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Focal blast crisis in concomitant myelodysplastic syndrome and chronic myelogenous leukemia

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ABSTRACT

Leukemic transformation of myelodysplastic syndrome (MDS) or chronic myelogenous leukemia (CML) is a well-established phenomenon. However, co-occurrence of MDS and CML is a rare phenomenon, with few reports to date. Though blast crisis typically occurs systemically with MDS or CML, rare reports of focal transformation with myeloid sarcoma (MS) have been described. We present the first known case of concomitant MDS and CML on imatinib that developed focal blastic transformation, where the leukemic clone was BCR-ABL1 positive. Local irradiation and second-generation TKI was enough to attain long-term remission. Herein, we discuss MS and its implications in both CML and MDS.

1. Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal diseases of the bone marrow defined by the presence of disordered cellular maturation, with clinical, morphological, and genetic features that are shared by other myeloid disorders [1]. Myeloproliferative neoplasms (MPN), in contrast, are characterized by overproduction of a particular hematopoietic cell lineage. They are broadly categorized by the presence or absence of the Philadelphia chromosome, with its presence being pathognomonic for chronic myelogenous leukemia (CML). Overlap syndromes between MDS and MPN exist, such as chronic myelomonocytic leukemia (CMML). Though initially believed to be distinct biological entities, a significant degree of overlap in genomic abnormalities between MDS and MPN has blurred these definitions in recent years [1]. Despite this, MPN and MDS tend to occur separately. The presence of concomitant MDS and CML is an unusual and rare finding.

Both MDS and CML have the potential to transform into secondary acute myelogenous leukemia (sAML). The boundary between sAML and MDS has been somewhat arbitrarily defined and refined over time, with the presence of greater than 20% blasts on bone marrow biopsy presently defining sAML [2]. The adoption of treatment with imatinib has markedly reduced the incidence of blast crisis development in CML, estimated to be 0.7 to 4.5% annually, with a decreasing incidence after the first year [3]. When either disorder transforms into acute leukemia, it typically occurs systemically. Less commonly, transformation in either disorder can occur in an isolated anatomic area, known as myeloid sarcoma. Myeloid sarcoma is present in about 3-5% of all AML cases and is typically treated similarly to systemic AML with induction AML-like chemotherapy [4]. Herein, we discuss the first described case of concomitant MDS and CML that developed myeloid sarcoma, his treatment course, and its potential therapeutic implications.

In 2007, a 78-year-old gentleman presented for the evaluation of a progressively worsening macrocytic anemia. Bone marrow biopsy at that time demonstrated morphological trilineage dyspoiesis, consistent with myelodysplastic syndrome. Cytogenetics and karyotype were normal. Other causes of anemia were excluded and there was not evidence of granulocytosis or basophilia. In September 2009, his hemoglobin dropped to 8 g, with new onset granulocytosis with basophilia. Repeat bone marrow biopsy confirmed identical morphological findings to prior, consistent with MDS, but cytogenetics demonstrated a positive Philadelphia chromosome in 1 of 20 metaphases. Peripheral blood FISH

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demonstrated that 20% of the cells were positive for a BCR/ABL fusion transcript, confirming concomitant diagnosis of CML. He was started on imatinib and became PCR negative within 3 months, with return of his hemoglobin to baseline.

In May 2010, he noted discomfort in his left arm. X-rays demonstrated the presence of a large lytic lesion within the left humerus. He underwent humeral biopsy and operative fixation with intramedullary nail placement. Pathology demonstrated acute myeloid leukemia and FISH for *BCR/ABL1* was positive in the majority of cells, thus proving that it was a blastic transformation from the CML clone. Bone marrow biopsy performed at the same time of the blastic transformation demonstrated MDS with normal cytogenetics and was negative for BCR/ABL, thus proving that the blastic transformation was focal in nature.

He was treated with postoperative radiation and skeletal survey demonstrated no evidence of lytic disease elsewhere. Systemic chemotherapy was not pursued in his case owing to his advanced age at the time of diagnosis. Imatinib was changed to nilotinib 400 mg twice daily and maintained a major molecular response but developed a 10-fold increase in his pancreatic enzymes. He was then changed to dasatinib but, despite dose reduction to 80 mg daily, developed bilateral pleural effusions that required multiple thoracenteses and so in July 2012 was changed back to nilotinib at a lower dose of 300 mg twice daily, without recurrence of pancreatitis. He thereafter remained in major molecular remission and without local or systemic leukemic recurrence. For his anemia, he required darbopoetin q3-4weeks and his hemoglobin remained 11-12 g/dL. Though he remained in remission with respect to his blastic transformation, he ultimately died of pneumonia in 2014.

2. Discussion

Myeloid sarcoma (MS) is a fairly common finding in patients with AML, present in approximately 2 to 8% of patients and appearing at the time of diagnosis and 15 to 35% of cases. After the diagnosis of AML, it can be seen even more frequently, in up to 50% of cases. There is large variability in its phenotypic presentation. Age at presentation ranges from 1 to 81 years old, tumors can range from 2 to 20 cm in size, and most commonly it occurs at intramedullary sites. Of extramedullary sites, the skin is the most common site, seen in 54% of cases, and can be mistaken for non-Hodgkin lymphoma, malignant melanoma, and extramedullary hematopoiesis, or inflammation [5]. There is no definitive consensus on the treatment of MS, though the current recommended treatment regimen for AML with MS or isolated MS is conventional AML-type chemotherapy [4].

The development of myeloid sarcoma is less commonly seen in MDS and far less commonly seen in CML. The presence of MS in either of these two conditions is considered de facto evidence of transformation into acute leukemia. There are rare case reports of the two diseases occurring concurrently [6]. In a small study by Lan et al, the presence of accompanying CML or MDS was associated with a worse outcome as compared with MS seen with isolated AML [7]. To the best of our knowledge, our case is the first reported of MS appearing in a patient with concomitant MDS and CML and, despite the association of a less favorable prognosis with either condition separately, a good clinical outcome was able to be achieved with TKI therapy and radiation alone.

CML blast crisis is defined by a blast count of at least 20% blasts in the peripheral blood or by the presence of an extramedullary blast perforation such as a myeloid sarcoma. Of those in blast phase, 7 to 17% are found to have extramedullary disease at the time of diagnosis. In the post-imatinib era, the median survival of blast crisis was estimated at approximately 7 to 11 months [8]. According to the German CML Study Group, 3-year survival of imatinib-pretreated patients in blast crisis was 59%. However, with the progressive adoption of next-generation TKIs such as bosutinib and ponatinib, this will likely improve further [9].

3. Conclusions

In cases of blast crisis arising from both CML or MDS, delineatiation of the leukemic cell-of-origin is critical to determine proper therapy. As was seen in our case, analysis for the presence of BCR/ABL1 within the leukemic clone established that the MS arose from his underlying CML clone and not MDS. It is not known what resistance mutation was present, for our case predated resistance mutational testing. Systemic therapy was not pursued due to his advanced age at the time of diagnosis. Additionally, confirming the absence of BCR/ABL1 in his bone marrow corroborated that his blast crisis was focal in nature and was critical in determining treatment. The treatment with a second generation TKI and local irradiation to the MS site was enough to maintain disease control and preserve major molecular remission.

The best management of a blast crisis, and by proxy MS associated with CML, is to attain an prompt and considerable reduction and elimination of detectable BCR/ABL1 with TKIs, when possible [10,11]. In fit individuals, treatment with AML-type induction chemotherapy is felt to be standard. Surgical resection or radiation may be considered for local symptom relief. Local radiation to the site of disease improves failure-free survival but has not been shown to improve overall survival [12]. Nonetheless, it is still commonly performed for local control and symptomatic relief. Further systemic AML-type chemotherapy and/or consolidative allogeneic stem cell transplantation should be considered in disease not able to be controlled with TKI therapy alone [13]. Attainment of complete remission of MS prior to transplantation appears an essential factor for long-term remission following transplantation and optimization of long-term outcomes [14].

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