Chronic Myeloproliferative Diseases With the t(5;12)(q33;p13)

Clonal Evolution Is Associated With Blast Crisis

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Abstract

Chronic myeloproliferative diseases (CMPDs) associated with t(5;12)(q33;p13) are reported to be responsive to imatinib mesylate. We studied 5 cases of CMPD with isolated t(5;12) treated at our hospital between January 1993 and October 2004. All were men with a median age of 55 years (range, 18-68 years). In the peripheral blood, each had marked leukocytosis, with variable eosinophilia (n = 4), monocytosis (n = 3), or basophilia (n = 2). Bone marrow specimens were hypercellular (70%-100%) with marked myeloid hyperplasia in each patient, but only 1 patient had eosinophilia, monocytosis, and basophilia. Follow-up ranged from 23 to 182 months (median, 48 months). Four died 23 to 182 months after initial diagnosis, 3 of blast crisis and 1 of cardiac complications of severe eosinophilia. Additional cytogenetic aberrations were identified at the time of blast crisis. Of 3 patients treated with imatinib, 2 responded, but only 1 had a sustained response. CMPD with t(5;12) commonly transforms to blast phase, and transformation is associated with cytogenetic evidence of clonal evolution.

Chronic myeloproliferative disease (CMPD) associated with t(5;12)(q33;p13) has been recognized as a rare, distinctive subgroup of CMPDs characterized by marked neutrophilia, eosinophilia, and variable monocytosis.[1] The t(5;12)(q33;p13) juxtaposes the *ETV6* (also known as *TEL*) gene at 12p13 with the platelet-derived growth factor receptor-β (*PDGFRB*) gene at 5q33.[2] The *PDGFRB* gene encodes a class III receptor tyrosine kinase. The t(5;12) results in constitutive activation of PDGFRB and downstream activation of signaling pathways regulating hematopoiesis.

Approximately 40 cases of CMPD with t(5;12) have been reported.[3,4] Although neutrophilia and eosinophilia in peripheral blood and bone marrow have been described commonly in this neoplasm, the full range of clinicopathologic features is not clear. Cases of CMPD with t(5;12) have been classified morphologically into a variety of disease entities, including chronic myelomonocytic leukemia (CMML), eosinophilic leukemia, atypical chronic myelogenous leukemia, and Philadelphia or *bcr-abl*–negative chronic myelogenous leukemia, suggesting that the clinicopathologic features of neoplasms associated with t(5;12) may be more variable than previously recognized. Furthermore, most published studies have focused on the chronic phase of CMPD associated with the t(5;12)(q33;p13). Reports of cases with cytogenetic evidence of clonal evolution and the frequency and clinicopathologic features of blast transformation have not been emphasized. Because recent studies have shown that CMPD with t(5;12) can respond to imatinib mesylate,[4] recognition of this neoplasm has important clinical implications.

We describe the clinical, pathologic, and cytogenetic features of 5 patients with CMPD associated with t(5;12)(q33;p13). In particular, we focus on the morphologic spectrum of this

neoplasm at the time of initial diagnosis and the frequency of cytogenetic changes and blast phase over time. We also report response to therapy with imatinib in 3 patients.

Materials and Methods

The files of the Department of Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, were searched for cases of t(5;12)(q33;p13) between January 1993 and October 2004. Clinical information was obtained from the medical records.

Wright-Giemsa–stained peripheral blood and bone marrow aspirate smears, bone marrow touch imprints, and H&E-stained bone marrow aspirate clot and trephine biopsy specimens were retrieved for review. We performed 200-cell manual differential counts on bone marrow aspirate smears. Basophilia was defined as a basophil count greater than 200/μL (0.2×10^9/L) in the peripheral blood and greater than 1% in bone marrow aspirate smears. Eosinophilia was defined as an eosinophil count greater than 600/μL (0.6×10^9/L) in the peripheral blood and greater than 4% in bone marrow aspirate smears. Monocytosis was defined as a monocyte count greater than 1,000/μL (1.0×10^9/L) in the peripheral blood and greater than 5% in the bone marrow aspirate smears. Each case was classified according to the World Health Organization classification scheme.[5]

Cytochemical studies for myeloperoxidase and α-naphthyl butyrate esterase were performed using standard methods on bone marrow aspirate smears. Reticulin stain was performed on bone marrow biopsy specimens in 4 cases, and fibrosis was scored according to the Bauermeister system using a scale of 1+ to 4+.[6] Immunohistochemical stains were performed on formalin-fixed, paraffin-embedded tissue sections using monoclonal antibodies specific for myeloperoxidase (dilution 1:20; Becton Dickinson, San Jose, CA) and CD68 (KP-1, dilution 1:500; DAKO, Carpinteria, CA).

Flow cytometric immunophenotypic studies were performed using 3- or 4-color analysis and a FACScan or FACSCalibur instrument (Becton Dickinson Biosciences, San Jose, CA) as described previously.[6] Blasts were gated for analysis using CD45 expression and side scatter. The panel of monoclonal antibodies included those specific for CD45 (peridinin-chlorophyll-α–protein 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), and CD117 (FITC or PE). All antibodies were purchased from Becton Dickinson Biosciences. For each antibody, negative staining levels were set by comparison with an isotype-matched control.

Conventional cytogenetic studies were performed on bone marrow aspirate samples using standard Giemsa trypsin G-banding procedures as described previously.[7] Karyotypes were recorded using the International System of Human Cytogenetic Nomenclature. Fluorescence in situ hybridization analysis for *bcr-abl* was performed using the LSI *BCR/ABL* ES dual-color translocation probe (Vysis, Downers Grove, IL) according to the manufacturer's instructions. Reverse transcriptase–polymerase chain reaction assay for detection of *bcr-abl* fusion transcripts was performed as described previously.[7]

Results

There were 5 patients, all men, with a median age of 55 years (range, 18-68 years). At the time of initial diagnosis, 3 patients complained of nonspecific constitutional symptoms such as weight loss and fatigue. One patient had visual disturbance and numbness of his jaw. One patient was asymptomatic. Physical examination revealed mild to massive splenomegaly in 4 patients and mild hepatomegaly in 3 patients. The clinical features of these patients are summarized in **Table 1**.

A CBC count showed that each patient had leukocytosis, with a median WBC count of 37,000/μL (37.0×10^9/L; range, 12,000-92,000/μL [$12.0\text{-}92.0 \times 10^9$/L]). The hemoglobin level

Table 1
Clinical Findings in Five Cases of CMPD Associated With t(5;12)(q33;p13)

Case No./ Age (y)/Sex	Primary Diagnosis	Hepatomegaly	Splenomegaly	Previous Treatment	Imatinib/ Response	Other Treatments	Outcome	Cause of Death	Interval to Progression (mo)	Survival (mo)
1/68/M	CMPD-U	None	Moderate	Hydroxyurea	Yes/CR	None	Alive, CR	—	—	29
2/57/M	CMML-Eos	Mild	Massive	Hydroxyurea	Yes/no	Chemo	Died	MVR	44	48
3/55/M	CMML	None	None	None	Yes/good	Chemo/ABMT	Died	BP	15	23
4/18/M	CMML	Mild	Moderate	Hydroxyurea/ IFN-α	—	Chemo	Died	BP	36	60
5/40/M	CMPD-U	Mild	Mild	None	—	Chemo	Died	BP	178	182

ABMT, allogeneic bone marrow transplantation; BP, blast phase; Chemo, chemotherapy (see text for regimens); CMML-Eos, chronic myelomonocytic leukemia with eosinophilia; CMPD, chronic myeloproliferative disease; CR, complete remission; IFN-α, interferon alfa; MVR, mitral valve rupture; NA, not applicable; U, unclassifiable.

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was normal in 2 patients and slightly decreased in 3 patients, with a median of 13.5 g/dL (135 g/L; range, 9.6-15.4 g/dL [96-154 g/L]). Three patients had mild to moderate thrombocytopenia with a median platelet count of 104 × 10^3/μL (104 × 10^9/L; range, 69-165 × 10^3/μL [69-165 × 10^9/L]). Four patients had mild to marked absolute eosinophilia (eosinophil count, 700-4,543/μL [0.70-4.54 × 10^9/L]; reference range, ≤600/μL [0.60 × 10^9/L]), 2 patients had mild to moderate absolute basophilia (basophil count, 222-1,950/μL [0.22-1.95 × 10^9/L]; reference range, ≤200/μL [0.20 × 10^9/L]), and 3 patients had absolute monocytosis (1,332-2,604/μL [1.33-2.60 × 10^9/L]; reference range, ≤1,000/μL [1.00 × 10^9/L]) **Image 1A** and **Image 1B**. Three patients had a mild to moderate left shift in neutrophilic maturation, with up to 24% of metamyelocytes and myelocytes. The peripheral blood findings for each patient are summarized in **Table 2**.

Bone marrow aspirate smears were available in 4 cases. In case 5, bone marrow aspiration yielded a dry tap; a touch imprint was not available. All 4 cases showed marked granulocytic hyperplasia with a mild left shift in maturation. In addition, case 2 showed eosinophilia (18% [0.18]), basophilia (6% [0.06]), and mild monocytosis (6% [0.06]) **Image 1C**. There was no evidence of eosinophilia, basophilia, or monocytosis in cases 1, 3, and 4. Dysplasia was not detected in the granulocytic and erythroid series.

The bone marrow biopsy specimens were hypercellular (70%-100%) with marked myeloid hyperplasia **Image 1D** in each case. The megakaryocytes were adequate in number without dysplastic features, except in case 3 in which there was a slightly increased number of small hypolobated megakaryocytes. Increased paratrabecular cuffing of immature myeloid cells and megakaryocytic hyperplasia or clustering (as frequently seen in chronic myelogenous leukemia) were not present. Reticulin fibrosis was mild (1+) in case 1, and moderate (3+) in case 2. Reticulin fibrosis was not present in cases 3 and 4. Reticulin stain was not performed on case 5. The bone marrow morphologic findings at the time of initial diagnosis are summarized in **Table 3**.

On the basis of the morphologic findings, 1 case was classified as CMML with eosinophilia, 2 cases were classified as CMML, and 2 cases as CMPD, unclassifiable.

Follow-up

The follow-up period ranged from 23 to 182 months with a median of 48 months. Three patients initially were treated with hydroxyurea and 2 patients were untreated before they were seen at our hospital.

Case 1 was treated initially with hydroxyurea followed by imatinib when the latter became available. The patient achieved complete hematologic and cytogenetic remission 3 months after the start of imatinib at 400 mg/d and remained in complete remission for 26 months at time of last follow-up.

In case 2, worsening leukocytosis (WBC count up to 123,000/μL [123 × 10^9/L]) and eosinophilia (eosinophil count, 29% [0.29]) developed with progressive splenomegaly that required splenectomy 2 years later. His disease was refractory after 2 months of imatinib at 400 mg daily and hydroxyurea. He subsequently died of sudden rupture of the mitral valve, considered a complication of severe eosinophilia.

In 3 other patients (cases 3, 4, and 5), blast crisis developed 15, 36, and 178 months, respectively, after initial diagnosis. In case 3, the patient transiently responded to imatinib with improved hematologic indices, but blast crisis occurred 5 months later. The onset of blast crisis was accompanied by fever and shortness of breath. Following treatment with anti-CD33 antibody, fludarabine, melphalan, and anti–T-lymphocyte globulin, he received a matched unrelated bone marrow transplant. The posttransplantation course was complicated by graft-vs-host disease. The patient finally died of complications 5 months after transplantation.

In case 4, the disease initially was controlled with hydroxyurea and interferon alfa. However, 3 years later he was found to have an enlarged left tonsil, and biopsy confirmed myeloid sarcoma. Two months later, systemic disease with progressive hepatosplenomegaly and cervical lymphadenopathy developed. His symptoms improved after treatment with idarubicin and cytarabine and splenectomy. He finally achieved complete remission after further treatment with cyclophosphamide, cytarabine, and topotecan. However, he eventually died of infection 24 months after he was diagnosed with myeloid sarcoma of tonsil.

The disease in case 5 was stable for 13 years after initial diagnosis without chemotherapy. A rapidly enlarging parasternal mass, 5.4 × 3.4 × 3.1 cm, then developed. Fine-needle aspiration demonstrated immature myeloid cells consistent with myeloid sarcoma, and bone marrow biopsy showed acute leukemia. He received 2 cycles of fludarabine, cytarabine, anti-CD33 antibody, and cyclosporine and 1 cycle of troxacitabine and idarubicin. The patient subsequently died of persistent disease refractory to treatment.

Table 4 and **Table 5** summarize the peripheral blood and bone marrow findings in cases 3, 4, and 5 at the time of blast crisis. In all 3 cases, the peripheral blood smears showed anemia and thrombocytopenia, and cases 3 and 5 had increased circulating blasts. The bone marrow aspirate smears in cases 3 and 5 showed markedly increased blasts and trilineage hypoplasia **Image 1E**. The blast crisis in case 4 manifested as myeloid sarcoma of tonsil **Image 1F**, and the bone marrow aspirate smear showed no increased blasts. The bone marrow biopsy specimens of all 3 cases were hypercellular (80%-95%). The neoplastic cells in the tonsil were immature with fine chromatin and were immunohistochemically positive for myeloperoxidase and CD68.

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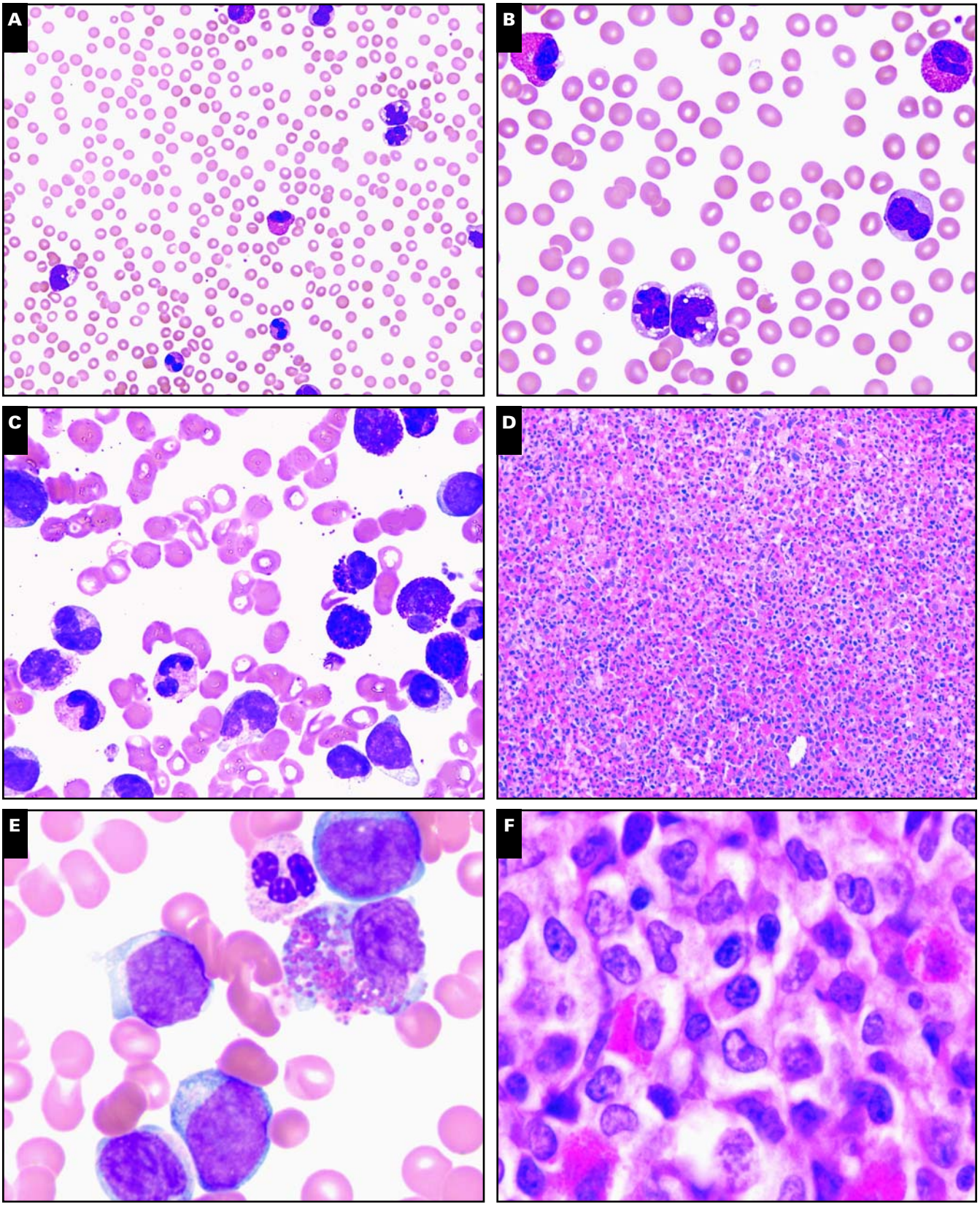

Image 1 **A**-**D** (Case 2), Chronic myelomonocytic leukemia with eosinophilia. **A** and **B**, Peripheral blood smear shows monocytosis and marked eosinophilia (**A**, Wright-Giemsa, ×400; **B**, Wright-Giemsa, ×1,000). **C**, Bone marrow aspirate smear showing monocytosis, eosinophilia, and basophilia (Wright-Giemsa, ×1,000). **D**, Bone marrow biopsy specimen shows nearly 100% cellularity with myeloid hyperplasia and marked eosinophilia (H&E, ×100). **E** (Case 5), Blast phase. Increased myeloblasts in bone marrow aspirate smear (Wright-Giemsa, ×1,000). **F** (Case 4), Blast phase. Infiltration of immature myeloid precursors and immature eosinophils in tonsil (H&E, ×1,000).

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Table 2
Peripheral Blood Findings in Five Cases of Chronic Myeloproliferative Disease Associated With t(5;12)(q33;p13) at Initial Diagnosis

Case No.	Hemoglobin	WBCs	Neutrophilic Series	Eosinophils	Basophils	Monocytes	Platelet Count
Reference Range	14.0-18.0 g/dL (140-180 g/L)	4,000-11,000/μL (4.0-11.0 × 10^9/L)	42%-66% (0.42-0.66)	≤600/μL (0.6 × 10^9/L)	≤200/μL (200 × 10^9/L)	≤1,000/μL (1.0 × 10^9/L)	140-440 ×10^3/μL (140-440 ×10^9/L)
1	9.6 (96)	92,000 (92.0)	90 (0.9)	<600 (0.60)	<200 (0.20)	<1,000 (1.00)	69 (69)
2	14.1 (141)	37,000 (37.0)	92 (0.9)	4,543 (4.54)	1,950 (1.95)	1,652 (1.65)	140 (140)
3	13.5 (135)	43,000 (43.0)	85 (0.9)	1,302 (1.30)	<200 (0.20)	2,604 (2.60)	101 (101)
4	12.4 (124)	22,000 (22.0)	67 (0.7)	700 (0.70)	222 (0.22)	1,332 (.133)	104 (104)
5	15.4 (154)	12,000 (12.0)	71 (0.7)	979 (0.98)	122 (0.12)	610 (0.61)	165 (165)

Table 3
Initial Bone Marrow Findings in Five Cases of Chronic Myeloproliferative Disease Associated With t(5;12)(q33;p13)*

Case No.	Cellularity (%)	Blasts (%)	Eosinophils (%)	Basophils (%)	Monocytes (%)	Myeloid Series	Megakaryocytes	Reticulin Fibrosis
1	90	1	2	1	3	↑, LS	Unremarkable	1+
2	100	6	18	6	6	↑, LS	Unremarkable	3+
3	80	0	2	0	1	↑, LS	Few small forms	None
4	100	1	2	0	1	↑, LS	Unremarkable	None
5	70	—	—	—	—	—	Unremarkable	—

LS, left-shifted maturation.
* The initial bone marrow aspiration from case 5 was a dry tap.

Table 4
Peripheral Blood Findings in Three Cases of Chronic Myeloproliferative Disease Associated With t(5;12)(q33;p13) at Time of Blast Crisis

Case No.	Hemoglobin	WBCs	Neutrophilic Series	Eosinophils	Basophils	Monocytes	Platelet Count	Blasts (%)
Reference Range	14.0-18.0 g/dL (140-180 g/L)	4,000-11,000/μL (4.0-11.0 × 10^9/L)	42%-66% (0.42-0.66)	≤600/μL (0.6 × 10^9/L)	≤ 200/μL (200 × 10^9/L)	≤1,000/μL (1.0 × 10^9/L)	140-440 ×10^3/μL (140-440 ×10^9/L)	
3	12.3 (123)	13,000 (13.0)	59 (0.6)	665 (0.67)	0 (0.00)	393 (0.39)	82 (82)	11
4	13.0 (130)	12,000 (12.0)	81 (0.8)	720 (0.72)	0 (0.00)	396 (0.40)	101 (101)	0
5	10.1 (101)	29,000 (29.0)	15 (0.2)	0 (0.00)	293 (0.29)	879 (0.88)	56 (56)	55

Table 5
Bone Marrow Findings in Three Cases of Chronic Myeloproliferative Disease Associated With t(5;12)(q33;p13) at Time of Blast Crisis

Case No.	Cellularity (%)	Blasts (%)	Eosinophils (%)	Basophils (%)	Monocytes (%)	Megakaryocytes
3	95	36	12	0	1	Adequate number; focal clustering
4	80	2	3	0	3	Increased
5	90	64	0	0	11	Decreased

Flow cytometric immunophenotypic studies were performed in 2 cases. The blasts in case 3 were positive for CD13, CD33, CD64, CD117, CD34, and HLA-DR and negative for B- and T-cell markers and terminal deoxynucleotidyl transferase. The blasts in case 5 were positive for CD7, CD9, CD14, CD33, CD34, CD38, CD52, and myeloperoxidase and negative for CD10, CD19, and T-cell markers.

Cytogenetic Abnormalities

At the time of initial diagnosis, conventional cytogenetic studies of bone marrow aspirate material detected the t(5;12)(q33;p13) in all 5 cases. In each case, the t(5;12) was the sole abnormality detected. Conventional cytogenetic, fluorescence in situ hybridization, and reverse transcriptase–polymerase chain reaction analyses excluded the presence of the Philadelphia chromosome and the *bcr-abl* fusion gene. At the time of blast crisis, cytogenetic analysis of bone marrow aspirate material demonstrated additional cytogenetic abnormalities in the 3 patients (cases 3-5). These abnormalities included +8, +11, +14, +19, +21, add(17)(p10), add(19)(p13), del12(p12p13), and i(6)(p10) **Table 6**.

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Table 6
Cytogenetic Findings in Five Cases of Chronic Myeloproliferative Disease Associated With t(5;12)(q33;p13) at Initial Diagnosis and Three Cases at Time of Blast Crisis

Case No.	Karyotype
Initial diagnosis	
1	Pseudodiploid clone, 46,XY,t(5;12)(q33;p13)[20]
2	Pseudodiploid clone, 46,XY,t(5;12)(q33;p13)[20]
3	Pseudodiploid clone, 46,XY,t(5;12)(q33;p13)[20]
4	Pseudodiploid clone, 46,XY,t(5;12)(q33;p13)[20]
5	Pseudodiploid clone, 46,XY,t(5;12)(q33;p13)[20]
Blast crisis	
3	Hyperdiploid clone, 48,XY,t(5;12)(q33;p13),+8, +11[18]
4	Pseudodiploid clone, 46,XY,t(5;12)(q33;p13), add(17)(p10)[14]
	Pseudodiploid clone, 46,XY,t(5;12)(q33;p13), del12(p12p13)[12]
5	Hyperdiploid clone, 50,XY,t(5;12)(q33;p13),i(6)(p10), +8,+14,add(19)(p13),+21[13]
	Hyperdiploid clone, 50,XY,t(5;12)(q33;p13),i(6)(p10), +8,+14,+19,+21[7]

Discussion

Since Keene et al[1] first described the association of chronic myelogenous leukemia with eosinophilia and abnormalities of chromosome 12q13 in 1987, approximately 40 cases of CMPD associated with the t(5;12)(q31-35;p13) have been reported in the literature. Golub et al[2] demonstrated that the t(5;12) creates a novel fusion gene composed of the *ETV6* (*TEL*) gene at 12p13 and the *PDGFRB* gene at 5q33. Owing to its rare frequency, the clinicopathologic features and natural course of this disease are not well defined. Recent reports that CMPDs with the t(5;12) respond to imatinib, however, have heightened interest in recognizing this disease. In the present study, we analyzed the clinicopathologic and cytogenetic findings in 5 cases of CMPD associated with t(5;12), and we report the response to imatinib mesylate in 3 cases.

All 5 patients in this study were men, consistent with the striking male predilection described in the literature. The patients had nonspecific symptoms or were asymptomatic at the time of diagnosis. Moderate splenomegaly and mild hepatomegaly were common. All 5 patients had leukocytosis with granulocytic hyperplasia. While 3 patients had concurrent eosinophilia and monocytosis, only 1 had a peripheral blood eosinophil count more than 1,500/μL (1.5×10^9/L), meeting the World Health Organization classification criteria for CMML with eosinophilia. One patient had only mild eosinophilia, and 1 patient had none of the aforementioned features. These findings indicate that eosinophilia and monocytosis are not constant. Furthermore, although the absolute monocyte count in peripheral blood samples of the 3 patients with monocytosis was more than 1,000/μL (1.00×10^9/L), the monocytes only accounted for 4% to 6% (0.04-0.06) of total leukocytes, in contrast with greater than 10% in most cases of CMML. Similarly, peripheral eosinophilia and basophilia were absent in 9 cases of CMPD associated with t(5;12)(q31;p13) reported in abstract form by Hanson et al.[8]

The initial bone marrow specimens demonstrated increased cellularity (80%-100%) with myeloid hyperplasia and slightly left-shifted maturation. All cases, including those diagnosed as CMML, showed predominantly proliferative features with minimal or no dysplasia. Unlike typical chronic myelogenous leukemia, however, there were no increased paratrabecular immature myeloid precursors. Only 1 case showed simultaneous basophilia and eosinophilia, and only 1 case showed slightly increased small monolobated megakaryocytes.

All 5 cases initially had t(5;12)(q33;p13) as the sole cytogenetic abnormality. Progression to blast crisis occurred in 3 patients and was associated with cytogenetic evidence of clonal evolution. These findings indicate that the t(5;12) is associated with a chronic phase of disease and support the hypothesis that an additional "hit" is required for disease transformation. It is interesting that among the additional chromosomal aberrations identified, 2 of 3 cases had trisomy 8, known to be involved commonly in clonal evolution in chronic myelogenous leukemia. Trisomy 8 has been postulated to be associated with overexpression of the *myc* gene located at 8q24, conferring a proliferative advantage in chronic myelogenous leukemia.[9]

Blast crisis occurred as early as 15 months (range, 15-178 months) after initial diagnosis, and all 3 patients died of disease 8, 24, and 4 months after the onset of blast crisis. Features indicative of disease progression included progressive splenomegaly unresponsive to therapy, resistance to imatinib, extramedullary disease, increased blast counts, and cytogenetic evidence of clonal evolution. In contrast, none of 9 cases reported by Hanson et al[8] transformed during a 1- to 5-year follow-up period. One patient in this study did not develop blast crisis but died of cardiac complications of severe eosinophilia. Only 1 patient, among the 3 patients treated with imatinib, currently is in clinical and cytogenetic remission.

Table 7 summarizes the response to imatinib mesylate therapy in cases of CMPD with associated 5q33 translocations reported in the literature.[4,10-18] Most cases have responded, even though these translocations involve different partner genes, indicating that *PDGFRB* has an important role in the pathogenesis of this disease. It is interesting that 1 of the reported cases resistant to the treatment was in the accelerated phase of disease, suggesting that additional mechanisms were involved in the progression of the disease. Similar findings were seen in case 3 of our study. This patient initially responded to imatinib, but his disease became resistant 5 months later when there was cytogenetic evidence of clonal evolution. It also is interesting that case 2 in our study did not respond to

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Table 7
CMPD With 5q33 Abnormalities and Response to Imatinib Therapy Reported in Literature

Study	No. of Cases	Age/Sex	Diagnosis	Cytogenetic Data	Molecular Data	Response	Imatinib Dose (mg/d)
Apperley et al[4]	4	32, 50, 68, 6/M	CMPD, Eos	t(5;12)(q33;p13)	ETV6/PDGFRB (n = 3)	CR, 4	400
Magnusson et al[10]	1	29/M	CMML	t(5;17)(q33;p13)	Rabaptin5/PDGFRB	CR	400
Pitini et al[11]	1	68/M	CMML	t(5;12)(q33;p13)	ETV6/PDGFRB	CR	400
Garcia et al[12]	1	44/M	aCMPD	t(5;10)(q33;q22)	H4(D10S170)/PDGFRB	CR	400
Wilkinson et al[13]	1	11 mo/F	aCMPD	t(1;5)(q23;q33)	PDE4DIP/PDGFRB	CR	NA
Bastie et al[14]	1	49/M	aCMPD, AP	t(5;10)(q33;q21)	H4(D10S170)/PDGFRB	NR	400
Vizmanos et al[15]	1	35/M	aCML	t(5;14)(q33;q24)	NIN/PDGFRB	CR	400
Wittman et al[16]	1	2/F	aCML	t(5;12)(q33;p13)	ETV6/PDGFRB	CR	200
Grand et al[17]	1	79/M	aCML, Eos	t(5;15)(q33;q22)	TP53BP1/PDGFRB	PR/5 mo	400
Levine et al[18]	1	42/M	CMML	t(5;14)(q33;q32)	KIAA1509/PDGFRB	CR	400

aCML, atypical chronic myelogenous leukemia; aCMPD, atypical chronic myeloproliferative disease; AP, accelerated phase; CMML, chronic myelomonocytic leukemia; CMPD, chronic myeloproliferative disease; CP, chronic phase; CR, complete remission; Eos, eosinophilia; NA, not available; NR, no response; PDGFRB, platelet-derived growth factor receptor-β; PR, partial response.

treatment with imatinib despite absence of cytogenetic evidence of clonal evolution, suggesting that other mutations not identifiable by conventional cytogenetic analysis might be involved. It is unknown whether cases with fusion genes involving *PDGFRB* and other reported partner genes, such as *HIP1, CEV14,* and *HCMOGT,* will respond to imatinib.[19-21]

In summary, CMPD associated with t(5;12) is a rare disease that has variable morphologic features. Absolute eosinophilia and monocytosis are common but are not consistently present in every case, and basophilia may occur in a subset of cases. Absence of atypical megakaryocytic hyperplasia distinguishes this group from chronic myelogenous leukemia. This disease has a tendency to progress to blast phase, at which time cytogenetic evidence of clonal evolution often is detected. Responses to imatinib are variable, and resistance may occur in the chronic or blast phase of disease.

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References

1. Keene P, Mendelow B, Pinto MR, et al. Abnormalities of chromosome 12p13 and malignant proliferation of eosinophils: a nonrandom association. *Br J Haematol*. 1987;67:25-31.
2. Golub TR, Barker GF, Lovett M, et al. Fusion of PDGF receptor beta to a novel ets-like gene, *tel,* in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. *Cell*. 1994;77:307-316.
3. Steer EJ, Cross NC. Myeloproliferative disorders with translocations of chromosome 5q31-35: role of the platelet-derived growth factor receptor beta. *Acta Haematol*. 2002;107:113-122.
4. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. *N Engl J Med*. 2002;347:481-487.
5. Jaffe ES, Harris NL, Stein H, et al. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001:17-44, 49-52.
6. Bauermeister DE. Quantitation of bone marrow reticulin: a normal range. *Am J Clin Pathol*. 1971;56:24-31.
7. Yin CC, Medeiros LJ, Glassman AB, et al. t(8;21)(q22;q22) in blast phase of chronic myelogenous leukemia. *Am J Clin Pathol*. 2004;121:836-842.
8. Hanson CA, Persons DL, Kurtin PJ, et al. t(5;12)(q31;p13): a distinct chronic myeloproliferative disorder (CMPD) with marrow eosinophilia [abstract]. *Mod Pathol*. 1995;8:112A.
9. Fugazza G, Bruzzone R, Dejana AM, et al. Trisomy 8 detection in Ph+ CML patients using conventional cytogenetic and interphase fluorescence in situ hybridization techniques. *Cancer Genet Cytogenet*. 1994;72:24-27.
10. Magnusson MK, Meade KE, Brown KE, et al. Rabaptin-5 is a novel fusion partner to platelet-derived growth factor beta receptor in chronic myelomonocytic leukemia. *Blood*. 2001;98:2518-2525.
11. Pitini V, Arrigo V, Teti D, et al. Response to STI571 in chronic myelomonocytic leukemia with platelet derived growth factor beta receptor involvement: a new case report [abstract]. *Haematologica*. 2003;88:ECR18.
12. Garcia JL, Font de Mora J, Hernandez JM, et al. Imatinib mesylate elicits positive clinical response in atypical chronic myeloid leukemia involving the platelet-derived growth factor receptor beta [letter]. *Blood*. 2003;102:2699-2700.
13. Wilkinson K, Velloso ER, Lopes LF, et al. Cloning of the t(1;5)(q23;q33) in a myeloproliferative disorder associated with eosinophilia: involvement of PDGFRB and response to imatinib. *Blood*. 2003;102:4187-4190.
14. Bastie JN, Garcia I, Terre C, et al. Lack of response to imatinib mesylate in a patient with accelerated phase myeloproliferative disorder with rearrangement of the platelet-derived growth factor receptor β-gene [letter]. *Haematologica*. 2004;89:1263-1264.
15. Vizmanos JL, Novo FJ, Roman JP, et al. *NIN,* a gene encoding a CEP110-like centrosomal protein, is fused to PDGFRB in a patient with a t(5;14)(q33;q24) and an imatinib-responsive myeloproliferative disorder. *Cancer Res*. 2004;64:2673-2676.

DOI: 10.1309/Y3Y5G01443AD5L48

16. Wittman B, Horan J, Baxter J, et al. A 2-year-old with atypical CML with a t(5;12)(q33;p13) treated successfully with imatinib mesylate. *Leuk Res*. 2004;28(suppl 1):S65-S69.
17. Grand FH, Burgstaller S, Kuhr T, et al. p53-Binding protein 1 is fused to the platelet-derived growth factor receptor beta in a patient with a t(5;15)(q33;q22) and an imatinib-responsive eosinophilic myeloproliferative disorder. *Cancer Res*. 2004;64:7216-7219.
18. Levine RL, Wadleigh M, Sternberg DW, et al. KIAA1509 is a novel PDGFRB fusion partner in imatinib-responsive myeloproliferative disease associated with a t(5;14)(q33;q32). *Leukemia*. 2005;19:27-30.
19. Ross TS, Bernard OA, Berger R, et al. Fusion of Huntingtin interacting protein 1 to platelet-derived growth factor β receptor (PDGFβR) in chronic myelomonocytic leukemia with t(5;7)(q33;q11.2). *Blood*. 1998;91:4419-4426.
20. Abe A, Emi N, Tanimoto M, et al. Fusion of the platelet-derived growth factor receptor β to a novel gene *CEV14* in acute myelogenous leukemia after clonal evolution. *Blood*. 1997;90:4271-4277.
21. Morerio C, Acquila M, Rosanda C, et al. HCMOGT-1 is a novel fusion partner to PDGFRB in juvenile myelomonocytic leukemia with t(5;17)(q33;p11.2). *Cancer Res*. 2004;64:2649-2651.

DOI: 10.1309/Y3Y5G01443AD5L48