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Thoracic t(9;22)-Positive Granulocytic Sarcoma as Initial Presentation of Chronic Myeloid Leukemia

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Keywords

Granulocytic sarcoma; Chronic myeloid leukemia; t(9;22); *BCR-ABL*

Introduction

Granulocytic sarcoma (GS) is a rare type of soft tissue tumor consisting of myeloid immature cells and blasts that can occur at extramedullary sites. GS is an uncommon manifestation of acute myeloid leukemia (AML), but it can also occur in patients with other myeloid disorders such as chronic myeloid leukemia (CML). Nonetheless, it is very rare for a thoracic GS to be the first manifestation of CML. In this report, we describe a patient with CML who presented with a t(9;22)(*BCR-ABL*)⁺ thoracic GS. Interestingly, despite peripheral blood neutrophilic leukocytosis, both peripheral blood and bone marrow (BM) were morphologically and phenotypically normal despite exhibiting the t(9;22) translocation. With a combination of chemotherapy and nilotinib, the patient achieved a major molecular remission.

Case Report

A previously healthy 73-year old white man presented with progressive dyspnea of 2 weeks' duration. He reported intermittent fevers, night sweats, and weight loss. Blood test results showed a white blood cell count (WBC) of 52,000/ μ L (normal range [NR], 4500-11,000/ μ) with 94% neutrophils. Hemoglobin value was 14.9 g/dL (NR, 13.9-16.3 g/dL), and platelet count was 332,000/ μ (NR, 150,000-350,000/ μ). A computed tomographic scan of the chest showed a left-sided pleural effusion and multiple masses in the left side of the chest,

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Disclosure

The authors have stated that they have no conflicts of interest.

including a left parasternal mediastinal mass, left thoracic masses, and left axillary adenopathy. A core biopsy specimen from the parasternal mass showed fibroadipose tissue and atrophic muscle fibers dissected by an infiltrate of large cells with fine chromatin and moderate amounts of cytoplasm (Figure 1A). The nuclear contours were folded and irregular, consistent with monocytic differentiation. On immunostaining, these malignant cells were positive for CD34 (Figure 1B), CD117, CD33, CD43, and vimentin, were weakly positive for CD45, but were negative for CD3, CD5, CD20, CD30, CD138, kappa and lambda light chains, CD56, PAX-5, S100, and SMA. The Ki-67 proliferative index was > 80%. These findings were consistent with GS, so the patient was transferred to Johns Hopkins Hospital, where the pathologic diagnosis was confirmed. The WBC count was 25,000/ μ (differential: neutrophils, 89%; bands, 1%; metamyelocytes, 1%; lymphocytes, 4%; monocytes, 4%; eosinophils, 1%), hemoglobin value was 12.8 g/dL, and platelet count was 506,000/ μ . Peripheral blood film was noted for neutrophilic leukocytosis and thrombocytosis but without immature granulocytic precursors or blasts. BM examination showed hypercellularity (80%-90%) with trilineage hematopoiesis with no increase in blasts or dysplasia (Figure 1, C and D). The myeloid-erythroid ratio was increased at 5 to 10:1, but all 3 lineages showed full maturation, with most of the cells being maturing granulocytes. Flow cytometry analysis of the BM did not show phenotypic abnormalities. CD34⁺ blasts constituted less than 0.5% of cells. Computed tomography of the chest confirmed the left anterior parasternal GS, enlarged left axillary lymph nodes, and left-sided thoracic GS (Figure 1E). There was no mediastinal lymphadenopathy or hepatosplenomegaly.

Because of the recognized association of GS preceding AML, treatment with an antileukemic induction regimen using cytarabine and daunorubicin was started. However, after 3 days of chemotherapy, results of the cytogenetic analysis of the BM came back positive for translocation [t](9;22)(q34;q11.2) in 20 of 20 metaphases analyzed, without other karyotypic abnormalities, and FISH of the BM also showed t(9;22) in 100% of nuclei examined. Real-time quantitative polymerase chain reaction (PCR) of the BM revealed *BCR-ABL* transcript with an expression level equivalent to 488 copies per 1000 copies ABL, which corresponds to an International Standard *BCR-ABL1/ABL1* ratio of 137%. Given the extramedullary location of t(9;22)⁺ GS, these findings suggested a diagnosis of CML in blast crisis. Therefore, chemotherapy was stopped and the patient was prescribed the *BCR-ABL* tyrosine kinase inhibitor (TKI) nilotinib 400 mg orally twice daily, which he tolerated well. Nilotinib was chosen because the patient had had a big pleural effusion drained a few days earlier, and there was concern about effusion recurrence if dasatinib was used. Imatinib was not used because it was believed that a second-generation TKI was needed for a CML presenting with GS, which is a form of blast crisis.

Subsequently a FISH assay of the original parasternal GS biopsy specimen was positive for t(9;22)(*BCR-ABL1*) translocation in all 100 nuclei examined. By day 30, the WBC and differential count normalized, *BCR-ABL* evaluation by FISH was negative in all 200 nuclei examined, and *BCR-ABL* transcripts were less than the level of detection (< 0.05 copies *BCR-ABL1* per 1000 copies of ABL1) by real-time quantitative PCR assay, consistent with complete cytogenetic and major molecular responses. Computed tomography/positron emission tomography done on day 60 after diagnosis showed complete resolution of the GS

(Figure 1F) and complete metabolic response to therapy on positron emission tomography imaging. Three months after diagnosis, the patient continues to be in major molecular remission on nilotinib and is currently being evaluated for nonmyeloablative allogeneic bone marrow transplantation (alloBMT).

Discussion

GS is a rare type of soft tissue tumor consisting of immature myeloid cells and blasts found at extramedullary sites. The first case was described in 1811 and the term *chloroma* was used to refer to GS for first time in 1853.^{1,2} “Chloroma,” derived from the Greek word *chloros*, meaning green, reflected the characteristic green appearance resulting from the presence of the enzyme myeloperoxidase in the cells.^{3,4} In 1893, the association between the tumor and acute leukemia was made by Dock.⁵ The tumor was finally called *granulocytic sarcoma* by Rappaport in 1966 because not all the cells are green, depending on the concentration of myeloperoxidase in the cells.⁶ More recently, the World Health Organization reclassified GS and monoblastic sarcoma as 2 separate categories under the term *myeloid sarcoma*, because they are not always derived from granulocytes.⁷ GS can be very difficult to diagnose morphologically, especially in the absence of a history of or a concurrent myeloid neoplasm.⁴ The morphologic features of GS can mimic other malignancies and can therefore be misdiagnosed as lymphomas or other malignancies.^{3,4,8,9} Therefore, immunohistochemical stains and cytogenetic/molecular studies are important to establish the diagnosis.^{3,4,8}

GS can occur at any extramedullary site, but the most common sites include the skin and soft tissues, lymph nodes, gastrointestinal tract, and bone.^{3,8,10} Thoracic GS can present in different forms, including mediastinal masses, pleural effusions, and superior vena cava obstruction.^{3,8} Although GS is an uncommon manifestation of AML, it is acknowledged that it can precede, occur simultaneously, or follow the diagnosis of AML. Most patients presenting with aleukemic GS progress to a leukemic phase within 1 year of diagnosis.¹¹ The initial manifestation of relapse after alloBMT for patients with AML can be in the form of GS. It can also occur, although even more rarely, in patients with other myeloid neoplasms, such as myelodysplastic syndrome, myeloproliferative disorders, or CML.¹² Paydas et al reviewed 32 cases of GS, 11 of which were associated with CML. Six of the GSs were in patients with chronic-phase CML, 3 were in patients with accelerated-phase CML, and 2 were in patients with CML in blast crisis.⁸ It is very rare for GS to be the first manifestation of CML as in our patient. Although a few reports in the literature described patients with t(9;22)⁺ GS in the thigh, groin, nose, kidney, iliac bone, and larynx as the initial presentation of CML, we could not find other cases of thoracic GS localization or of response of t(9;22) GS to TKI therapy.^{4,8,11-15} Jenkins et al reported a patient who presented with an aleukemic right-sided groin GS.⁴ The BM evaluation of this patient showed only mild myeloid and eosinophilic hyperplasia without increased blasts, but, similar to our patient, the t(9;22)(q34;q11) and *BCR-ABL* fusion were detected on karyotypic and FISH evaluation of the BM. Testing of the groin GS for the *BCR-ABL* translocation was not done. In another report, Kuan et al described a patient who presented with nasal GS and whose BM examination was negative with a normal karyotype.¹² The patient received intensive AML-type chemotherapy but subsequently relapsed with scalp GS that was positive for

BCR-ABL fusion by FISH. Repeated BM examination, including cytogenetic and FISH analysis, was still negative. The patient's disease failed to respond to chemotherapy, radiation, or imatinib and died without a leukemic phase developing. Retrospective FISH analysis for *BCR-ABL* fusion of the original nasal GS could not be done.¹²

Conclusion

GS is generally sensitive to chemotherapy and radiotherapy, and most patients receive AML chemotherapy regimens.³ In patients with AML, GS has been reported to convey a worse prognosis, and prompt initiation of antileukemic treatment has been recommended in an effort to improve survival and reduce the leukemia transformation rate.^{3,9,10} In contrast to AML, CML is currently managed with TKI therapy, therefore raising the question of whether TKI monotherapy would be an appropriate initial treatment for aleukemic *BCR-ABL*⁺ GS or whether it should be used in combination with intensive chemotherapy. Given that the extra-medullary location in CML is associated with poor risk, consideration of second-generation TKI therapy and subsequent alloBMT is appropriate. The report by Kuan et al¹² suggests that evaluation of aleukemic GS for t(9;22)(*BCL-ABL*) translocation by FISH or PCR should be considered even in the absence of BM involvement by cytogenetic analysis or FISH.¹² In addition, our case suggests that patients with t(9;22)⁺ GS might respond to TKI therapy and therefore further supports consideration of testing of GS for *BCR-ABL* fusion.

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Clinical Practice Points

- Granulocytic sarcoma (GS) is a soft tissue tumor consisting of myeloid blasts that can occur at any extramedullary site.
- It is extremely rare for GS to be the first manifestation of chronic myeloid leukemia (CML). We present the first report, to our knowledge, of thoracic localization of t(9;22)-positive [t(9;22)⁺] GS as the initial presentation of CML.
- Evaluation of aleukemic GS for t(9;22) translocation by fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR) assays should be considered even in the absence of bone marrow (BM) involvement by cytogenetic or FISH analysis.
- t(9;22)⁺ GS might respond well to tyrosine kinase inhibitor (TKI) therapy and therefore further supports consideration of testing of GS for *BCR-ABL* fusion.

Figure 1.

(A) Mediastinal Biopsy Specimen Showing the Leukemic infiltrate, Indicated by Arrows, Composed of Immature Cells With Folded Nuclei and Moderate Cytoplasm. Arrowheads Depict the Hemophagocytic Histiocytes Engorged With Engulfed Red Blood Cells (H&E; Magnification, $\times 40$). (B) These Cells are Diffusely and Strongly Positive for CD34 (Magnification, $\times 20$). (C and D) The Bone Marrow Biopsy Specimen at Diagnosis Showed Maturing Trilineage Hematopoiesis With no Left Shift or Increase in Blasts (C, H&E; Magnification, $\times 40$; D, Diff Quick, Magnification, $\times 40$). (E) Computed Tomographic Scan on Initial Presentation Before Treatment Showing Granulocytic Sarcomas (GSs) in Chest and Left Axillary Nodes (Arrows). (F) Posttreatment Computed Tomographic Scan Showing Complete Resolution of the GS