Uncommon phenotypes of *BCR::ABL1*-positive chronic myelogenous leukemia

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Received: March 18, 2025.
Accepted: May 5, 2025.
Early view: May 15, 2025.

https://doi.org/10.3324/haematol.2025.287792

Abstract

BCR::ABL1-positive chronic myelogenous leukemia (CML) presents with a typical phenotype in over 95% of cases. These phenotypical cases are associated with a p210 oncoprotein (M-*bcr* genotype). In these cases, the consideration of CML is high on the list of differential diagnoses and appropriate genetic studies to confirm the *BCR::ABL1* oncogene are *de rigueur*. The elevated white cell count, dominant granulocytes, myeloid immaturity and the absent to low blast concentration in the blood, the mild anemia, the normal platelet count or mild thrombocytosis and the frequency of basophilia usually point to the tentative diagnosis of CML or CML is included in the differential diagnosis without ambiguity. In a very small fraction of cases, the diagnosis of *BCR::ABL1*-positive CML is less evident. These syndromes include (i) *BCR::ABL1*-positive thrombocythemia, (ii) so-called neutrophilic *BCR::ABL1*-positive CML and (iii) the m-*bcr* ($p190^{BCR-ABL1}$) variant of CML, often with an absolute and relative monocytosis. In these uncommon forms, there are often misleading blood cell counts. An interesting biological feature is the striking predominance of females in these three atypical presentations. In the fourth variant, (iv) eosinophilic predominant CML, the five reported cases have all been in males. We also consider the very rare phenomenon of (v) smoldering CML (synonyms pre-CML and aleukemic CML), which also has a female predominance. The misdiagnosis or delayed diagnosis of these atypical syndromes is consequential because of the beneficial response to tyrosine kinase inhibitors in affected patients.

Introduction

The designation "atypical chronic myeloid leukemia (CML)" was initially chosen by the World Health Organization (WHO) Committee on the Classification of the Myeloid Malignancies to designate a *BCR::ABL1*-negative myeloid neoplasm that broadly fits into the non-specific category of "the chronic myeloid or myelogenous leukemias". The reason that this designation can be misleading relates to the ambiguity of the term *chronic myeloid or myelogenous leukemia*. This term is considered the common designation of *BCR::ABL1*-positive CML, but it can also refer to other chronic myeloid malignancies such as chronic neutrophilic or chronic myelomonocytic leukemia or any of several even less common phenotypes.[1] If one puts "chronic myelogenous leukemia" in an online search function, *BCR::ABL1*-positive CML is the primary outcome. The fifth edition of the WHO classification of myeloid neoplasms has changed the disease designation "atypical CML" to "myelodysplastic syndrome/myeloproliferative neoplasm with neutrophilia". However, the literature is replete with the obsolescent terminology; moreover, some classifications, such as the 2022 International Consensus Classification of myeloid neoplasms and acute leukemias, continue to use it.

Another reason why the term atypical CML is ambiguous is that there are several uncommon, but striking, atypical forms of *BCR::ABL1*-positive CML. These include (i) *BCR::ABL1*-positive thrombocythemia, (ii) *BCR::ABL1*-positive CML usually with uncharacteristically low white cell counts and concurrent neutrophilia, (iii) *BCR::ABL1*-positive CML with absolute and relative monocytosis, (iv) eosinophilic *BCR::ABL1*-positive CML and (v) smoldering *BCR::ABL1*-positive CML.

BCR::ABL1-positive CML can be, very infrequently, a genetically heterogeneous event.[2] The fusion oncogene results

from a breakpoint within the 5' segment of the *ABL1* gene such that the relevant *BCR* exons fuse with exon a2 of the *ABL1* gene. In contrast, the breakpoint in the *BCR* gene may occur, principally, at three different sites, resulting in a 190 kiloDalton (kDa), 210 kDa or 230 kDa isoform of the BCR::ABL1 oncoprotein (Table 1). Different disease phenotypes may be associated with the resultant $p190^{BCR\text{-}ABL1}$, $p210^{BCR\text{-}ABL1}$ or $p230^{BCR\text{-}ABL1}$ oncoproteins. The designation m-*bcr* indicates a $p190^{BCR\text{-}ABL1}$ fusion oncogene product, M-*bcr* a $p210^{BCR\text{-}ABL1}$ fusion oncogene product and μ-*bcr* a p230 fusion oncogene product (Table 1). In over 98% of cases of *BCR::ABL1*-positive CML, the major breakpoint cluster region is M-*bcr*, resulting in a $p210^{BCR\text{-}ABL1}$ oncoprotein. In the latter case, M-*bcr* may result in e13a2 (b2a2) or e14a2 (b3a2) fusion transcripts or both in approximately 20% of cases.

When an atypical phenotype is present that is different from classical *BCR::ABL1*-positive CML, the diagnosis may be overlooked, if there is not awareness of these atypical forms. Proper diagnosis through identification of the *BCR::ABL1* oncogene is critically important because of the responsiveness of patients who carry it to tyrosine kinase inhibitors (TKI). Here we review five aberrant phenotypes of *BCR::ABL1*-positive CML, which in two circumstances are associated, usually, with an atypical breakpoint in the *BCR* gene. Among these five is smoldering *BCR::ABL1*-positive CML, a rare situation in which the hemoglobin concentration, white cell count and platelet count may be normal but the patient's cells have the *BCR::ABL1* oncogene and the evolution to overt and progressive chronic phase or blast crisis CML occurs months or years later.

Expected demographic and hematologic values in patients with *BCR::ABL1*-positive chronic myelogenous leukemia

Large series of patients provide information on the demographic and hematologic values that serve as a standard to determine how atypical cases of *BCR::ABL1*-positive CML deviate from the expected phenotype.[3,4] According to the United States (U.S.) National Cancer Institute Surveillance, Epidemiology and End-Results (SEER) database, there is a male predominance (male-to-female ratio [M:F] 1.7:1.0) in classical *BCR::ABL1*-positive CML. The difference in incidence rate by sex begins at the age of 20 years and increases with age.[1] The M:F incidence ratio is pertinent because of the lower M:F ratio in the first three types of atypical *BCR::ABL1*-positive CML, and in the fifth, smoldering CML, each discussed below. Moreover, the fourth variant, eosinophilic CML, has been reported only in males.

The atypical cases tend to have a lower total white cell count and a lower frequency of immature myelocytic cells in the blood. The difference is striking since the mean white cell count of large series is usually 80-100x10^9/L in *BCR::ABL1*-positive CML (or higher depending on the accessibility to healthcare) with an M-*bcr* oncogene. However, the range of white cell counts at diagnosis is so broad that it may not always be a harbinger that an individual case is atypical. Taken together, however, the presence of singular thrombocytosis, neutrophilia, or eosinophilia in the absence of significant immature myelocytes in the blood or the presence of absolute and relative monocytosis in the absence of the typical array of immature myelocytes in the blood should raise consideration of atypical *BCR::ABL1*-positive CML. Another distinction among these atypical cases is that the total white cell count may not only be relatively low, it does not increase inexorably as does the white cell count in classical cases if untreated. The following descriptions characterize the five major atypical variants of CML.

BCR::ABL1-positive thrombocythemia

Apparent thrombocythemia may result from a *BCR::ABL1* rearrangement and precede the overt signs of CML.[5-12] Approximately 5% of patients with apparent essential thrombocythemia have a Philadelphia (Ph) chromosome.[13] The disease closely mimics classical essential thrombocythemia, initially. The signs are marked elevation of the platelet count, arbitrarily set by some at 1,000x10^9/L or higher, a striking increase in marrow megakaryocytes, frequently with a normal or mildly elevated white cell count with neutrophilia, no or very slight myeloid immaturity in the blood and no or minimal anemia. Setting a specific platelet count is unwise and can be misleading. In circumstances in which the platelet count is strikingly elevated but not yet at the 1,000x10^9/L level and the white cell count is relatively low and myeloid immaturity less prominent, consideration of *BCR::ABL1* thrombocythemia is advisable. Otherwise, one risks not diagnosing *BCR::ABL1*-thrombocythemia and not providing TKI therapy. In contrast to classical *BCR::ABL1*-positive CML, marrow granulopoiesis may be increased but it is usually not as

Table 1. Molecular versions of oncoproteins in chronic myelogenous leukemia.[29,34]

Designation	BCR::ABL1 oncoprotein size, kDa	*ABL1* fusion locus (exon)	*BCR* fusion locus (exon)	Frequency %
μ-*bcr*[29]	p230	a2	e19	<0.5
M-*bcr*[34]	p210	a2	e13	>98
M-*bcr*[34]	p210	a2	e14	
m-*bcr*[34]	p190	a2	e1	<1.0

Twenty percent of cases with M-*bcr* have a combination of a2e13 and a2e14 oncogenes. Very rarely, other breakpoints in the *BCR* gene have been documented with a classical chronic myeloid leukemia phenotype. kDa: kiloDaltons.

significantly expanded. The incidence of this variant is heavily skewed toward women[10] (Table 2). The oncogene is usually the classical *BCR::ABL1* (M-bcr).

The marrow megakaryocytes in *BCR::ABL1*-positive thrombocythemia are, invariably, smaller than those in normal marrow and have hypolobulated round nuclei. There is little or no clustering of megakaryocytes. These findings are in consistent and distinct contrast to the marrow morphology in essential thrombocythemia, which is often normocellular or moderately hypercellular with increased megakaryocytes that are large to giant in size, have hyperlobulated nuclei, and are distributed in loose clusters. The distinction in the marrow megakaryocyte pattern between *BCR::ABL1*-positive-thrombocythemia and essential thrombocythemia is so striking that a hematopathologist may advise the hematologist to test for *BCR::ABL1* in this situation.[10-12]

Approximately 20% of patients have triple-negative essential thrombocythemia lacking oncogenic *JAK2*, *CALR* and *MPL* mutations in their blood cells.[13] Marrow megakaryocytes should be investigated in those patients for features compatible with *BCR::ABL1*-positive thrombocythemia. As a failsafe, blood cells should be tested for *BCR::ABL1*.[14] Thus, the diagnostician should think in terms of quadruple-negative thrombocythemia (*JAK2*, *CALR*, *MPL* or *BCR::ABL1*). The ability to induce long remissions with TKI therapy is the most important reason to consider this fourth possible molecular alteration as the cause of thrombocythemia.

Minor bleeding, such as epistaxis, erythromelalgia, aquagenic pruritis or signs of thrombosis, such as cerebral or limb ischemia, are rarely present in patients with *BCR::ABL1*-positive thrombocythemia, in contrast to their frequency in essential thrombocythemia.[11,12] In some cases, the absolute basophil count is mildly elevated.

In one study of 1,591 patients with extreme thrombocytosis, 87 Ph-positive patients (5.4% of cases) were found.[15] There was a striking female predominance. The M:F ratio was 24:63 cases or 0.38:1.0 compared to a 1.7:1.0 M:F ratio in all patients with *BCR::ABL1*-positive CML in the U.S. National Cancer Institute SEER database. There was usually an e14a2 fusion transcript (Table 1), and the Sokal or Euro prognostic score indicated an intermediate or high-risk profile. Those cases, however, had good clinical, cytogenetic and molecular responses to TKI therapy. The disease in these patients was usually *JAK2*-negative,[16] but there are uncommon cases of *BCR::ABL1*-positive thrombocythemia with coexisting *JAK2* or, much less often, *CALR* mutations.[17-20]

Evolution from *BCR::ABL1*-positive thrombocythemia to blast crisis may occur,[21,22] and was frequent in the pre-TKI era. In one report, all seven cases were in women and all developed blast crisis.[23] The frequency of this variant of *BCR::ABL1*-positive CML depends on the platelet count threshold used for inclusion.

Simultaneous *BCR::ABL1*-positive thrombocythemia and *JAK2* or *CALR*-mutant essential thrombocythemia

Approximately 0.8% of patients with *BCR::ABL1*-positive CML have a coexisting *JAK2* or, far less frequently, *CALR* mutation.[17-20] In this case, the patient may go into a complete cytogenetic and deep molecular remission as a result of TKI treatment but has either sustained or increased thrombocytosis and splenomegaly. This situation can be misinterpreted as an incomplete effect of the TKI therapy. Thus, in such situations especially with a complete cytogenetic response and a deep molecular response, but with persistent thrombocytosis, a search for a mutation associated with essential thrombocythemia is required to decide that TKI therapy was incompletely effective. Management of the effects of the coincidental *JAK2* or *CALR* mutation is required in addition to the TKI therapy.

Neutrophilic *BCR::ABL1*-positive chronic myelogenous leukemia

A rare variant of *BCR::ABL1*-positive CML has been described in which the white cell count is composed principally of mature neutrophils.[24-32] In a review of 23 cases culled from the literature, there was an increased representation of females.[32] The M:F ratio was 7:16 or 0.4:1.0 compared to a M:F ratio of 1.7:1.0 in the classical form of *BCR::ABL1*-positive CML. The white cell count is lower at the time of diagnosis than is the case in most patients with classical CML (Table 3). The median white cell count was 31x10^9/L in these 23 cases compared to mean white cell counts of 80-100x10^9 in large series of classical CML at diagnosis.[3,4] However, three

Table 2. Features of 87 patients with *BCR::ABL1*-positive thrombocythemia.[15]

Variable	Median	Range
Hemoglobin, g/L	118	77-133
White cell count, x10^9/L	31.6	6.34-390
Platelet count, x10^9/L	1,466	1,054-4,720

Of 87 patients, accumulated from 16 Italian medical centers, 24 were male and 63 female, for a male:female ratio of 0.27:1. The patients were aged 18-87 years old. Only patients with a platelet count above the arbitrary threshold of 1,000 x10^9/L were included.

Table 3. White cell counts in 23 patients with neutrophilic *BCR::ABL1*-positive chronic myelogenous leukemia.[32]

White cell count, x10^9/L, range	Number of patients	Percent of patients
1-24	6	26
25-49	8	35
50-74	5	22
>75	4	17

The 23 patients were aged from 13-78 years. There were seven males and 16 females for a male:female ratio of 0.43:1. Fifteen of the 23 did not have splenomegaly.

of the 23 patients had white cell counts of 136, 203, and 205x10^9/L. Thus, the white cell count is markedly skewed to the low side, but not invariably. Patients with neutrophilic *BCR::ABL1*-positive CML usually do not have basophilia, notable myeloid immaturity in the blood or splenomegaly. They may have thrombocytosis and, thus, their condition can mimic *BCR::ABL1*-positive thrombocythemia. Indeed, an observer has suggested that this variant should not be given the special standing of neutrophilic CML;[28] however in their rebuttal, the Italian group that has championed its special designation provides a counterargument in support of neutrophilic CML.[28]

The cells of these patients have the Ph chromosome but have an unusual *BCR::ABL1* fusion arising from a breakpoint in the *BCR* gene between exons 19 and 20 (μ-*bcr*). This fuses most of the *BCR* gene with *ABL1*, generating a larger fusion protein (230 kDa) than that observed in classical CML (210 kDa). This very rare fusion was found in approximately 0.3% of 988 cases of CML in one center.[29] This correlation between genotype and phenotype, however, has not been observed in all cases.[30] Indeed, most cases of this rare genotype (μ-*bcr*) have a classical CML phenotype and respond to TKI.[29] The quality of that response has been inferior compared to the response to the classical disease and later generations of TKI are more effective.[33] This CML variant may have an indolent course, which has been ascribed to the low levels of p230 mRNA transcripts and the undetectable or barely detectable p230 protein expression in some cases.[32] The p230 BCR::ABL1 oncoprotein has the weakest transforming activity. As a result it exhibits the lowest intrinsic tyrosine kinase activity and reduced phosphorylation of downstream signaling proteins, compared to the p210 and p190 BCR::ABL1 oncoproteins. The view that this form of CML may have a benign course, as a generalization, has been challenged.[27,28,31]

p190$^{BCR-ABL1}$ chronic myelogenous leukemia

Less than 1% of patients with *BCR::ABL1*-positive CML have the breakpoint on the *BCR* gene in the first intron (m-*bcr*), resulting in a 190 kDa fusion protein, instead of the classical 210 kDa protein observed in the overwhelming fraction of patients with *BCR::ABL1*-positive CML.[34] In a report from the M.D. Anderson Cancer Center, 14 of 1,292 patients (1.1%) with *BCR::ABL1*-positive CML had a p190$^{BCR-ABL1}$ oncoprotein and of those 14 patients, nine were in chronic phase (0.7%) and seven of the nine were woman.[34] Although a small sample, this M:F ratio of 0.28:1.0 differs significantly from the M:F ratio of 1.7:1.0 for classical *BCR::ABL1*-positive CML in the U. S. National Cancer Institute SEER database. This report did not provide a description of the blood cell counts. The m-*bcr* molecular lesion is similar to that observed in approximately 65% of patients with Ph-positive B-acute lymphoblastic leukemia.[35] The determinants of this variation in phenotype with the same oncogene have not been elucidated (see later “Phenotypic variation”).

In a report reviewing 18 cases of p190$^{BCR-ABL1}$ CML extracted from the medical literature, the M:F ratio was about 1:1 among the 13 cases for which sex was reported.[36] In an effort to verify the impression that this variant has an increased frequency of monocytosis, occasionally dominantly so, this feature was examined explicitly. Cases were divided into those with a monocyte count over 1x10^9/L and a percent of monocytes greater than 8% and those without those dual findings. Ten of 18 patients had that degree of monocytosis (absolute and relative) but there was an absolute monocytosis in four of seven of the eight cases in which a monocyte count was available despite the absence of a percentage of over 8%. Thus, 14 of 18 cases had an absolute monocytosis. Since many cases of classical CML have a monocytosis, despite a low percent of monocytes, because the total white cell count is very high, considering the percent monocytes helps to distinguish this variant as having a higher degree of monocytosis than cases harboring the classical p210$^{BCR-ABL1}$ (M-*bcr*).

In a review of 23 cases of m-*bcr* CML reported in the medical literature, the white cell count was frequently lower than expected and basophilia was less frequent (9 of 20 cases had 0 to 1% basophils).[37]

Isolated case reports highlight the dramatic deviations of blood counts from the classical expectation. For example, a case with a hemoglobin concentration of 15.6 g/L, an initial white cell count of 11.8x10^9/L composed of 50% neutrophils, 19% monocytes and 2% basophils and with an uninformative bone marrow examination was a diagnostic enigma. Sequencing for gene mutations associated with chronic myelomonocytic leukemia was unrevealing. A karyotype eventually led to the diagnosis of p190$^{BCR-ABL1}$ CML.[36] Other case reports of striking monocytosis as the principal feature highlight its presence in most cases of p190$^{BCR-ABL1}$ CML.[38-40] In one report reviewing ten cases of p190$^{BCR-ABL1}$ with monocytosis, the monocyte count ranged from 2.5 to 38.4x10^9/L with a median of 20.2x10^9/L.[36] Splenomegaly is less prominent than in CML with the classical *BCR* breakpoint (M-*bcr*). Thirteen of 20 cases of m-*bcr* CML did not have splenomegaly at the time of diagnosis.[37] These reports highlight the importance of testing for the *BCR::ABL1* oncogene in cryptic cases of apparent myeloid neoplasms with monocytosis, low white cell counts, and the absence of basophilia and splenomegaly. This need is made poignant by the availability of TKI therapies, although m-*bcr* CML is associated with an inferior response to TKI compared to M-*bcr* CML.[34,41] Not infrequently, the initial consideration is chronic myelomonocytic leukemia but gene sequencing does not disclose the somatic mutations most often associated with that diagnosis. A rare case of the coexistence of *BCR::ABL1*-positive CML and chronic myelomonocytic leukemia with the characteristic genetic changes of each has been reported.[42]

Eosinophilic variant of *BCR::ABL1*-positive chronic myelogenous leukemia

Rarely, *BCR::ABL1*-positive CML presents with an isolated or pronounced eosinophilia that may clinically resemble other reactive or neoplastic eosinophilic disorders. In a review of five patients with the eosinophilic variant of *BCR::ABL1*-positive CML, all were male and three were diagnosed before the age of 35 years.[43] Clinical and laboratory features of these patients at the time of initial diagnosis are summarized in Table 4. All five patients presented with unusual and disabling findings. These included peripheral vasculitis progressing to digital gangrene,[44] superficial thrombophlebitis,[45] recurrent episodes of fever and painful mucocutaneous ulcers,[46] a liver mass composed of an extensive eosinophilic infiltrate[47] and dry gangrene of the toes.[48] Recognizing the eosinophilic variant of *BCR::ABL1*-positive CML is important so patients can be treated with TKI therapy to minimize, and potentially reverse, tissue damage caused by direct infiltration by eosinophils and/or the systemic release of eosinophilic granules into the blood.

Smoldering *BCR::ABL1*-positive chronic myelogenous leukemia

In 1972, a case of what was designated "preleukemic CML" was described in a patient with a normal white cell count but a low percentage of blood myelocytes and metamyelocytes, and on further study, the Ph chromosome was found in 22% of metaphase marrow cells.[49] The patient had no significant changes in his blood counts for 5 years at which time he developed a blast crisis of *BCR::ABL1*-positive CML. After a hiatus of 35 years, 14 subsequent cases were reported of similar patients, some with normal hemoglobin, white cell counts and platelet counts and in some cases very slight increases in myelocytes and metamyelocytes in the white cell differential count and occasionally a mildly elevated basophil count.[50-57] These findings prompted cytogenetic and/or genetic studies that found the Ph chromosome and/or the *BCR::ABL1* oncogene in a significant percentage of blood cells. The patients' disease evolved into overt *BCR::ABL*-positive CML months or years later. This situation has been dubbed "preleukemic" or "smoldering" CML. In a few cases, the patient had received cytotoxic therapy for lymphoma or had an alternative myeloproliferative disease (e.g., polycythemia vera) prior to the discovery of the *BCR::AB*L-positive blood cells. In several cases, the clues were subtle, such as an unexplained low percentage of myelocytes in the blood and a barely elevated basophil count, just exceeding normal.

One report compared the marrow cellular composition and vasculature of seven patients with smoldering *BCR::ABL1*-positive CML with five cases of classical *BCR::ABL1*-positive CML in chronic phase and five marrow specimens from patients with a leukemoid reaction.[55] Reticulin, CD34, and CD61 immunostains were performed on all marrow biopsy specimens. Blood absolute basophilia (≥200x10^9/L) was present in four of seven patients with smoldering *BCR::ABL1*-positive CML, but was present in all the patients with classical *BCR::ABL1*-positive CML and was absent in the cases of leukemoid reaction. The mean (± standard deviation) microvascular density of smoldering CML cases (10.0±4.3 vessels/200X field) was twice that of the leukemoid reaction cases (5.0±1.0) (P=0.02) but similar to that of the five cases of classical *BCR::ABL*-positive CML (12.5±3.6). The percentage of small, hypolobated megakaryocytes, highlighted by a CD61 stain in the cases of smoldering CML, was 40%, three times that found in cases of leukemoid reaction (13%) but less than that in *BCR::ABL1*-positive CML cases (86%). These authors indicated that smoldering *BCR::ABL1*-positive CML should be considered in patients with a normal to slightly elevated white blood cell count and absolute basophilia. An increased percentage of small, hypolobulated megakaryocytes is another feature suggesting smoldering *BCR::ABL1*-positive CML. Examining blood cells for *BCR::ABL1* is advisable if there is either unexplained myeloid immaturity, even if slight, or slight basophilia or both in the blood.

Table 4. Features of the eosinophilic variant of chronic myelogenous leukemia.[44-48]

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	25	55	34	26	67
Sex	M	M	M	M	M
Hemoglobin, g/L	14.1	NR	7.7	"Normal"	NR
WBC count, x10^9/L	44.4	12.3	14.8	25.4	155.6
Eosinophil count, x10^9/L (eosinophil %)	33.3 (75)	10.5 (85)	11.5 (78)	18.7 (74)	59.1 (38)
Platelet count, x10^9/L	135	NR	NR	"Normal"	842
Splenomegaly	Yes	No	No	No	No
BCR::ABL oncoprotein	NR	NR	NR	p210	p190
Reference	44	45	46	47	48

M: male; NR: not reported; WBC: white blood cell.

In a review of 31 cases of what was dubbed aleukemic CML, the selection of patients was based on two criteria: (i) a white blood cell count less than $12x10^9$/L or neutrophil count less than $8x10^9$/L if there was an accompanying lymphocytosis and (ii) platelet count less than $470x10^9$/L to avoid including *BCR::ABL1*-positive thrombocythemia.[58] Patients with a myeloid malignancy who had received chemotherapy were excluded. The population comprised 13 men and 18 women in an age range of 35 to 82 years old and a M:F ratio of 0.72:1.0 as compared to the expected ratio of 1.7:1.0. Three groups of patients were analyzed: (i) eight patients who had received cytotoxic therapy for a carcinoma or lymphoid neoplasm, (ii) nine patients who had a non-myeloid neoplasm but had not received cytotoxic therapy and (iii) 12 patients without a history of a neoplasm. Table 5 summarizes the features of the blood cell counts in these patients. An interesting feature of some of these cases was the reluctance of the consulting hematopathologist to diagnose an early or indolent form of CML, even after obtaining molecular evidence of a *BCR::ABL1* fusion, presumably because of the absence of "compatible" blood cell counts. The two most frequent findings were an unexplained, persistent low percentage of myelocytes in the blood or a slight increase in basophils. These clues each occurred in about half the patients.

Twenty-five of these patients received TKI therapy. One patient developed a blast crisis soon after diagnosis, despite being on TKI therapy. Twenty-two patients who received TKI therapy and for whom detailed follow-up information was available were observed for a median of 46 months. Twenty achieved a complete cytogenetic remission. Fifteen of these 20 achieved a major molecular remission or deeper. Ten achieved molecularly undetectable disease.

Although a rare abnormality, these oversights emphasize the importance of enhanced awareness in the hematopathology and hematologic oncology community. We favor "smoldering CML" as the designation. The condition is not preleukemic since the fusion gene is expressed and there are at least subtle phenotypic changes in most cases. The term aleukemic is ambiguous since it is unequivocally a "leukemia" in the modern diagnostic meaning of the designation, although the white cell count may be normal or low. The white cell count has not been a diagnostic criterion for leukemia for over 100 years. Thus, "smoldering" seems like the most specific and informative designation since it is not "preleukemic." The term "aleukemic" is superfluous in our current understanding since a low or normal white count is compatible with myeloid leukemia.

Table 5. Blood count findings in 31 patients with smoldering *BCR::ABL1*-positive chronic myelogenous leukemia.[58]

Variable	Median value	Range
Hemoglobin concentration, g/dL	11.9	8.0-16.8
White cell count, $x10^9$/L	8.4	2.9-26.4
Neutrophil count, $x10^9$/L	5.6	1.3-8.7
Basophil count, $x10^9$/L	0.14	0.0-0.67
Eosinophil count, $x10^9$/L	0.22	0.0-0.91
Monocyte count, $x10^9$/L	0.44	0-1.44
Platelet count, $x10^9$L	248	20-462

Sixteen of 30 (53%) patients had immature granulocytes in the blood. Three of 30 (10%) had 1%, 3% or 8% blasts in the blood. Four (13.3%) had mildly increased blood monocytes. Eight of 30 (26.7%) had mild neutrophilia. Seventeen (56.7%) had basophilia (>$0.2x10^9$/L). Four (13.3%) had eosinophilia. There were 13 males and 18 females, for a male:female ratio of 0.72:1.

Philadelphia chromosome-positive myelodysplastic syndrome

In our discussion of atypical and uncommon presentations of *BCR::ABL1*-positive CML, we have not included patients who present with phenotypic and genotypic features of a myelodysplastic syndrome and who have a concomitant or subsequent *BCR::ABL1* fusion oncogene, usually with a classical *BCR-ABL1* fusion (M-*bcr*), rarely with a m-*bcr* fusion. Twenty-two cases of this neoplasm, designated Ph^+ myelodysplastic syndrome, have been described.[59] Dual therapy with a TKI and treatment of the myelodysplastic syndrome may be required.

Phenotypic variation

Classic CML arises from a primitive hematopoietic pluripotential stem cell or a very closely related cell that acquires a *BCR::ABL1* rearrangement encoding a constitutively active chimeric oncoprotein.[60] The inherent or acquired lineage potential of the cell-of-origin in which the *BCR::ABL1* fusion arises may help to explain the typical blood findings in CML, involving increased production of various myeloid cells, as well as the ability to progress to myeloid or lymphoid blast crisis upon acquiring additional molecular alterations. In the atypical presentations of CML described here, one might speculate that the *BCR::ABL1* rearrangement arises in a lineage-committed myeloid progenitor cell with a propensity to develop into megakaryocytes, neutrophils, monocytes, or eosinophils in the case of *BCR::ABL1*-positive thrombocythemia, neutrophilic CML, $p190^{BCR\text{-}ABL1}$ CML, and the eosinophilic variant of CML, respectively. Alternatively, in these atypical forms of CML, additional genetic or epigenetic alterations beyond *BCR::ABL1* may restrict or strongly favor cell differentiation toward specific lineages independent from the cell-of-origin in which the *BCR::ABL1* fusion arises, a more likely option.[61] There is evidence, for example, that epigenetic changes may determine the type of blast crisis that evolves in CML, lymphoblastic or myeloblastic.[62]

Given the rarity of these atypical forms of CML, broad genomic and transcriptomic profiling has not been performed, except in the case of $p190^{BCR\text{-}ABL1}$ CML. Compared

to p210$^{BCR-ABL1}$ CML, p190$^{BCR-ABL1}$ CML showed upregulation of tumor necrosis factor, interferon, interleukin-1 receptor, and p53 signaling by whole-transcriptome sequencing.[63] We are not aware of genetic studies on sorted cell populations designed to elucidate the specific myeloid cell types harboring the *BCR::ABL1* fusion in each of these atypical forms of CML. Gene expression profiling of *BCR::ABL1*-positive B-acute lymphoblastic leukemia has revealed three distinct disease subtypes that transcriptionally resemble normal B-cell progenitors at different (early, intermediate, and late) stages of maturation.[63] Each transcriptomic subtype contained patients with both the p210 and p190 isoforms, but showed distinct patterns of cooperating genetic events. Further molecular characterization of these atypical forms of CML may help to reveal the pathophysiology underlying these distinct clinical phenotypes, potential differential response to TKI therapy and improved therapeutic approaches.[64]

One could look at *BCR::ABL1*-positive thrombocythemia as a statistical anomaly. That is, if one uses an arbitrary cutoff such as 1x10^6/L platelet count to define this entity, it may just be the upper end of the distribution curve of platelet count among CML cases. This explanation does not account for the high frequency of a lower white cell count and higher hemoglobin concentration or less intense hematopoietic proliferation in the marrow of these patients. The striking female predominance of this variant suggests that potential hormonal effects and/or molecular alterations affecting the sex chromosomes may contribute to this variation in phenotype. Hormonal effects could act either through epigenetic pathways involving DNA methylation or histone modifications, or, alternatively, through the effects of microRNA.[65] The existence of these mechanisms and their effects on therapeutic response to TKI have been explored.[66]

In neutrophilic CML and p190$^{BCR-ABL1}$ CML, the oncogene is different from that in classical CML in most cases. However, in the case of neutrophilic CML, occasional cases have a classical genotype (p210$^{BCR-ABL1}$). Contrariwise, many cases of the rare p230 genotype have a classical presentation, whereas a few are of the uncommon neutrophilic CML phenotype.

There has been no comprehensive study of the relationship of genotype to phenotype in atypical *BCR::ABL1*-positive CML nor of the mechanism of the effect of sex on phenotype. This deficiency relates, in part, to the infrequency of the aberrant phenotypes, the inability to accumulate cases in which genomic and transcriptosome sequencing are performed and the absence of the technical expertise to perform these studies at many hospitals. There is a well-established excess M:F incidence ratio in virtually all types of myeloid neoplasms. Genomic studies may shed light on the determinants of oncogenesis and the molecular explanation for the striking female predominance in these uncommon phenotypes of CML. The significance of the male predominance in the eosinophilic variant of CML is difficult to evaluate because of the small number of cases.

Disclosures

No conflicts of interest to disclose.

Contributions

ANJ and MAL each contributed to the conception of the review, literature search and preparation of the manuscript.

Acknowledgments

We acknowledge Dr. Josef T. Prchal, University of Utah Medical Center, who read a draft of the manuscript and made helpful suggestions.

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