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CASE REPORT

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An unusual response to 5-azacitidine by a patient with chronic myelomonocytic leukemia

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Key Clinical Message

Hypomethylating agents may be useful in some but not all cases of myelodysplastic syndromes. In some versions of these conditions, this treatment may yield deleterious results.

Abstract

Chronic myelomonocytic leukemia (CMML) is considered to be a heterogeneous group of hematopoietic neoplasms. Usually it shares the features of myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) and is known as MDS/MPN. It occurs mostly in the elderly and has an inherent tendency to transform to acute myeloid leukemia. FDA has approved hypomethylating agents (HMAs) such as 5-azacitidine (AZA) and decitabine (DEC) for the treatment of this disorder. The extent of response rate to AZA varies considerably among patients. Our report describes a patient with CMML who not only did not respond to a conventional dose of intravenous (IV) therapy with AZA, but showed marked progression of the disease with the leucocyte count rising exponentially while undergoing the aforesaid treatment. We believe this is the first such case reported in the currently extant literature.

KEYWORDS

5-azacitidine (AZA), chronic myelomonocytic leukemia (CMML), decitabine (DEC), hypomethylating agents (HMAs), MDS/MPN, myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN)

1 | INTRODUCTION

CMML is considered to be a diverse hematopoietic stem cell disorder characterized by persistent peripheral blood monocytosis, bone marrow dysplasia with features of both myelodysplastic and myeloproliferative neoplasms (MDS/MPN).[1] It primarily affects older people (median age at diagnosis, 72 years). Approximately 30% of patients present with clonal cytogenetic abnormalities, while almost 90% have molecular aberrations involving epigenetic regulation, the spliceosome complement machinery, tumor suppressor genes and transcription factors/regulators.[2] Prognosis in general has been poor, with a median overall survival of 30 months and relatively high risk, up to 30%, of leukemic transformation.[3] HMA such as azacitidine has demonstrated a significant and clinically meaningful prolongation of survival in patients with CMML.[4] To the contrary, utilization of HMA in CMML has also been reported with seemingly unsatisfactory results, with an overall response rate between 30% and 60%

and median overall survival between 12 and 37 months.[5,6] In the case brought for analysis in this report, we describe an elderly patient with CMML (MDS/MPN) who was not only unresponsive to AZA, but showed progression of the disease as evidenced by exponential proliferation of the leukemic cells. This untoward result may bring to question the efficacy of AZA in certain patients with CMML.

2 | CASE REPORT

The patient was a 76-year-old white male with past medical history significant for nicotine dependence, COPD, hypertension and alcohol dependence, who presented to emergency department with the complaints of bilateral lower extremity swelling and shortness of breath that had been progressively worsening over the previous 3 months. The patient reported that the day prior to his admission he was very short of breath but without any abdominal or chest pain.

On initial evaluation, the patient was noted to be severely anemic with shortness of breath, but he was not in acute distress. He had bilateral lower extremity edema but there was no jaundice or cyanosis. His abdomen was soft and mostly non-tender. Bowel sounds were heard. The liver, spleen, and kidneys were not palpable. There was no palpable lymphadenopathy. Heart sounds S1 and S2 were identifiable, along with a soft ejection systolic murmur. His chest was clear to auscultation and vital signs were stable. The blood pressure was 125/70 mm Hg; pulse 72 PM; respiration 18 PM; temperature 97.6 F. The patient's B-Type Natriuretic Peptide (BNP) was elevated, and his chest x-ray showed vascular congestion without opacification. Laboratory studies revealed WBC 23.1×10^9/L; hemoglobin of 4.8 g/dL; normal MCV 93.7 fL; normal MCH (30.2 pg); and platelet count of 49×10^9/L. The patient denied the passage of black stools. He was transfused and admitted for further evaluation, diagnosis, and management.

Further work-up with a manual differential count of his peripheral blood smear revealed neutrophils 60%; lymphocytes 18%; monocytes and monocytoid cells 15% (Figure 1); absolute monocyte count 4.3×10^9/L (normal ≤1.0); neutrophil myelocytes 1%; metamyelocytes 2%; eosinophils 2%; basophils 1%; neutrophil bands 1%; and blast cells 2%. There was 1 nucleated RBC per 100 WBC. The peripheral blood smear revealed hypogranularity and hypolobation (pseudo-Pelger-Huet anomaly) of neutrophils, multinuclear, and bizarre nuclear forms (Figure 2). Red cells showed marked anisocytosis, a dimorphic blood picture, presence of ovalocytes, and macro-ovalocytes (Figure 3). The peripheral blood smear also displayed platelet clumps, platelet anisocytosis, and giant platelets (Figure 4). His serum iron level

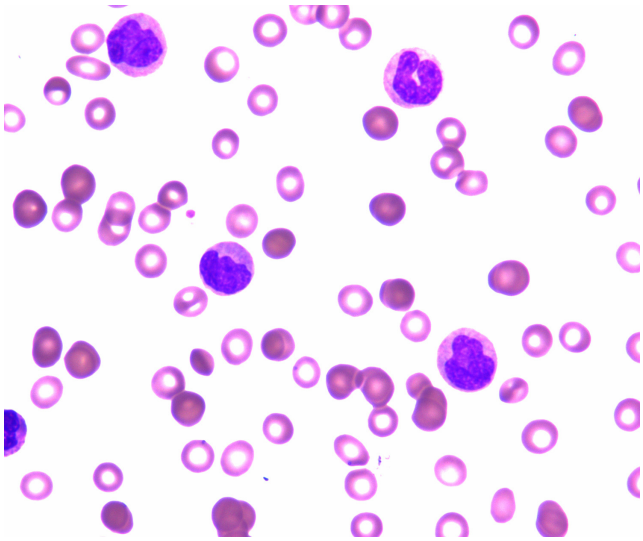

FIGURE 1 Peripheral blood smear showing an increased number of monocytes and monocytoid cells.

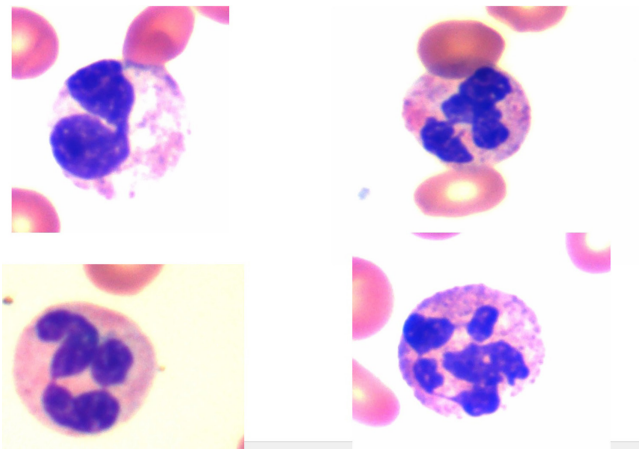

FIGURE 2 Peripheral blood smear showing dysgranulopoiesis. Note hypogranularity and hypolobation (pseudo Pelger-Huet anomaly—bilobed and "spectacle" forms), multinuclear and bizarre nuclear forms.

was raised, at 348 µg/dL (normal range 30–125). The total iron-binding capacity was normal at 336 µg (normal range 250–450) and the percent saturation was slightly high at 100% (normal range 20–55). His ferritin level was raised at 927 ng/mL (normal 30–400). Vit B12 was raised at 1309 pg/mL (normal 200–950) and folate level was normal at 39.5 ng/mL (normal ≥3.0). His reticulocyte count was normal at 1.8%, and the absolute reticulocyte count was normal at 31 (normal range 20–150). His erythropoietin level was markedly raised 2636 mU/mL (normal range 2.6–18.5 mU/mL). His complete metabolic profile was mostly normal except for the glucose level, which was slightly increased at 130 mg/dL (normal range 60–100 mg/dL). His JAK2 mutation was negative.

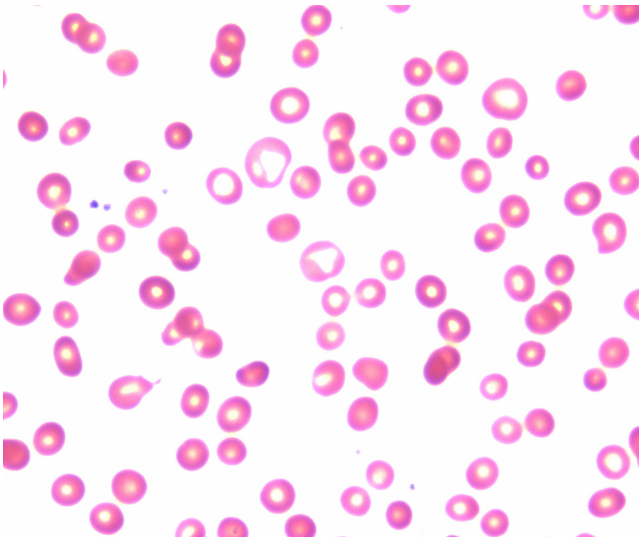

FIGURE 3 Peripheral blood smear showing dimorphic blood picture along with anisocytosis, poikilocytosis and presence of ovalocytes and macro-ovalocytes.

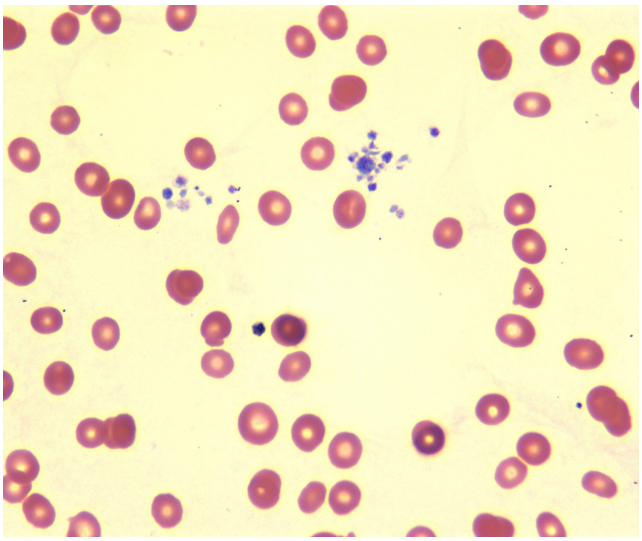

FIGURE 4 Peripheral blood smear showing platelet clumps, platelet anisocytosis, and giant platelets.

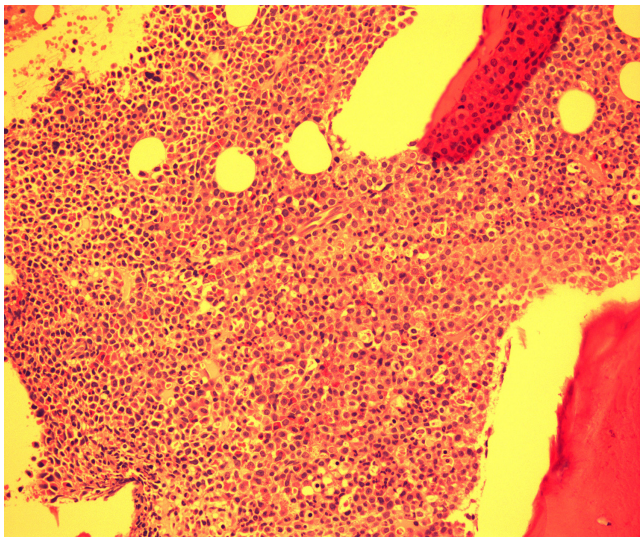

FIGURE 5 Bone marrow biopsy section showing a markedly hypercellular marrow (>90%).

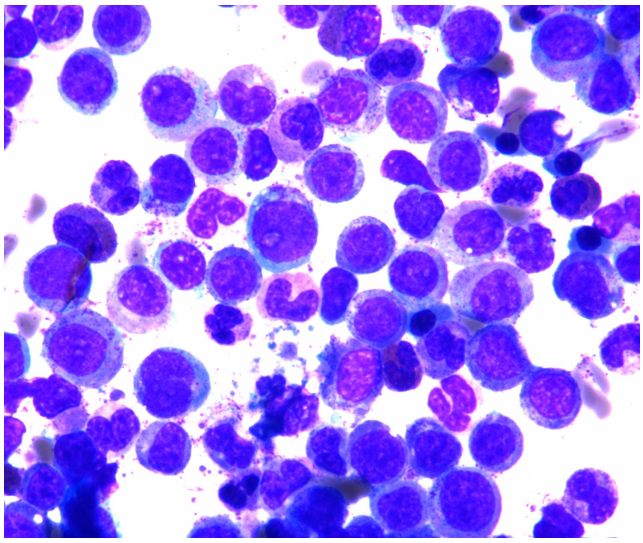

FIGURE 6 Bone marrow aspirate smear showing myeloid hyperplasia with blast cells.

The stool occult blood test X3 was negative and routine urine analysis was normal.

Because of leucocytosis, markedly low hemoglobin, moderately low platelet count, and abnormal cytologic findings in the peripheral blood smear, including monocytosis and markedly raised erythropoietin level, hematological malignancy was suspected, and the patient underwent a bone marrow examination. It revealed a markedly hypercellular (>90%) marrow for age (Figure 5) with myeloid hyperplasia, mildly increased frequency of blast cells (3%–5%) (Figure 6) and dysplastic changes in all three (erythroid, leucocytic, and megakaryocytic) cell lineages (Figures 7–9). The erythroid lineage was markedly reduced and displayed megaloblastoid change, binucleated erythroid precursors, inter-cytoplasmic bridging, altered nuclear cytoplasmic ratios, nuclear cytoplasmic maturation asynchrony, and nuclear budding (Figure 7). Myeloid changes included hypogranularity and hypolobation (pseudo-Pelger-Huet anomaly), multinuclear and bizarre nuclear forms (Figure 8). Megakaryocytes were decreased with some atypical forms including small hypolobated forms and rare forms with widely spaced nuclei (Figure 9). No ring sideroblasts were seen. Cytogenetic studies of the bone marrow showed a normal male karyotype and absence of BCR/ABL1 gene rearrangement.

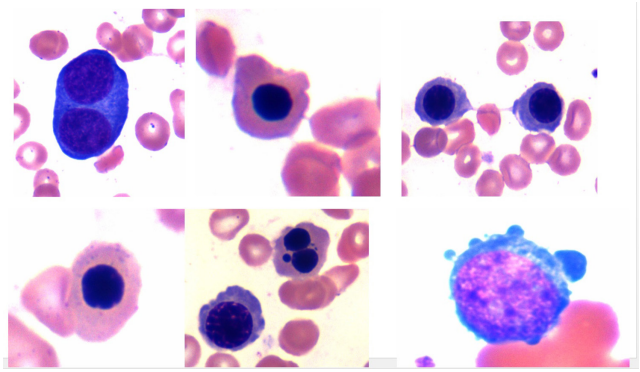

FIGURE 7 Dyserythropoiesis: bone marrow aspirate smear showing binucleated megaloblastoid erythroid precursors, cytoplasmic blebs, inter-cytoplasmic bridging, altered nuclear cytoplasmic ratios, nuclear cytoplasmic maturation asynchrony, nuclear budding.

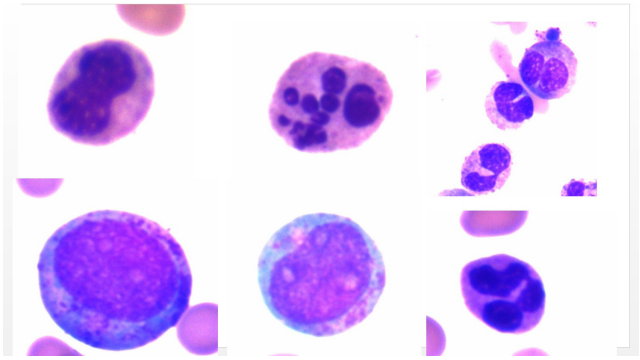

FIGURE 8 Neutrophilic dysgranulopoiesis that was observed in the bone marrow aspirate smear. Note the pseudo Pelger-Huet anomaly, bilobed and "spectacle' forms, and bizarre nuclei along with a blast and blast like cell.

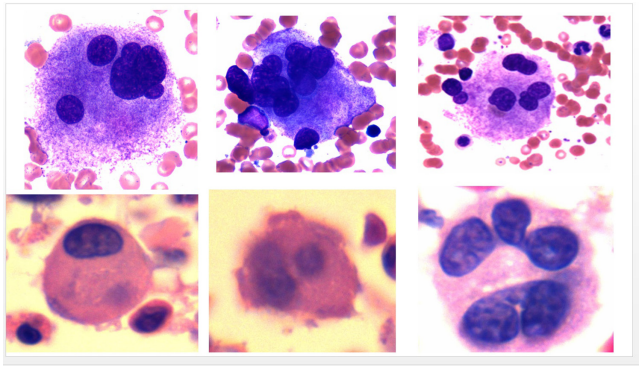

FIGURE 9 Dysmegakaryopoiesis: multi nuclear megakaryocytes, top row-bone marrow aspirate smear. Mono, bi and multi-nucleated megakaryocytes, bottom row, bone marrow biopsy section.

Flow cytometry studies of the bone marrow aspirate sample revealed a CD34 positive blast population, comprising 2% of total events, also positive for dim CD45,

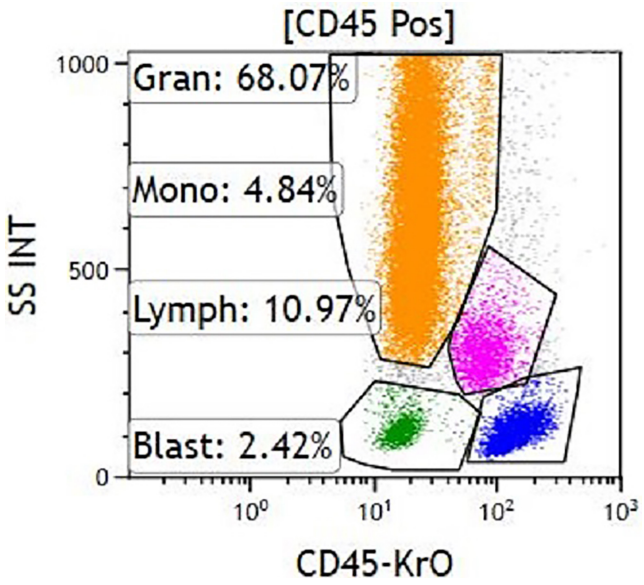

FIGURE 10 Cluster analysis of blasts using CD45/side scatter characteristics. Green, blasts; blue, lymphocytes; pink, monocytes; orange, granulocytes.

CD117, HLA-DR, CD33, and CD38 while negative for CD19, CD20, CD10, CD2, CD3, CD7, CD56, CD15, CD14, CD64, CD16, and CD11b. The granulocyte gate contained 83% of total events. The monocyte gate contained 4% of total events and consisted phenotypically of mature appearing monocytes (CD13, CD33, CD14, and HLA-DR) with partial CD56 expression (Figure 10).

No evidence was seen of MLL (KMT2A) rearrangement, and no abnormalities were detected in the following genes: FLT3, IDH1, IDH2, NPM1. But next generation sequencing (NGS) myeloid disorders profile revealed that he was positive for ASXL1, ETV6, EZH2, and SMC1A. Smears of peripheral blood and bone marrow aspirate were reviewed in the context of the molecular studies—ASXL1 mutations, found in 37% of chronic myelomonocytic leukemia[7]—and all together a diagnosis of CMML (MDS/MPN) was made.

Because of the patient's age (76 years) and a diagnosis of CMML-MDS/MPN with the presence of circulating and bone marrow blasts (3%–5%), presence of ASXL1 mutation, and the degree of anemia (transfusion dependent), thrombocytopenia, and rapidly increasing WBC count, the patient was considered at higher risk (IPSS-R score 3)[8] and was referred to hospice care. However, the patient's family declined this option and requested a treatment that did not involve chemotherapy.

At this point, the patient was started on hydroxyurea 500 mg orally three times daily, low-dose prednisone 20 mg orally daily, and epoetin (Procrit) 30,000 units subcutaneously once a week. The patient did not receive any other cytokines or chemotherapy. However, as his

TABLE 1 The hematological parameters of the patient following initiation of treatment with azacitidine (AZA).

	Day 1 of AZA treatment	Day 2 of AZA treatment	Day 3 of AZA treatment	Day 4 of AZA treatment
WBC (10^9/L)	104.8	239.9	384.2	473.5
Hemoglobin (g/dL)	8.3	7.8	7.2	7.0
Hematocrit (%)	27.3	25.5	23.5	25.0
MCV (fL)	83.5	94.8	92.8	83.9
MCH (pg)	28.3	27.3	26.3	22.6
Platelet (10^9/L)	20	23	21	25
Monocyte and promonocyte (%)	62	65	65	75
Blasts (%)	4	2	2	4
Promyelocytes (%)	0	0	0	4
Neutrophil (%)	10	12	5	4
Lymphocytes (%)	7	5	1	1
Basophils (%)	0	0	0	0
Eosinophils (%)	10	13	13	6
Myelocytes (%)	1	2	11	6
Metamyelocytes (%)	2	1	3	0
Bands (%)	4	0	0	0

WBC count continued to rise, the dose of hydroxyurea was increased to 1 g per oral three times daily to which he had a modest response, and his WBC count started to decline. Despite receiving epoetin 30,000 units subcutaneously once a week he remained blood transfusion dependent when lenalidomide (15 mg by mouth daily) was started. However, lenalidomide did not seem to have any significant effect on his blood transfusion requirement. With continued blood transfusions approximately every 2 weeks, his hemoglobin concentration and platelet count remained low—Hb ~8 g/dL, platelet ~40–60,000/μL—but stable, and did not require any platelet transfusion. The peripheral blood smear continued to show a small number (2%–4%) of blast and blast-like cells but no overt signs of leukemic transformation. However, despite high-dose hydroxyurea, his WBC count started to increase, rising to over 80,000 with 50% monocytes. He was then started with AZA 75 mg/m^2 intravenously daily for 7 days with allopurinol cover. On the first day of treatment his WBC count was 104,000; on the second day of treatment his WBC count was 239,000; on the third day of treatment his WBC count was 384,000; on the fourth day of treatment his WBC count was 473,000 (see Table 1). At this point it was clearly evident that the patient was not responding to AZA and the treatment was stopped. No further treatment was given and the patient was referred to hospice care where he died peacefully 3 days later.

3 | DISCUSSION

CMML is believed to be a distinct clinical pathologic entity recognized by the World Health Organization (WHO) and is characterized by: (1) persistent peripheral blood monocytosis $>1\times10^9$/L; (2) absence of the Philadelphia chromosome and the BCR-ABL1 fusion oncogene; (3) absence of the PDGFRA or PDGFRB gene rearrangements; (4) less than 20% blasts and pro-monocytes in the peripheral blood and bone marrow; and (5) dysplasia involving one or more myeloid lineages.[9] In recent years, CMML has undergone several revisions in its classification, reflecting the complexity of the disease.[10] By all accounts our patient met the contemporary diagnostic criteria for CMML. Currently no CMML-specific treatments exist. At present the treatment of CMML is largely restricted to unspecific use of cytotoxic drugs and hypomethylating agents (HMA). The treatment of CMML by HMA such as AZA was approved by the US Food and Drug Administration on the basis of a Phase III randomized trial conducted by the cancer and leukemia group B, for the treatment of myelodysplastic syndrome (MDS). In a retrospective study of 39 patients with CMML, AZA was found to be effective and well tolerated. Although our patient met the criteria for the diagnosis of CMML, the condition failed to respond to conventional doses of AZA. In fact, following the initiation of treatment, his WBC count rose and continued to rise (without frank blast cell transformation). Our study demonstrates that although

the diagnosis of CMML (MDS/MPN) can be effectively made on morphological grounds, there must be some inherent differences that made this patient's condition completely refractory to azacitidine. Perhaps this was because his blast cell counts were always low; in other words, he never showed a tendency for blast cell transformation. Numerous prognostic models exist for CMML, with more recent models incorporating prognostic mutations, such as those involving ASXL1. Other variables that seem to consistently affect outcomes include the degree of leukocytosis/monocytosis, anemia and thrombocytopenia.[11] Our patient did have mutations involving ASXL1 and persistent leukocytosis/monocytosis, anemia and thrombocytopenia, supporting the possibility that these features can affect the outcome and herald a poor prognosis.

It is believed that in appropriate circumstances, cytoreduction with hydroxyurea still has a role in the care of patients with CMML.[10] However, our patient did not respond even to very high doses (1 g per oral dose three times daily) of hydroxyurea. Unlike some typical MDS cases in which a combination of lenalidomide, steroid and erythropoietin have proven effective in reducing or even eliminating the need for repeated blood transfusion,[12] our patient failed to show any response to such therapy. The case presented here may be unique in that the patient was diagnosed correctly as CMML but failed to respond to any conventional therapy. We have found only one such report[13] where a modest (compared to the case presented here) myeloid leukocytosis/leukemoid reaction was observed in a patient after initial azacitidine therapy for a patient with CMML. It would be pertinent to know if any other investigators have encountered similar situations in which a patient with CMML not only did not respond to AZA, but in which, instead, the WBC count rose exponentially during the treatment.

AUTHOR CONTRIBUTIONS

Anwarul Islam: Conceptualization; formal analysis; investigation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Author elects to not share data

CONSENT

The author confirms that the patient consent has been signed and collected in accordance with the journal's patient consent policy.

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