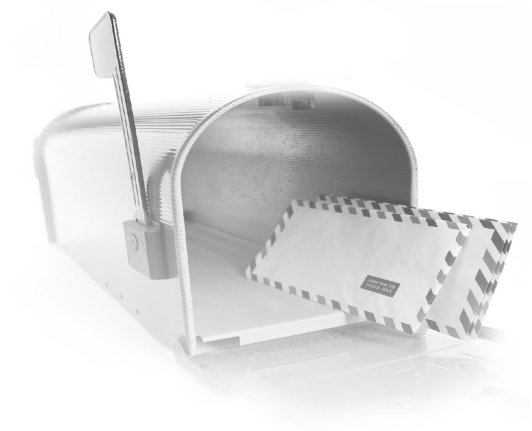

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Letters to the Editor

Acute myeloid leukemia arising from chronic myelomonocytic leukemia during hypomethylating therapy

TO THE EDITOR: Acute myeloid leukemia (AML) arising from chronic myelomonocytic leukemia (CMML) exhibits a poor prognosis [1, 2] and represents a great challenge during hematological clinical practice. The introduction of hypomethylating therapies, such as azacitidine [3, 4] and decitabine [5], in CMML management has provided some important advances; however, currently the majority of CMML cases progress into AML. We present the characteristics of 2 patients, in whom the atypical and sudden progression from CMML to AML was observed when they were administered azacitidine. Previously, both cases had achieved a very good response to this agent.

The first case is a 60-year-old man with a suspected therapy-related CMML, which arose 3 years after receiving chemo-radiotherapy treatment for a solid head and neck tumor. When diagnosed as having CMML, hypercellular bone marrow (BM) with 15% blasts was noted. Furthermore, the *JAK2* V617F mutation was identified by quantitative PCR analysis, whereas standard cytogenetic and FISH analysis using BM and peripheral blood showed no abnormalities (normal karyotype). The MD Anderson Prognostic Scoring System (MDAPS) [6] classification was 4 (high risk). The patient received azacitidine at a dosage of 75 mg/m^2 for 5+2 days (excluding weekends) every 4 weeks. After the fourth cycle of azacitidine, complete remission (CR) of CMML (BM blasts $<$5%) was recorded, although the patient continued the treatment during allogeneic hematopoietic stem cell transplantation. However, soon after the sixth cycle of azacitidine, a sudden evolution into AML (myelomonoblastic subtype) occurred. A very rapid transition from near normal peripheral blood counts to a very marked level of blastic leukocytosis was observed within 4 days: the WBC count was 120×10^9/L and 70% of myelomonoblastic cells were positive for HLA-DR, CD4, CD13, CD15, CD33, CD64, CD45, CD34, CD56, and CD117. Furthermore, an abnormal karyotype, i.e., 46,XY,del(7)(q31)[7]/46, XY[13], was found. FISH analysis confirmed a deletion of the long arm of chromosome 7 in 80% of blastic cells. Molecular studies detected the previously observed *JAK2* V617F mutation, as well as the *IDH2* R172K mutation; however, no AML-related alterations, such as *CBFb/MYH11, DEK/CAN, NPM1, FLT3*, and *RUNX1/ETO*, were identified. The patient received 1 course of chemotherapy for AML but soon died of disease progression.

The second case was a 72-year-old-man who was attended to because of pancytopenia with monocytosis. A BM aspirate and trephine biopsy showed hypercellular BM with 18% blasts, resulting in a diagnosis of CMML. The *JAK2* V617F mutation was detected and chromosomal analysis revealed an abnormal karyotype, i.e., 46,XY,inv(12)(p13.3q15). The patient was classified by MDAPS as high-risk. He was treated with azacitidine according to the same schedule reported above, achieving a hematological and cytogenetic CR after the sixth cycle. The hypomethylating regimen was continued for additional 7 cycles; however, before starting the fourteenth cycle, the patient complained of a sudden deterioration of his general condition. A marked peripheral blastosis (WBC=140×10^9/L) was identified and 90% of immature monoblasts were positive for the immunophenotype HLA-DR, CD15, CD33, CD64, CD45, CD34, CD56, and CD117. A diagnosis of AML (French-American-British classification: M5b) was made. The same karyotypic abnormality that had been detected when diagnosed as having CMML was again identified. Molecular studies showed no abnormalities. The patient's condition rapidly worsened, and he died a few days after AML diagnosis because of cardiac and pulmonary complications. He had not been able to receive any chemotherapeutic treatment.

In conclusion, we reported 2 atypical cases dealing with a sudden and devastating transformation of high-risk CMML into AML during azacitidine treatment while in CR. Although new effective treatments such hypomethylating agents have been introduced, CMML remains a severe and incurable disease, for which allogeneic hematopoietic stem cell transplantation represents the only potentially curative treatment [1]. The evolution into AML can be delayed, but not avoided, in patients treated with hypomethylators. Moreover, AML can arise from CMML during its natural

course [1]. AML transformation during hypomethylating therapy for CMML is quite common because of the lack of response to the hypomethylating agent and/or of disease progression [3, 7-9]. The present 2 cases did not provide any evidence that hypomethylating therapy is related to leukemic transformation, clonal selection, or evolution into AML. However, what makes these cases unusual is that the evolution into AML occurred within a few days without any prodromal clinical signs or anticipatory hematological features. Although presented with negative prognostic features both patients achieved a good response to the treatment; however, the responses were transient (2 and 7 months, respectively), and the particularly devastating evolution into AML was characterized by a rapid and prominent leukemic spread and a rapidly fatal clinical course. The biological and clinical features of AML transformation in patients who have received hypomethylators is not fully elucidated and understood; hence, further research into this issue is required to optimize the salvage treatment in this very challenging setting.

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A rare case of isolated myeloid sarcoma of the small gut with inv(16)(p13;q22) without bone marrow involvement

TO THE EDITOR: Granulocytic sarcoma (GS) or myeloid sarcoma (MS) is an extramedullary tumor comprising myeloblasts or immature myeloid cells. This type of tumor commonly occurs in subperiosteal bone structures of the skull, paranasal sinuses, as well as the sternum, ribs, vertebrae, pelvis, lymph nodes, and skin [1]. GS is frequently mistaken for non-Hodgkin lymphoma (NHL), small round cell tumors (neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma/primitive neuroectodermal tumor, and medulloblastoma), or undifferentiated carcinoma. The diagnosis is overlooked in about 50% of the cases when immunohistochemistry (IHC) analysis is not performed [2]. The most common diagnosis, suggested in these situations, is NHL [3]. MS may be the first manifestation of AML, preceding it by months or years, or represent the initial manifestation of relapse in previously treated AML in the remission stage [4]. Isolated MS, defined by the absence of a history of leukemia, myelodysplastic syndrome (MDS), or myeloproliferative neoplasm along with a negative bone morrow biopsy has been described in only a few case reports [5].

Here we report a case of a small gut mass that presented with features of intestinal obstruction necessitating exploratory laparotomy and resection anastomosis of a segment of the small gut. The mass was evaluated for lineage differentiation by IHC and the results correlated with clinicopathologic findings as well as cytogenetic and molecular studies.

CASE

A 27-year-old woman presented with recurrent, colicky abdominal pain associated with occasional vomiting for 2 months. There was no history of fever, jaundice, hematemesis, or melena. She had been hospitalized several times and treated conservatively. The patient was conscious, alert, oriented, and afebrile, and her vitals were within normal limits. No pallor, edema, jaundice, clubbing, or superficial