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A Rare Case of Systemic Mastocytosis with Associated Hematologic Neoplasm (SM-AHN) Involving Chronic Myeloid Leukemia: A Case Report and Literature Review

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Patient: Male, 28-year-old
Final Diagnosis: Chronic myeloid leukaemia
Symptoms: Splenomegaly
Medication: —
Clinical Procedure: Bone marrow biopsy
Specialty: Hematology

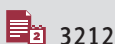
Objective: Rare co-existence of disease or pathology
Background: Single or multiple cell line dysplasia is a characteristic feature of myelodysplastic syndrome. However, significant dysgranulopoiesis is not a feature of chronic myeloid leukemia (CML). Systemic mastocytosis (SM) with an associated hematologic neoplasm (SM-AHN) comprises 5% to 40% of cases of SM. All types of hematologic neoplasms have been previously reported, although CML has been rarely encountered.

Case Report: A 28-year-old male presented with a 3-month-history of weight loss and massive splenomegaly. Peripheral blood revealed marked leukocytosis, shift to left with 13% blasts. There was evident dysgranulopoiesis that raised a provisional diagnosis of myelodysplastic/myeloproliferative neoplasm. Bone marrow (BM) examination revealed granulocytic hyperplasia with 10% blasts and significant dysgranulopoiesis. Unexpectedly, cytogenetic analysis revealed t(9;22) with *BCR/ABL1* rearrangement, diagnostic of chronic myeloid leukemia in an accelerated phase. The patient was started on dasatinib 100 mg upfront, however, he failed to respond, with increasing leukocytosis. Repeat BM examination showed persistence of the findings with 8% blasts. At this time, aggregates of mast cells with aberrant expression of CD25 were elicited, thus concluding the diagnosis of SM-AHN. The patient failed multiple lines of treatment (dasatinib, nilotinib, hydroxyurea, cytarabine subcutaneous, 6-mercaptopurine and interferon) and progressed to the blast phase a few months later.

Conclusions: We report an unusual case of CML, presented with significant dysgranulopoiesis with an aggressive clinical course including SM uncovered during the disease course with subsequent transformation to the blast phase. The different biological behavior of this case underscores the need for studies on a larger number of cases to explore the significance of the aforementioned coexistent features.

MeSH Keywords: Leukemia, Myelogenous, Chronic, BCR-ABL Positive • Mastocytosis, Systemic • Myelodysplastic-Myeloproliferative Diseases

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/923354>



Background

Mastocytosis is a rare heterogeneous disorder characterized by neoplastic proliferation of mast cells in the skin and/or visceral organs. Based on the tissue affected, mastocytosis is subclassified into cutaneous mastocytosis, systemic mastocytosis (SM), and localized mast cell tumor. The clinical behavior and prognosis of patients with systemic mastocytosis are variable, ranging from indolent to aggressive. The World Health Organization (WHO) classification identifies this by subdividing this entity into 5 distinct subgroups; indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL) [1].

In SM-AHN, the hematologic neoplasm can be diagnosed before, after, or concurrently with SM [1]. Depending on the study, the frequency of this category varies widely from 5% to 40% of all SM cases [2,3].

All types of hematologic neoplasms have been previously reported. However, myeloid disorders stand as the most common, and comprise 80% to 90% of the SM-AHNs, including myeloproliferative neoplasms, myelodysplastic syndrome, myelodysplastic/myeloproliferative neoplasms including chronic myelomonocytic leukemia, atypical chronic myeloid leukemia (CML), and acute myeloid leukemia (AML) [1,4]. Although SM is more frequently associated with myeloid malignancy, an association with CML is rarely encountered.

Single or multiple cell line dysplasia is a characteristic feature of myelodysplastic syndrome and may be seen as well in other hematologic neoplasms as in some cases of AML and in myelodysplastic/myeloproliferative neoplasm. Dysgranulopoiesis is not a feature of CML with only a few studies reporting dysplasia in the accelerated phase and less frequently reported in the blast phase CML.

The diagnosis of mastocytosis in bone marrow (BM) can be challenging especially when the aggregates of abnormal mast cell infiltrate are small or infrequent in the BM biopsy or masked by an associated hematologic malignancy. In this study, we reported a case of SM-AHN associated with CML that presented with unusual findings of severe dysgranulopoiesis features of disease progression, and poor response to treatment; we also provide a review of the literature.

Case Report

A 28-year-old male, not known to have any chronic illness, presented in 2018 with a 3-month-history of weight loss, fatigue,

and generalized tiredness. Physical examination revealed palmar and massive splenomegaly, 6 cm past midline. Peripheral blood analysis revealed severe normochromic normocytic anemia (hemoglobin: 6.1 g/dL), severe thrombocytopenia (platelets: $48 \times 10^9/L$) and severe leukocytosis at $119 \times 10^9/L$ with neutrophilia, eosinophilia, and basophilia. The patient's peripheral smear (PS) showed shift to left with the presence of different maturational stages of granulocytic cells (manual differential count showed: 59% segmented/band, 2% lymphocytes, 1% monocytes, 6% basophils, 5% eosinophils, 3% metamyelocytes, 7% myelocytes, 4% promyelocytes, and 13% blasts). There was evident dysgranulopoiesis noted in the form of pseudo Pelger-Huet nuclear hyposegmentation, nonsegmentation, hypersegmentation, miss shaped nuclear lobes, hypogranulation, and abnormal granular distribution that raised a provisional diagnosis of myelodysplastic/myeloproliferative neoplasm, possibly atypical CML (Figure 1). BM examination was recommended. Meanwhile, the patient was started on hydroxyurea (500 mg, orally, twice daily) and allopurinol (300 mg, orally, daily).

BM aspirate showed granulocytic hyperplasia with significant dysgranulopoiesis like those seen in peripheral blood with 10% blasts. BM biopsy reflected marked hypercellularity (~100% cellularity) with marked granulocytic hyperplasia and remarkably increased megakaryocytes with multiple dense clusters of micromegakaryocytes and abnormal paratrabecular localization (Figure 2A). Intrasinusoidal hematopoiesis noted with increased reticulin fibrosis (MF 1-2). CD117 immunostain included in the routine immunohistochemical (IHC) panel highlighted mildly increased mast cells (Figure 2B). Mast cell tryptase was requested then which revealed increased mast cells in a number that surpasses positivity for CD117; however, was scattered with no dense clustering (Figure 2C). No further workup for mastocytosis was conducted. Surprisingly, fluorescence *in situ* hybridization (FISH) analysis on peripheral blood revealed *BCR/ABL1* rearrangement, t(9;22) in 93.5% of cells, which was confirmed by karyotype that revealed Ph chromosome: 46,XY,t(9;22)(q34;q11.2)/ [20] (Figure 3) and real-time polymerase chain reaction (RT-PCR) revealed e13a2 *BCR-ABL1* gene fusion by single step RT-PCR.

Based on the detection of *BCR/ABL1*, a diagnosis of chronic myeloid leukemia in the accelerated phase associated with significant dysgranulopoiesis was made. The severe dysgranulopoiesis seen in this case was unusual and raised an interest to follow the patient's response to therapy and the effect of the dysgranulopoiesis on the patient's response to therapy and the patient's prognosis. The patient was started on dasatinib 100 mg as upfront therapy.

One month later, the patient developed dasatinib hematologic toxicity in the form of pancytopenia that required transfusions. The dasatinib therapy was stopped (drug holiday for

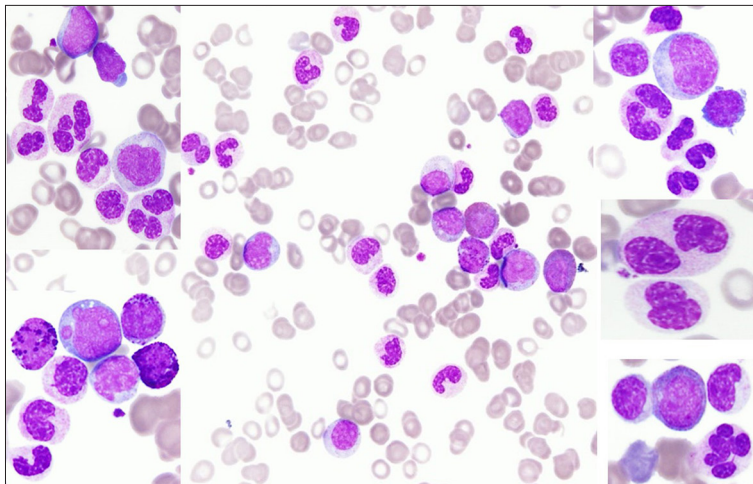


Figure 1. Peripheral smear shows leukocytosis with neutrophilia, eosinophilia, basophilia, shift to left and 13% blasts. There is evident dysgranulopoiesis; nuclear hypossegmentation, non-segmentation, hyper-segmentation, miss shaped nuclear lobes and hypogranulation (inserts). Wright stain 600× (inserts 1000×).

3 weeks), then restarted at 50 mg daily. The patient tolerated this dose well, however, follow-up 3 months later showed a white blood cell (WBC) of $5.7 \times 10^3/\mu\text{L}$ and BCR/ABL 82%, so he was shifted to nilotinib 300 mg twice daily. Then 2 months later, the patient had remarkable hyperleukocytosis, with WBC $260 \times 10^3/\mu\text{L}$, hence, he was started on hydroxyurea and a mutation analysis was requested.

One month later, the patient was admitted to the hospital with symptomatic anemia and persistent hyperleukocytosis. He received multiple packed red blood cells and platelets transfusions. He was started on low dose cytarabine subcutaneously to decrease the counts. Repeat BM examination was done, to exclude blast transformation. At the time of this BM examination, the peripheral blood still showed anemia (hemoglobin: 8.0 gm/dL), severe thrombocytopenia ($34 \times 10^3/\mu\text{L}$), and extreme leukocytosis ($287 \times 10^3/\mu\text{L}$) with marked neutrophilia, eosinophilia, and basophilia, shift to left with persistence of severe dysplastic features and increased blasts (12%). Evaluation of this BM showed persistence of remarkable hypercellularity with profound granulocytic hyperplasia with significant dysgranulopoiesis and 8% blasts. A BM biopsy revealed marked hypercellularity (~100%) with marked granulocytic hyperplasia including increased eosinophilic cells and Charcot-Laden crystals in the background and within macrophages (Figure 4A, 4B). Erythropoiesis was suppressed, and megakaryocytes were mildly reduced and there was no significant increase in reticulin fibrosis (grade 0–1). CD117 immunostain at this time highlighted increased mast cells, which were scattered and in aggregates (Figure 4C). This triggered the request for a secondary immunohistochemical panel (mast cell tryptase, CD25, and CD2) which highlighted phenotypically abnormal mast cells with aberrant expression of CD25, however, negative for CD2 (Figure 4D, 4E). Based on these findings, the diagnosis of SM-AHN was made. On re-examination of the BM aspirate smears, few morphologically atypical mast cells were recognized (Figure 4F), however, it was difficult to figure out

the mast cells as the BM showed increased basophilic cells of which many were morphologically severely dysplastic. The serum tryptase level in our case was elevated (122 mcg/L, normal <11). Repeated FISH continued to reveal *BCR/ABL1* rearrangement, t(9;22) in 98% of cells analyzed with the persistence of similar karyotype findings.

Mutation analysis on RNA extracted from peripheral blood reported a T315I mutation. Allele-specific oligonucleotide polymerase chain reaction (PCR) for KIT Asp816Val gene mutation was performed on peripheral blood (with a sensitivity of 0.01%) and the result was negative. Molecular profiling was performed on peripheral blood genomic DNA, enriched using a targeted myeloid panel of 66 genes (all or a subset of exons) together with Ion Torrent semi conductor sequencing. Clinically significant variants were assessed using the Association of Molecular Pathology (AMP) standards and guidelines for interpretation and reporting of sequence variants in cancer [5]. Apart from T315I mutation in the kinase domain of the ABL1 gene, no other mutations associated with myeloid neoplasia that were included in the panel we used were identified.

The increased mast cells in the BM at diagnosis raised the possibility that SM could have been there from the start, therefore, CD25 and CD2 were retrospectively performed on the initial BM biopsy and both were negative in the mast cells. The patient had no ascites/portal hypertension or impairment in liver function and no osteolytic lesion (SM-related C findings). The patient lost weight and became cachectic, but no endoscopy was done to document mast cell infiltration, if any.

Unfortunately, ponatinib was not readily available in our institute and had to be requested as non-formulary, at the same time results of HLA typing for the family were available and his sister was a full match. However, the disease had to be controlled with ponatinib before proceeding for transplantation. He was given 6-mercaptopurine (6-MP) and interferon but it did not help.

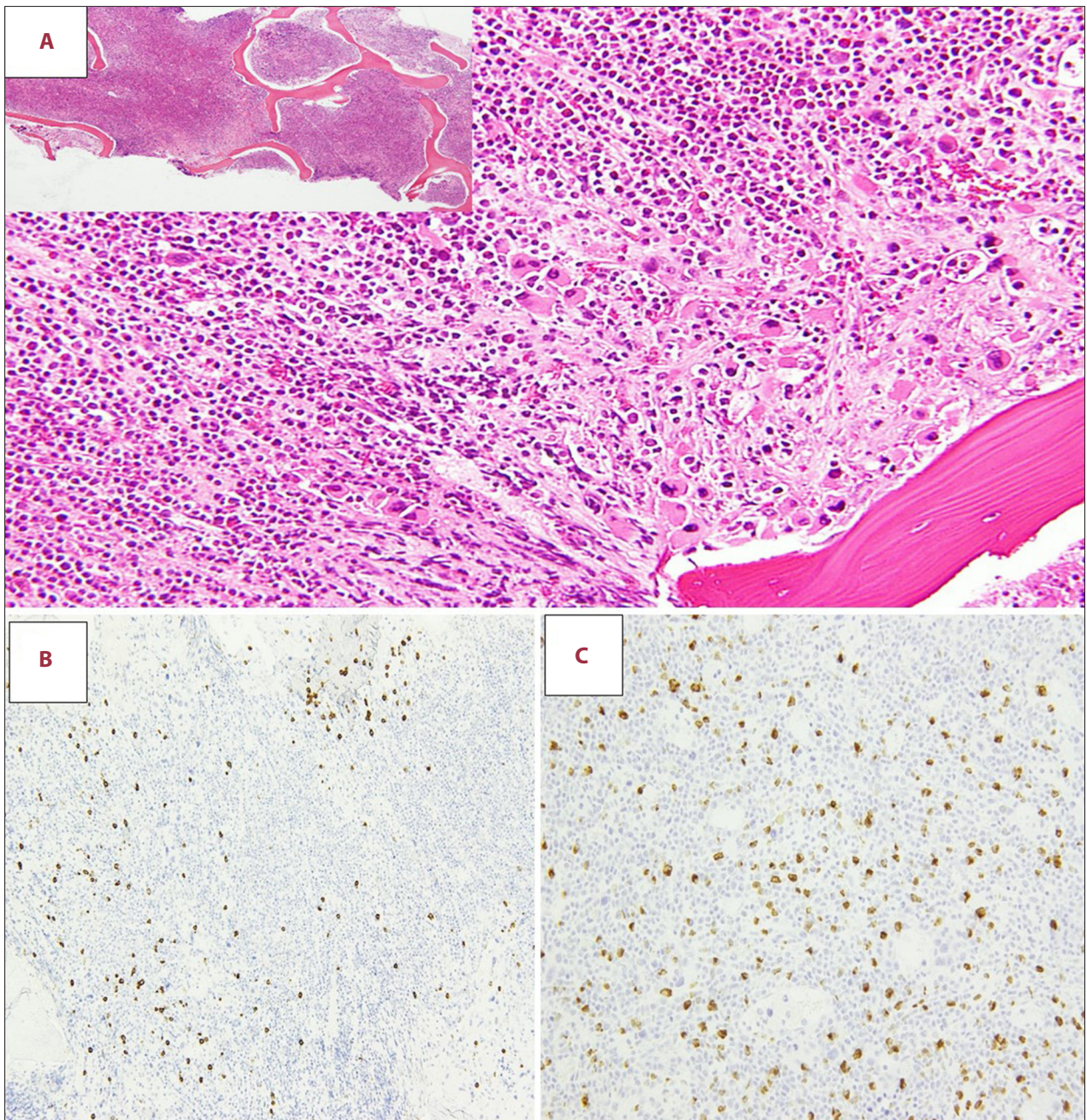


Figure 2. (A) Markedly hypercellular bone marrow biopsy with marked granulocytic hyperplasia and remarkably increased megakaryocytes with abnormal paratrabecular localization hematoxylin and eosin (H&E) 500 (insert H&E 40 \times). (B) CD117 immunostain highlights mildly increased mast cells (200 \times). (C) Mast cell tryptase shows increased mast cells; scattered with no dense clustering (200 \times).

Three months later, while still awaiting ponatinib, he was admitted with fever, still having low hemoglobin and platelets and hyperleukocytosis; he progressed to acute leukemia with 23% blasts in peripheral blood. The blasts were large with fine chromatin, prominent nucleoli, some were vacuolated, and some had cytoplasmic metachromatic granules (Figure 5). Flow cytometry on peripheral blood revealed 25% blasts expressing CD33, CD9, CD25, with a partial expression of CD13

and CD11c. A minority of cells express CD117 (heterogeneous) and there was a partial aberrant dim expression of CD5, CD4, and CD7 (Figure 4B). The blasts showed no significant expression of CD19, CD10, CD20, cCD79a, CD64, CD14, CD15, CD36, CD11b, HLA-DR, CD56, sCD3, cCD3, CD2, cMPO, TdT, CD34, CD41, CD61, and glycoprotein A (Figure 6). The immunophenotype raised a possibility of myeloid blast phase (favored by the absence of a specific T and B-cell markers and the expression

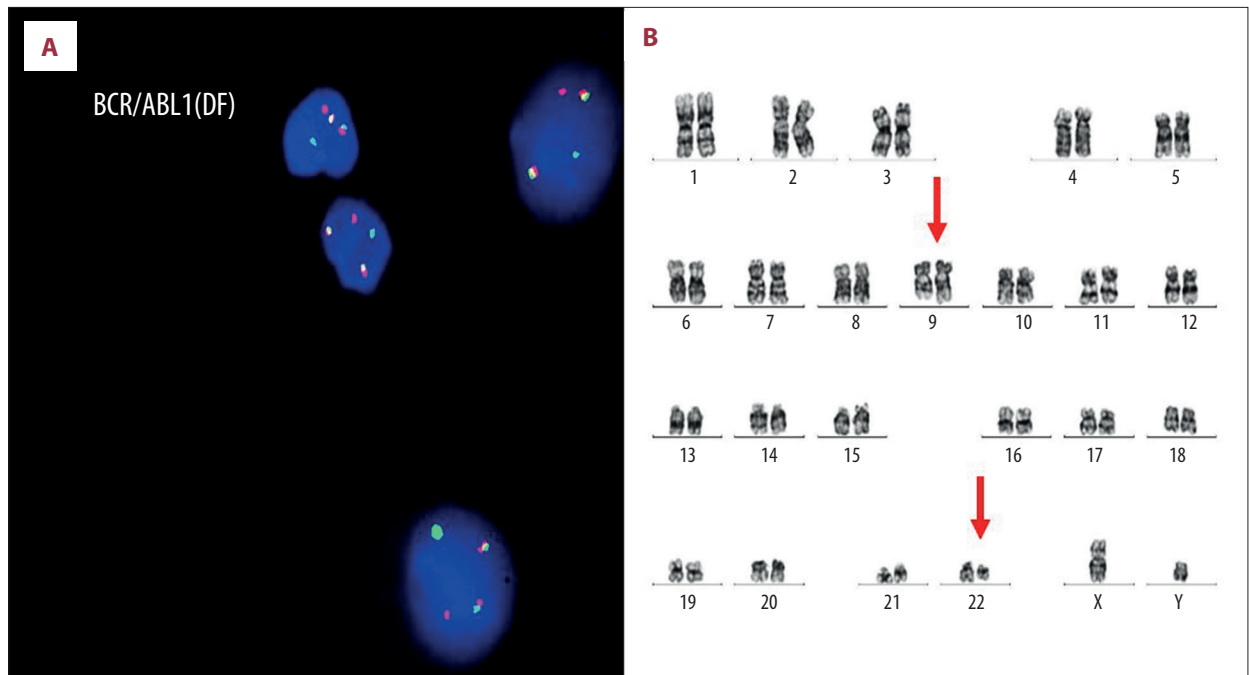


Figure 3. (A) Fluorescence *in situ* hybridization (FISH) analysis on peripheral blood revealed *BCR/ABL1* rearrangement, t(9;22) in 93.5% of cells analyzed. (B) Karyotype revealed Ph chromosome: 46,XY,t(9;22)(q34;q11.2)/ [20].

of CD33 with partial CD13 and CD117), possibly including mast cell precursors as well.

The patient had massive splenomegaly reaching the right iliac fossa. He was treated with AML induction protocol 3+7 (3 days idarubicin with 7 days cytarabine infusion), but his disease was refractory. During this time, he developed a severe neuropathic type of pain in his lower limbs; all investigations failed to show the cause. Two months later he was started on ponatinib. Another month later, due to massive splenomegaly and high transfusion requirements, a splenectomy was done. Best supportive care was then decided in agreement with the patient.

Discussion

Systemic mastocytosis with an associated hematological neoplasm (SM-AHN) is rather a common subtype of systemic mastocytosis. The diagnosis is established when WHO criteria for SM and a distinct non-mast cell hematologic neoplasm are met [1].

The WHO defines one major criterion: “multifocal, dense infiltrates of mast cells (≥ 15 mast cells) in bone marrow (BM) biopsy and/or other extracutaneous organs and 4 minor criteria for the diagnosis of SM: 1) more than 25% of mast cells in the aspirate smear or biopsy infiltrate display atypical morphology or are spindle-shaped; 2) codon 816 mutation of KIT in BM, blood, or other extracutaneous organs; 3) mast cells

aberrantly expressing CD25 and/or CD2; and 4) serum total tryptase levels persistently exceed 20 ng/mL (excluded from the criteria in cases associated with myeloid neoplasm, SM-AHN)”. The diagnosis is made when the major criteria and one of the minor criteria are present or 3 minor criteria are present.

In the case reported here, the criteria for the diagnosis of CML were fulfilled from the compilation of the peripheral blood and BM findings with FISH and karyotype results at the initial presentation. Whereas the diagnosis of SM was established on BM biopsy later in the disease course, 9 months after initiation of TKI therapy. SM diagnosis was based on the presence of multifocal dense infiltrates of mast cells (major WHO criteria) together with abnormal expression of CD25 (minor criteria). The serum tryptase level in our case was elevated (122 mcg/L; normal range < 11 mcg/L).

In SM-AHN, the clonal hematological non-mast cell lineage neoplasm may be diagnosed before, concurrently with, or after the diagnosis of SM. The diagnosis of SM using BM biopsy is usually difficult, as the compact mast cell infiltrates in the BM biopsy may be obscured/masked by the associated hematological neoplasm and due to the tendency of mast cells to localize within the stroma of the particles in BM aspirate [6]. In our case, the diagnosis of SM could not be made without the inclusion of CD117 in the IHC panel, since the patients did not show signs or symptoms related to mast cells mediator release that would raise the clinical suspicion of mastocytosis, and it was almost impossible to figure out morphologically atypical

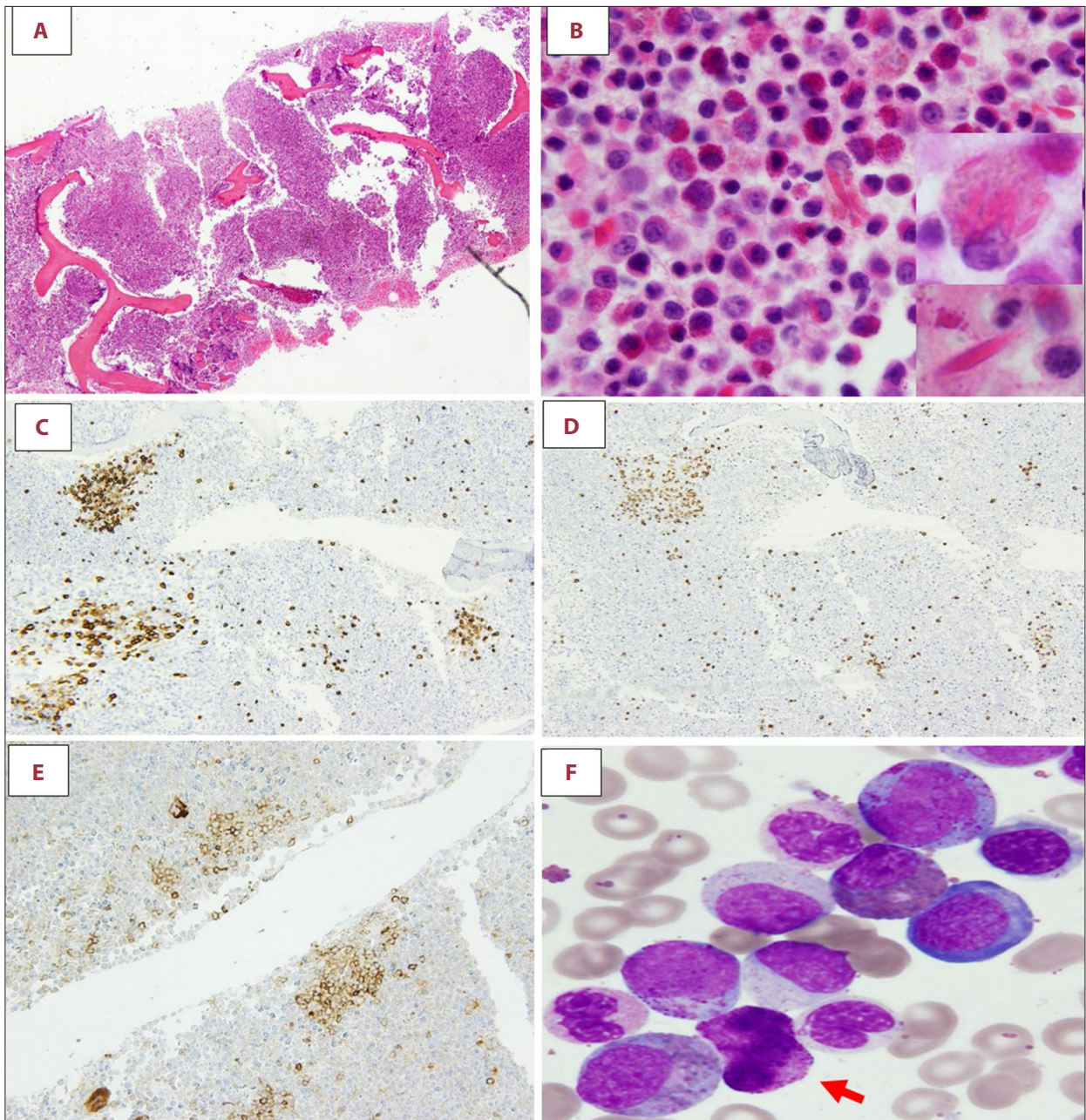


Figure 4. (A) Bone marrow biopsy is remarkably hypercellular; hematoxylin and eosin (H&E) 40×. (B) Marked granulocytic hyperplasia including increased eosinophilic cells, Charcot-Laden crystals in the background and within macrophage (2 inserts); H&E 1000×. (C) CD117 immunostain highlights increased mast cells, scattered and with multiple focal aggregates 100×. (D) Mast cell tryptase shows scattered and multiple focal aggregate of mast cells 100×. (E) CD25 shows aberrantly positive mast cells 100×. (F) Bone marrow aspirate shows morphologically abnormal mast cells (arrowed cells); Wright stain 1000×.

mast cells in the aspirate smears in the presence of the background of profound dysgranulopoiesis. Moreover, the atypical mast cells were not easily spotted on hematoxylin and eosin (H&E) sections of the core biopsy.

Systemic mastocytosis (SM) and chronic myeloid leukemia (CML)

Most cases of SM-AHN are associated with myeloid neoplasm. The most common being chronic myelomonocytic leukemia (CMML) followed by myelodysplastic syndrome, myeloproliferative neoplasms, AML, and ph-chromosome negative or

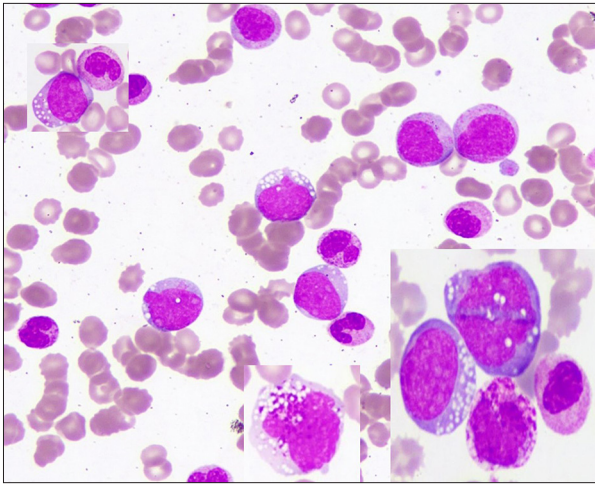


Figure 5. Peripheral blood shows leukocytosis with many blasts: large with fine chromatin, prominent nucleoli, some vacuolated and some with cytoplasmic metachromatic granules (insert); Wright stain 1000x.

atypical CML [4,7–10]. On the other hand, reports on SM in association with typical Ph chromosome-positive CML are scarce.

Agis et al. in 2005 [11] reported the first case of concurrent SM and CML in a 43-year-old female patient. The diagnosis of SM was based on the dense aggregates of spindle mast cells in the BM that aberrantly expressed CD25 and were positive for D816V KIT mutation. The mutation was only identified in microdissected marrow mast cells, not in the leukemic cells, a finding that led to the suggestion of 2 separate clones of

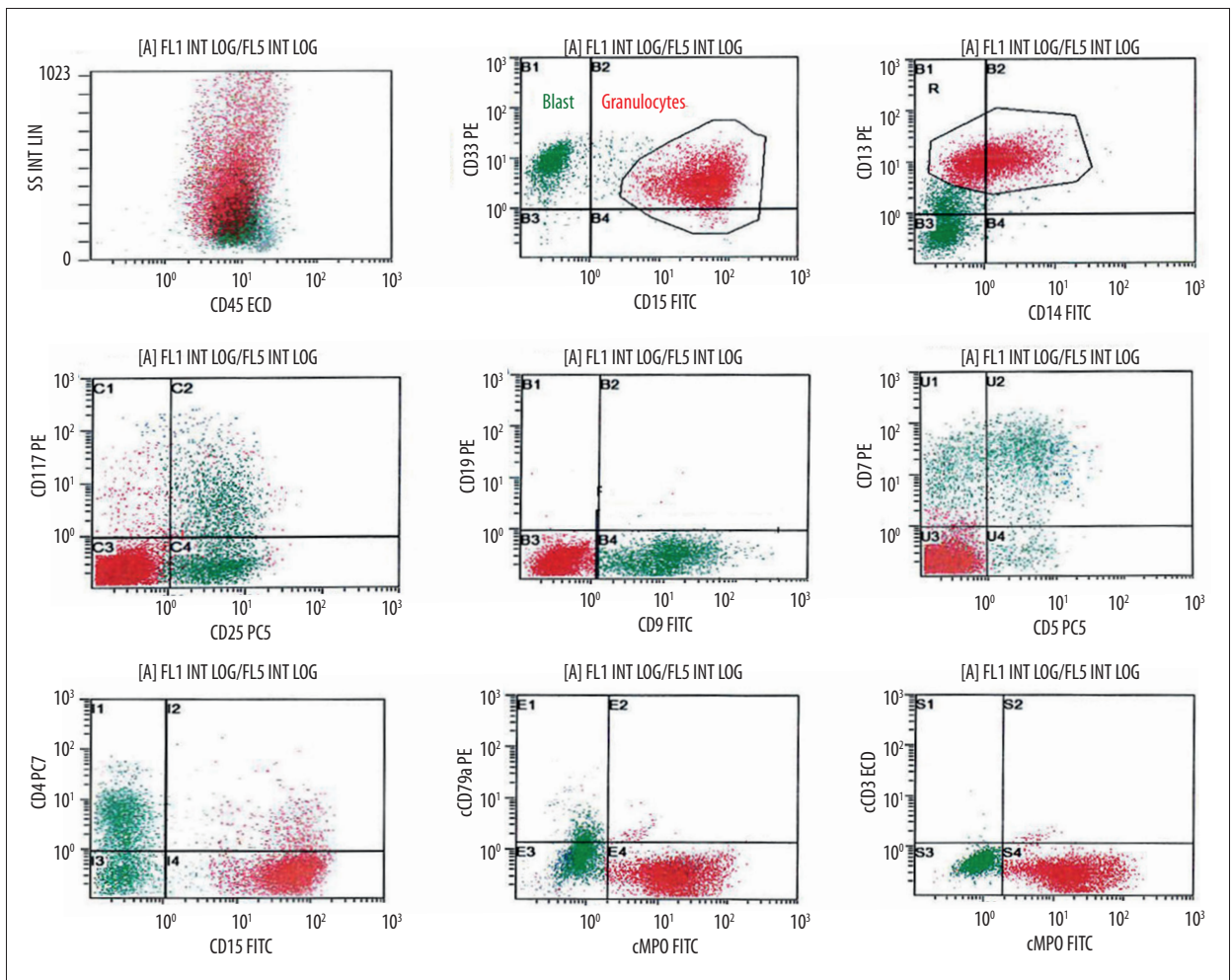


Figure 6. Flow cytometry on peripheral blood revealed 25% blasts (green) expressing CD33, CD9, CD25 with a partial expression of CD13, and CD11c (not shown). A minority of cells express CD117 (heterogeneous) and there was a partial aberrant dim expression of CD5, CD4, and CD7. Granulocytic cells (red) comprise 60%. The blasts show no significant expression of cMPO, CCD3, or cCD79a.

malignant cells in this patient. Although D816V activating KIT mutation is known to be resistant to imatinib [12], in the case reported by Agis et al. [11], treatment with imatinib led to complete hematological and cytogenetic remission of CML after 6 months and unexpectedly, no residual mast cells were detected in BM biopsy 18 months from diagnosis.

The second case was published a year later by Horny et al. in 2006 [13]. In their study on the significance of tryptase positive compact round cell infiltrate of the BM (TROCI-BM) in 88 cases of SM, 20 cases of CML, and 92 cases of other myeloid neoplasms, they came across a case CML concurrently having SM based on the demonstration of focal aggregates of phenotypically abnormal spindle mast cells. The case was positive for D816V KIT mutation.

Hussein et al. [14] in a 2011 retrospective study on BM samples from 82 CML cases, reported the third case of concomitant CML and SM. The diagnosis of SM was based on multifocal focal infiltrates of spindle-shaped mast cells aberrantly expressing CD25. The D816V KIT mutation was not identified in microdissected mast cells. Upon follow-up and while the patient was on imatinib, additional Ph, trisomy 17, and iso derivative Ph were also identified within the same CML clone. Using FISH technique, the authors failed to demonstrate t(9;22) and trisomy 17 in microdissected mast cells, suggesting no clonal relation between the mast cells and the leukemic clone.

The fourth case was reported in 2016 by Li et al. [15] in a 77-year-old male who was diagnosed with CML in November 2009 and who was started on imatinib (400 mg), and then shifted to dasatinib (100 mg) a year later due to disease progression. BM samples collected in June 2011 and February 2012 showed no morphologic evidence of CML, but revealed a complex karyotype including t(9;22). The patient's therapy was then changed to ponatinib therapy. In May 2013, the BM revealed morphological features suspicious for persistent CML. In addition, morphologically atypical mast cells with atypical immunophenotype by immunohistochemistry were detected (positive for tryptase, CD117, and CD25) with positive D816V KIT mutation, concluding a new diagnosis of SM-AHN.

In the current case, it was difficult to conclude confidently, whether the SM was concurrently present at diagnosis or developed later. Although IHC at diagnosis demonstrated increased mast cells in the biopsy, the diagnosis of SM-AHN was not met with the absence of dense aggregates and abnormal phenotype. It seems logical to assume that mastocytosis developed later during the disease course by clonal evolution. However, the possibility that both clones were there at the initial diagnosis, but that the mast cell clone was small and below the morphologic and immunophenotypic detection limit, could still be considered.

Studies on the clonal relationship between the mast cell and CML are still controversial. Studies done by Agis et al. in 2005 [11] and Hussein et al. in 2011 [14], as mentioned earlier, suggested 2 separate clones of malignant cells. On the other hand, Cairoli et al. [16] reported a case of CML in a 36-year-old male who, 5 years later, was found to have increased mast cells in the BM and D816Y variant mutation. As the mast cells were morphologically normal, the diagnosis of SM-AHN was not met. Monitoring of BCR/ABL level and KIT mutation post imatinib treatment demonstrated a simultaneous reduction in the BCR/ABL with the absence of KIT mutation. This led the authors to propose that BCR/ABL rearrangement and the variant KIT mutation might exist within the same cell clone. In keeping with this, Vigil et al. [17] reported a challenging case of CML which presented with an extramedullary blast phase in the form of different types of mast cell neoplasms, in whom treatment with dasatinib resulted in complete resolution of CML and the mast lesions, suggesting a single common clone rather than 2 different diseases.

Therefore, it seems that there is evidence both for and against the notion that SM associated with CML shares a single neoplastic clone. Further studies on a larger number of cases would be needed to clarify this. Unfortunately, studies addressing the clonal relationship between mast cells and CML clones were not conducted in our case study.

Chronic myeloid leukemia (CML) and dysgranulopoiesis

In comparison to the previously reported cases of SM in association with CML, our patient showed similar findings in many aspects, however, none of the previously published cases had dysgranulopoiesis. The severe dysgranulopoiesis noted in our case at the initial presentation raised a possible diagnosis of atypical CML, and the diagnosis of CML was reached only after the unexpected cytogenetic result. Severe thrombocytopenia seen at diagnosis is unusual in CML *per se* and in our case it was mostly a reflection of ineffective thrombopoiesis secondary to severely atypical/dysplastic megakaryocytes. The presence of 13% blasts in peripheral blood place indicates a case in the accelerated phase [18].

Dysplasia in different hematopoietic cells, including dysgranulopoiesis, is a characteristic feature of myelodysplastic syndrome, and it may be encountered as well in other hematologic neoplasms, such as in some cases of AML and in cases of myelodysplastic/myeloproliferative disorders. On the other hand, dysgranulopoiesis is not a feature of CML, and there have been only a few studies reporting dysplasia in the accelerated phase, and less frequently in the myeloid blast phase of CML [19,20]. Dysgranulopoiesis has been commonly associated with clonal evolution and secondary chromosomal abnormalities that often include abnormalities of 17p [20,21].

Furthermore, their appearance has been suggested to indicate impending disease progression [20,21]. Therefore, even with molecular monitoring, a vigilant morphologic evaluation of peripheral blood smears remains important for early detection of disease progression and subsequent timely treatment.

Conclusions

This is a report of an unusual case of CML that presented with significant dysgranulopoiesis with an aggregative clinical course including SM uncovered during the disease course with subsequent transformation to the blast phase. The SM in this case pointed to molecular heterogeneity with complex genetics that seemed to impact the patient's response to tailored tyrosine kinase inhibitor (TKI) treatment. The different

biological behavior of the current case may serve as a model of myeloid neoplasm with an overlapping feature of myeloproliferation, myelodysplasia, and systemic mastocytosis, underscoring the need for further studies with a larger number of cases to explore the significance of the aforementioned coexistent features.

Acknowledgments

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Conflicts of interest

None.

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