁹ /L)	LDH (IU/L)	Therapy Prior to del(15q)	Therapy Post del(15q)	Best Response Post del(15q)	Outcome (F/U)**
1	39/M	AP/present	14.0	14.9	637	925	NA	imatinib	MMR	AWD (Mol+) (35m/35m)
2	26/M	CP/absent	15.4	10.0	202	768	imatinib bosutinib	nilotinib cytarabine idarubicin	CHR	AWD (BP) (22m/6m)
3***	34/M	CP/absent	5.4	7.2	35	870	interferon cytarabine ASCT	imatinib	CHR	DOD (54m/16m)
4	58/F	BP/present	113.4	11.2	257	2735	NA	imatinib ASCT	MMR	AWD (Mol+) (64m/64m)
5	49/M	BP/present	62.2	9.1	21	2490	NA	imatinib dasatinib MK-0457 HHT	None	DOD (6m/2m)

* Age at initial diagnosis of CML

** Follow-up: time from initial CML diagnosis/time from occurrence of del(15q)

*** Patient 3 initially developed lymphoid BP, was treated with hyper-CVAD, and achieved cytogenetic remission. However, he relapsed in AP with increased myeloid blasts and occurrence of the del(15q).

Reference ranges: WBC, 4.0–11.0 x10⁹/L; Hb, 14.0–18.0 g/dL (men), 12.0–16.0 g/dL; Plt, 140–440 x10⁹/L; LDH, 313–618 IU/L.

Abbreviations: AP, accelerated phase; BP, blast phase; CP, chronic phase; WBC, white blood cells; Hb, hemoglobin; Plt, platelets; LDH, lactate dehydrogenase; CHR, complete hematologic response; MMR, major molecular response; F/U, follow-up; ASCT, allogeneic stem cell transplant; HHT, homoharringtonine; AWD, alive with disease; DOD, died of disease; Mol+, molecular evidence of CML; m, months

Table II

Karyotypes and percentage of blasts in the bone marrow

Case	Months post initial diagnosis	Blasts (%)	Karyotype
1	0	7	46,XY,t(9;22)(q34;q11.2),der(14)t(14;15)(q32;q22),del(15)(q21)[18]/46,XY[2]
	5	4	46,XY[20]
	0	6	46,XY,t(9;22)(q34;q11.2)[20]
	7	1	46,XY,t(9;22)(q34;q11.2)[20]
2	16	32	46,XY,t(9;22)(q34;q11.2),del(15)(q13q21),+der(22)t(9;22)[14]
	19	13	46,XY,t(9;22)(q34;q11.2),del(15)(q13q21),+der(22)t(9;22)[19]
	3	1	46,XY,t(9;22)(q34;q11.2)[20]
	8	2	//46,XX[20]
	18	50	46,XY,t(9;22)(q34;q11.2)[19]/46,XX[1]
	21	3	//46,XX[20]
	40	6	46,XY,t(9;22)(q34;q11.2),-17,+mar[8]/46,ide,t(6;12)(q13;q15),del(15)(q11q21)[10]
	50	24	46,XY,t(9;22)(q34;q11.2),-17,+mar[5]/46,ide,t(6;12)(q13;q15),del(15)(q11q21)[3]/46,XX[3]
4	0	20	46,XX,t(9;22)(q34;q11.2)[15]/46,ide,t(15)(q21),add(19)(p13)[5]
	4	1	46,XX,t(9;22)(q34;q11.2)[3]/46,ide,t(15)(q21),add(19)(p13)[1]
	7	1	//46,XY[20]
5	0	40	Not available
	4	70	46,XY,del(3)(q25q29),t(7;8)(q22;q13),inv(9)(p12q13),t(9;22)(q34;q11.2),del(15)(q22q26)[20]
	5	86	46,XY,del(3)(q25q29),t(7;8)(q22;q13),inv(9)(p12q13),t(9;22)(q34;q11.2),del(15)(q22q26)[20]