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CASE REPORT

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Cutaneous Granulocytic Sarcoma Responsive to Imatinib in an Elderly Patient with Myeloproliferative Disease

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INTRODUCTION

Granulocytic sarcoma is a rare extramedullary malignant lesion comprised of primitive bone marrow cells of granulocytic origin first described in 1811 (1). The association with leukemia was not recognized until 1893 (2). Although initially coined “chloroma” in 1853 because of its characteristic green hue due to the presence of granulocyte myeloperoxidase, the term granulocytic sarcoma was coined by Rapaport in 1967 since up to 30% of these tumors can be white, gray, or brown rather than green (3). These lesions can be found in any part of the body but the most common sites are cortical bone, skin, CNS and lymph nodes. Several factors have been associated with a high incidence of granulocytic sarcomas. They include chromosomal abnormalities [t(8;21), inv(16)], cell-surface markers (CD56, CD2, CD4, CD7), French-American-British (FAB) subtype (M2, M4, M5), blast differentiation and maturation, poor nutritional status, age, cellular immune dysfunction, high presenting leukocyte count, and decreased blast Auer rods (4).

The diversity in anatomical sites of involvement by granulocytic sarcomas reflects specific circulating cell homing and adhesion surface receptors. Circulating hematopoietic precursor cells can adhere to dermal fibroblasts through specific surface receptors resulting in skin granulocytic sarcomas (5). Similarly, the propensity for CNS and spinal granulocytic sarcomas in AML with t(8,21) translocation is attributed to high expression of CD56. CD 56 is a homophilic (CD56 to CD56) binding adhesion molecule that is highly expressed in neural tissues and on t(8;21) myeloblasts (6-7). Clinically, these malignant lesions are commonly detected in the setting of acute myelogenous leukemia, either in the relapse setting or initial onset. Granulocytic sarcomas also occur in patients with myelodysplastic syndrome or myeloproliferative disorders in leukemic transformation.

Currently, the field of myeloproliferative disorders is enjoying a period of rapid discovery regarding their pathogenic mechanisms and an improvement in targeted therapies. As a result of this new understanding, novel, small molecules have been designed to inhibit receptor-related tyrosine kinases. These tyrosine kinase inhibitors inhibit ATP binding sites and prevent the phosphorylation and subsequent activation of growth receptors and their downstream signal transduction pathways (8). Imatinib mesylate inhibits tyrosine kinases encoded by the bcr-abl oncogene as well as tyrosine kinase receptors encoded by the c-kit and platelet-derived growth factor receptor (PDGFR) oncogenes (9). Inhibition of the bcr-abl associated-tyrosine ki-

nase results in decreased proliferation and enhanced apoptosis in malignant cells of Philadelphia-positive (Ph+) hematological malignancies such as chronic myelogenous leukemia and acute lymphocytic leukemia (10). Imatinib's effect on c-kit associated tyrosine kinase activity inhibit mast-cell and cellular proliferation in those diseases over-expressing c-kit, such as mastocytosis and gastrointestinal stromal tumor (GIST) (11).

We report here a case that illustrates the response to specific tyrosine kinase inhibition with imatinib in a patient with a myeloproliferative disorder with extensive cutaneous granulocytic sarcomas without overt bone marrow signs of leukemic transformation.

CASE REPORT

The patient is an 85 year old male with severe degenerative joint disease who underwent a right total knee replacement. He developed significant postoperative wound bleeding. His CBC showed a WBC of 18, hemoglobin 10.3 and a platelet count of 602K and a monocytosis of 30%. His prothrombin time was 17.6 seconds and his partial thromboplastin time was 46 second with full correction on 1:1 mixing studies. His DIC parameters were positive. He was treated with fresh frozen plasma and transfusion therapy successfully.

Because of his abnormal CBC findings, he was evaluated with a bone marrow biopsy which indicated a hypercellular marrow with 85% cellularity and a predominance of monocytes. The blast count was only 5%. Cytogenetics analysis indicated a normal male karyotype and flow cytometry showed no clonality. The bone marrow did show an immunohistochemical rearrangement involving the platelet-derived growth factor receptor beta (PDGFR B) gene. Four months later, he developed an intensely diffuse pruritic erythematous maculopapular rash involving trunk, back and extremities. A skin biopsy showed a granulocytic sarcoma consisting of immature myeloid cell showing positivity for the platelet derived growth factor receptor beta (PDGFR B). A repeat bone marrow biopsy failed to reveal any change in hypercellularity, monocytosis or leukemia transformation.

His pruritis intensified seeking help from his dermatologist without response. He was then treated with imatinib at 200 mg BID and tolerated it well. The patient experienced complete relief of his pruritis and the rash disappeared completely within 2 weeks,

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His leucocytosis and monocyte predominance resolved. He remained in hematologic remission for 4 months. He later died of sepsis due to an infected knee prosthesis. The photo depicts the extent of the granulocytic sarcoma rash before and after imatinib treatment.



DISCUSSION

Granulocytic sarcomas usually occur in one of three clinical settings. The first is in a de novo acute leukemic presentation. The second setting is in patients treated successfully for AML and therefore possibly heralding a leukemic relapse. The third setting is in the transformative phase of CML or other myeloproliferative or myelodysplastic disorders. Most reported series of patients with granulocytic sarcoma have been on leukemic patients and therefore, selective in the type of patient population (12 and 13). Neiman et al reported the only autopsy series of 61 cases of granulocytic sarcomas (3). In this series, 48% of the cases were associated with myeloproliferative disorders. The patient age range was from 2-81 years with a mean of 48 years. Thirty percent presented with no overt leukemia and 22% occurred as the initial presentation or during the course of AML. The most common sites of involvement were bone, periosteum, soft tissue, lymph nodes and skin. As illustrated by this patient who presents with a myeloproliferative disorder, it is possible that some cases of granulocytic sarcomas in patients with myeloproliferative disorders are possibly misdiagnosed or potentially ignored and treated as benign dermatologic lesions given the slower and protracted clinical and cellular dynamics typical of myeloproliferative disorders especially in older patient populations.

This case report also delineates the progress in the understanding of the pathogenesis of myeloproliferative disorders. For decades, myeloproliferative disorders were largely neglected disorders. The finding of the JAK2V617F mutation was the first discovery that lead to a much needed improvement in understanding the diagnosis and treatment of myeloproliferative disorders. JAK2 and its gene product are felt to be important in signaling transduction by members of the several receptor families and are implicated in polycythemia vera, essential thrombocythemia, and other

myeloproliferative disorders. This gene mutation, a change of valine to phenylalanine at the 617 position, appears to render hematopoietic cells more sensitive to growth factors such as erythropoietin and thrombopoietin (14). This mutation has joined the growing list of constitutively active tyrosine kinases identified as playing a role in myeloid neoplasms. With this new basic understanding, the current WHO criteria for myeloproliferative disorders are undergoing a revision to incorporate the diagnostic implications of the new wave of mutations (15). Investigations into targeted therapies for myeloproliferative disorders are proceeding at a brisk pace with agents aimed at inhibition of tyrosine kinases, decreasing stromal reaction to aberrant clones and immunomodulation of the marrow microenvironment. This case report emphasizes the potential impact of one of these new targets in myeloproliferative disorders.

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