An Unlikely Rapid Transformation of Myelodysplastic Syndrome to Acute Leukemia: A Case Report

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ABSTRACT

Introduction: Myelodysplastic syndrome is characterized by stem-cell-derived clonal myelopoiesis with an alteration in proliferation and differentiation. This condition carries a potential for transformation to acute leukemia, primarily in cases that are accompanied by high-risk features at diagnosis.

Case Presentation: A 68-year-old man with recently diagnosed myelodysplastic syndrome and Sweet syndrome (acute febrile neutrophilic dermatosis) presented to our Emergency Department with shortness of breath. During his hospital course, he developed signs and symptoms, predominantly consisting of respiratory difficulties, that were not typically characteristic of transformation to acute leukemia. Several days into his hospitalization, it was determined that the patient's underlying hematologic process seemed to have rapidly evolved into an acute myeloid leukemia, which accounted for the progression of symptoms. This patient ultimately opted for comfort measures only and died shortly thereafter.

Discussion: Two important factors stood out as representing an atypical presentation. First, this patient lacked any of the high-risk features of myelodysplastic syndrome that typically portend transformation. In addition, his progression to acute leukemia in 28 days from the time of diagnosis was far more rapid than the 274-day median previously described in the literature. We theorize that the presence of Sweet syndrome may have served as a predisposing factor to transformation. This finding may offer benefit to physicians to potentially better predict this outcome and pursue more aggressive treatment measures earlier in the course of the disease in such a setting.

INTRODUCTION

Myelodysplastic syndrome (MDS) is characterized by stem-cell-derived clonal myelopoiesis with an alteration in proliferation and differentiation. Various transforming mutations that affect hematopoietic stem cells can lead to different patterns of dysregulated signal transduction, bringing rise to phenotypic diversity.[1] The wide range of disease manifestations includes persistent alterations in cell lines that cause their respective complications, and paraneoplastic syndromes. Sweet Syndrome (SS; also known as acute febrile neutrophilic dermatosis) is a systemic inflammatory disorder that is typically characterized by high fever, leukocytosis, and tender regions of erythema.[2] Although it carries a link to MDS, malignancy-associated SS is most often associated with acute myelogenous leukemia (AML), with a temporal pattern revolving around the onset and relapse of underlying disease.[3,4] In some cases of MDS, a transformation to acute leukemia can take place. This typically affects patients with high-risk MDS features, with a median time to transformation of 274 days from initial diagnosis.[1,5] This case outlines an atypical presentation of an extremely rapid transformation to acute leukemia in a patient with MDS in the absence of high-risk features.

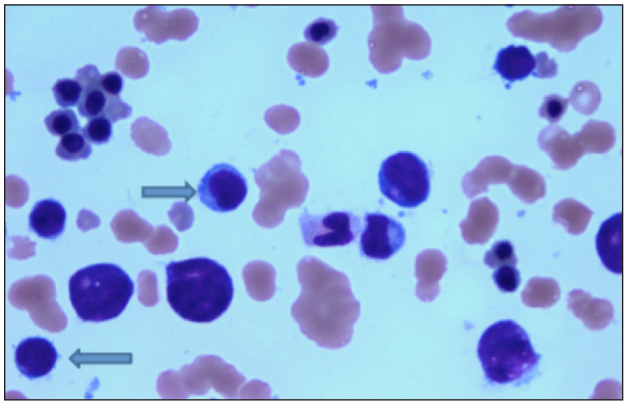

Figure 1. Bone marrow aspirate showing left-shifted granulocytes, including occasional atypical monocytes (arrows). Overall myeloblast percentage: 3% to 4%.

CASE PRESENTATION

Presenting Concerns

A 68-year-old man with a medical history of recently diagnosed MDS and SS presented to the Emergency Department (ED) with shortness of breath. About 1 month before this ED visit, he was hospitalized because of a similar presentation, in which painful skin lesions in his bilateral lower extremities also were noted. During that admission, he was found to be pancytopenic. Bone marrow aspirate and biopsy specimen were consistent with MDS without high-risk features (Figure 1). A skin biopsy specimen demonstrated SS (Figure 2). The patient was prescribed prednisone with a tapering dosage. His skin findings nearly resolved; however, his shortness of breath returned 2 weeks after discharge to home. A few days before representation to the ED, he was seen in an Urgent Care clinic, where he was prescribed oral antibiotics for treatment of a possible pneumonia. Despite this, his shortness of breath progressed.

On physical examination in the ED, the patient's vital signs were stable, and he had 100% oxygen saturation on room air. On auscultation, there were faint crackles (rales) at the bilateral bases

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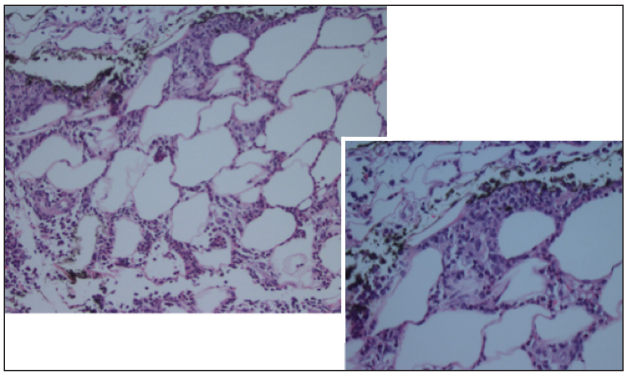

Figure 2. Skin (punch) biopsy showing subcutaneous atypical histiocytic/monocytic infiltrate with many neutrophils. The overlapping image is a magnification.

of the lungs. A small region of faint erythema was evident along his right lower extremity but was not tender. Results of laboratory tests showed a white blood cell count of 22,000/μL (15,000/μL 2 weeks earlier), hemoglobin level of 6.5 g/dL (baseline during the past month = 7-8 g/dL), and platelet count of 12,000 × 10^3/μL (baseline during the past month = 80,000-100,000). The white blood cell differential was as follows: neutrophils, 24%; bands, 1%; lymphocytes, 11%; monocytes, 12%; and eosinophils, 0%. The mean corpuscular volume was 100.6 $μm^3$. The result of the peripheral blood smear was unremarkable and unchanged from the laboratory test analyzed during the patient's hospitalization 1 month before.

A chest x-ray showed a mild infiltrate on the right middle lobe. A computed tomography scan of the chest demonstrated scattered, faint ground-glass opacifications with subcentimeter, reactive mediastinal lymph nodes.

Therapeutic Intervention and Treatment

The patient was started on a regimen of broad-spectrum antibiotics to treat a presumed pneumonia following the failure of outpatient treatment. Blood products were given as appropriate. Prednisone therapy was continued because of the possibility of an extracutaneous manifestation of SS. Written informed consent was obtained from the patient for blood transfusions and bronchoscopy.

Follow-up and Outcomes

On Day 2, the patient underwent bronchoscopy with bronchoalveolar lavage, but no biopsy was performed because of the risk of bleeding owing to thrombocytopenia. Normal airways were noted, with purulent secretion (easily suctioned) and friable mucosa. On Day 4, the patient's respiratory status began to worsen, requiring continuous oxygen administration via a nonrebreather mask (alternating with bilevel positive airway pressure) to maintain adequate oxygen saturation. Meanwhile, a repeated chest x-ray revealed worsening of the initial pulmonary infiltrate along with new, scattered infiltrates throughout both lung fields (Figure 3). Antifungal coverage was added to the antimicrobial regimen.

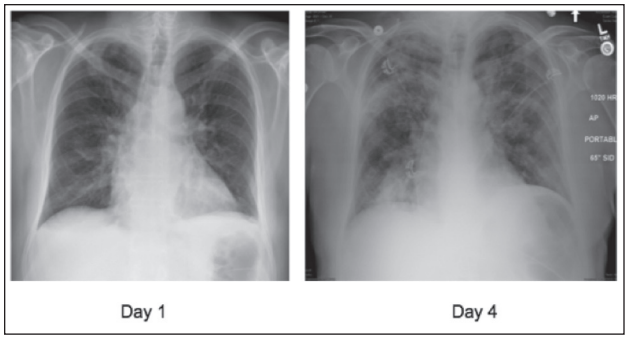

Figure 3. Anterior-view chest x-ray from Day 1 and Day 4.

On Day 5, the white blood cell count spiked to 67,000/μL (from 27,000/μL the day before), with monocytes predominant (33%). Cultures yielded no growth. A bone marrow biopsy could not be done because the patient was too unstable. A repeated peripheral blood smear specimen was collected. In the meantime, the prednisone regimen was switched to high-dose methylprednisolone to address the possibility of pulmonary SS. The peripheral blood smear result revealed monoblasts (Figure 4). Taking these findings into account, along with consideration for the underlying MDS and predilection for monocytes to deposit into tissues, it was determined that the presentation was secondary to an evolving AML with monocytic differentiation. The worsening pulmonary infiltrates were believed to be leukemic in nature as a result of a systemic transformation.

The patient and family were provided with our findings. They opted for a comfort-measures-only approach. The patient died less than 24 hours later. Figure 5 presents the case timeline.

DISCUSSION

MDS can transform into acute leukemia, which is often accompanied by a poor prognosis. This typically takes place in the refractory anemia that accompanies excess blasts-2 (RAEB-2) subtype or in non-RAEB-2 MDS, with excess blasts in the bone marrow, multilineage dysplasia, unfavorable cytogenetics,

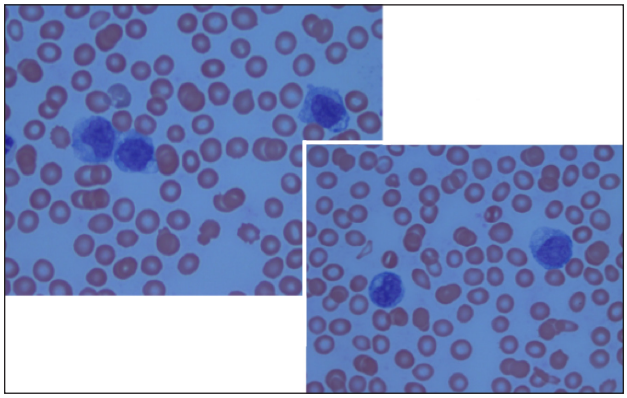

Figure 4. Peripheral blood smear revealing circulating myeloblasts. Findings are morphologically consistent with monoblasts, 32%. The overlapping image shows a separate portion of the same blood smear.

or lineage infidelity markers.[1] Such factors help to define the International Prognostic Scoring System and the World Health Organization classification-based Prognostic Scoring System.[5] Our patient did not fit under the category of high-risk at the time of diagnosis, carrying an International Prognostic Scoring System score of 0.5 because of cytopenias. The MDS-specific comorbidity index is another helpful tool that can add information to predict outcome.[6] On this index, our patient fit in the low-risk category.

Recent studies have shown a median time from the initial diagnosis of MDS to AML transformation (secondary AML) of 274 days (range = 16-4583 days). The time to transformation for our patient was 28 days. It has been noted that although many patients with secondary AML can tolerate aggressive-induction chemotherapy, the duration of response and chance of long-term survival are poor.[7]

This case demonstrated a transformation to acute leukemia in a manner that defied the typical presentation, in that it took place in the absence of high-risk MDS features and was very rapid. We bring to question whether SS represents a predisposing factor to AML transformation. Although it has been discovered that the most commonly SS-associated malignancy is AML[8,9] and an association does exist with myeloproliferative disorders and MDS,[10,11] research regarding a predictable progression to leukemia with underlying SS is lacking. Recently, *MEFV* gene mutations have been identified in patients with MDS and SS, which may lead to familial Mediterranean fever.[12] Studies that could potentially discover and link mutations to AML could help physicians to better predict deadly outcomes and pursue more aggressive treatment measures earlier in the course of disease in such a setting.

This case also reflects the value of the peripheral blood smear in helping to shed light on a complex situation. A quick and easy test to perform, the peripheral blood smear in this case allowed for a diagnosis to be made in a short time without invasive measures. We were able to provide fairly conclusive diagnostic information to the patient and family, allowing them an answer during a very difficult time. ❖

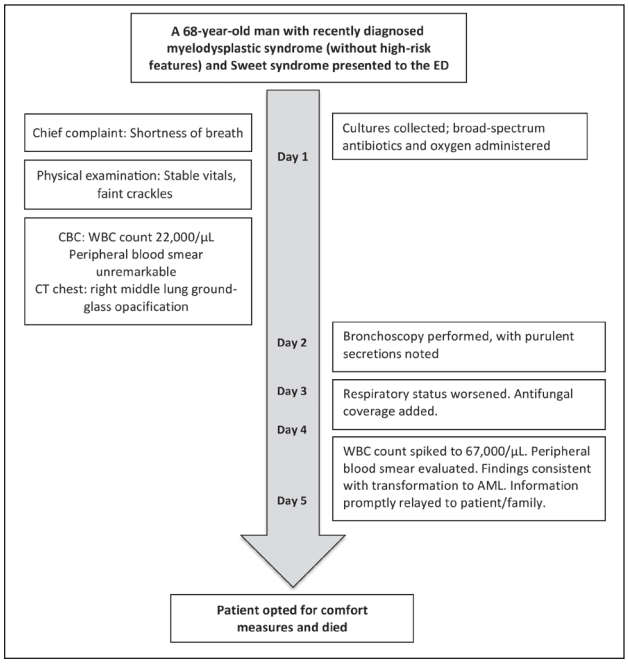

Figure 5. Timeline of the case.

AML = acute myelogenous leukemia; CBC = complete blood cell count; CT = computed tomography; ED = Emergency Department; exam = examination; vitals = vital signs; WBC = white blood cell.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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