

A Case of Chronic Myeloid Leukemia with Multiple Chloromas Treated Successfully with Dasatinib

Won Young Jang, M.D., Sei Myong Choi, M.D., Myeong Soon Park, M.D.,
Byung Chan Ahn, M.D., Mi Hwa Heo, M.D., Jin Young Kim, M.D., Ki Young Kwon, M.D.,
Young Rok Do, M.D.

*Division of Hemato Oncology, Department of Internal Medicine,
Keimyung University School of Medicine, Daegu, Korea*

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Corresponding Author: Young Rok Do, M.D.,
Division of Hemato Oncology,
Department of Internal Medicine,
Keimyung University School of Medicine,
56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
Tel: +82-53-250-7719
E-mail: dyr1160@dsmc.or.kr

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Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the primitive hematopoietic stem cells. CML is characterized by the overproduction of myeloid cells, which results in marked splenomegaly and leukocytosis. CML presented by multiple chloromas is extremely rare. Multiple chloromas in the skin and brain are quite rare as the initial presentation of CML. These rare manifestation should alert clinicians to include CML in the differential diagnosis of patients presenting with multiple non-pruritic skin nodules or neurologic symptoms. Dasatinib has promising therapeutic potential for managing intracranial leukemic disease. Here, we report the case of a patient who visited the hospital with multiple chloroma which is unusual presentation of CML, and treated with dasatinib successfully.

Key Words: Chloroma, Chronic myeloid leukemia, Dasatinib

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of primitive hematopoietic stem cells that manifests as overproduction of myeloid cells results in leukocytosis and marked splenomegaly. CML is arised by cytogenetic abnormalities in the form of fusion products of *BCR-ABL1* oncogenes. Granulocytic sarcoma is a tumor composed of immature cells of the granulocyte lineage and derived from an extramedullary mass. It is called chloroma since the color of tumor tends to green due to the presence of myeloperoxidase [1]. Patients with granulocytic sarcoma usually accompanies acute myeloid

leukemia and is more rarely found in myelodysplastic syndrome, CML, and other myeloproliferative disorders [2]. CML that manifests as multiple granulocytic sarcoma at an early stage is very rare. In fact, this usually develops during blast crisis and the occurrence of which is reported to suggest poor prognosis [3].

In CML, granulocytic sarcoma frequently occurred in the lymph nodes, skin, and soft tissues, but invasion of the central nervous system is extremely rare. Here, we report the case of a patient visited emergency room presented by multiple granulocytic sarcoma, and diagnosed as CML, *BCR-ABL1* positive.

Case Report

A previously healthy 37-year-old woman visited hospital presented with dizziness, and progressively aggravated headache. She experienced dizziness and right side headaches for 2 weeks, and then gradually spreaded to both sides. She had not felt any fever, weight loss, and night sweats. On physical examination, her vital signs were blood pressure, 130/80 mmHg; pulse, 120/min; respiratory rate, 20/minute; and body temperature, 37.8°C. Her general condition was fair but, her conjunctivas were pale. Abdominal examination revealed that the spleen was palpated 14 cm below the costal margin. There were 7 × 7 cm hard masses with relatively distinct edges located on both sides of the precordium, and about 5 cm masses on the right calf and left thigh, respectively. A neurological examination was done and showed no significant abnormalities.

Result of blood test showed the followings: leukocyte count, $57.7 \times 10^3/\mu\text{L}$; hemoglobin, 6.7 g/dL; platelet count, $395 \times 10^3/\mu\text{L}$; hematocrit, 20.1%; and reticulocyte, 6.67%. A differential counts of leukocyte showed 37% myelocyte, 8% promyelocytes,

6% metamyelocytes, 5% blasts, 10% band forms, 30% neutrophils, 1% lymphocytes, 1% basophils, 2% eosinophils. Peripheral blood smear test was done and showed absolutely increased in number of white blood cells with various stage of maturation (Fig. 1). Urinalysis and electrocardiograph results were normal.

Magnetic resonance imaging of brain revealed a 16 × 10 mm mass with relatively distinct edges in the right frontal lobe and two 15 × 20 mm masses with the same characteristics in the left cerebellum (Fig. 2A). Thoracic computed tomography showed two 7 × 7 cm masses with indistinct edges on the skin over the precordium (Fig. 3).

A bone marrow aspiration showed marked proliferation of myeloid cells occupying most of the marrow space and the marrow cells almost replaced by myeloid cells. And the numbers of other lineage of cell were dramatically reduced. A bone marrow biopsy showed abnormal cellularity in which cell fidelity reached up to 95% and abnormal infiltration of mature myeloid cells were observed. The diagnosis of chronic phase of CML could be obtained since cells of the myeloid and erythroid lineages as well as

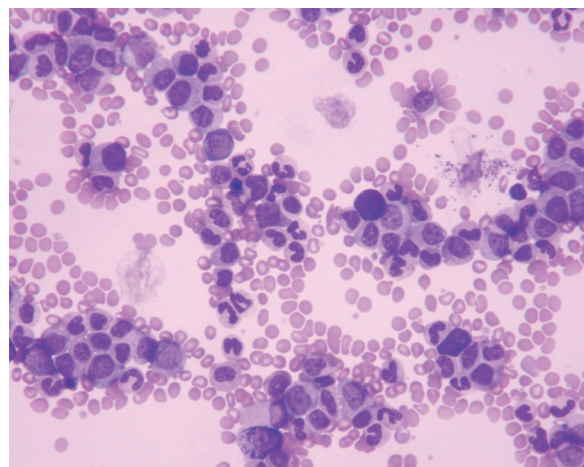


Fig. 1. PB smear shows that myeloid cells are markedly increased and various stages of maturation form.

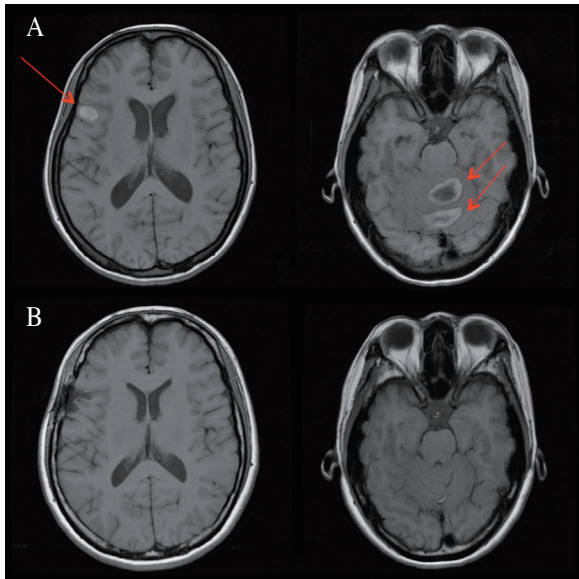


Fig. 2. (A) Multiple masses in the right subcortical area of the frontal lobe and the left cerebellum on brain MRI, T1WI (Arrow). (B) The previous masses were almost disappeared after 6 months dasatinib therapy.

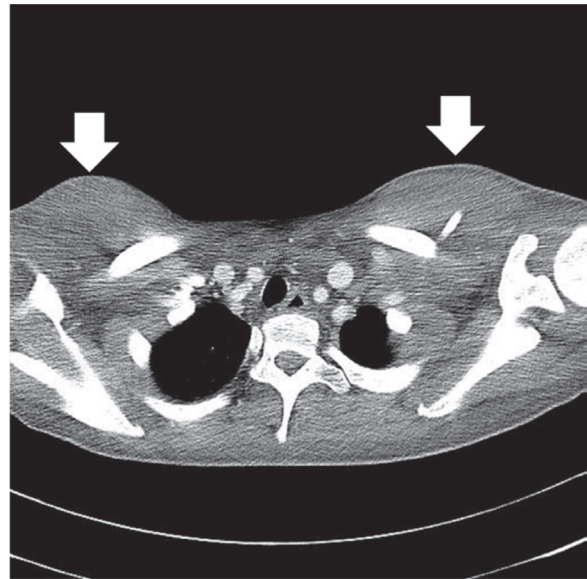


Fig. 3. Two ill-defined poorly enhancing mass-like lesions on the anterior side of both clavicles at chest CT scan.

megakaryocytes were also increased (Fig. 4). On cytogenetic study, karyotype with G banding study was 46,XX,t(9;22)(q34;q11.2) with Philadelphia chromosome positivity.

A skin biopsy of the precordial mass showed

infiltration of atypical hematopoietic stem cells, while the immunohistochemical staining represented myeloperoxidase positive, leading to diagnosis of granulocytic sarcoma (Fig. 5). Furthermore, an excision biopsy was conducted on the intracranial

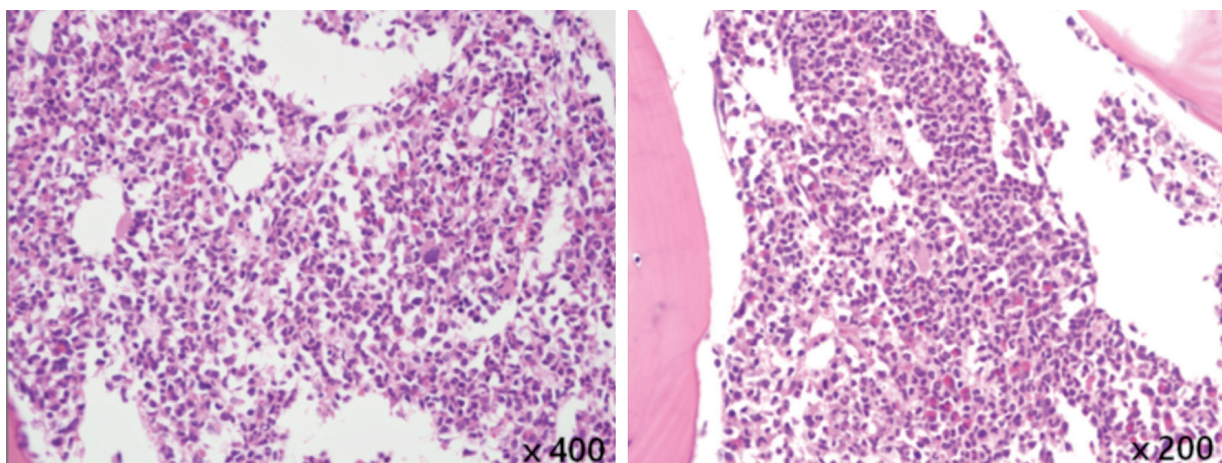


Fig. 4. Bone marrow biopsy showed hypercellular marrow (> 95%) with infiltrating an atypical mature myeloid cells. Myeloid, erythroid and megakaryocyte cell series are also increased.

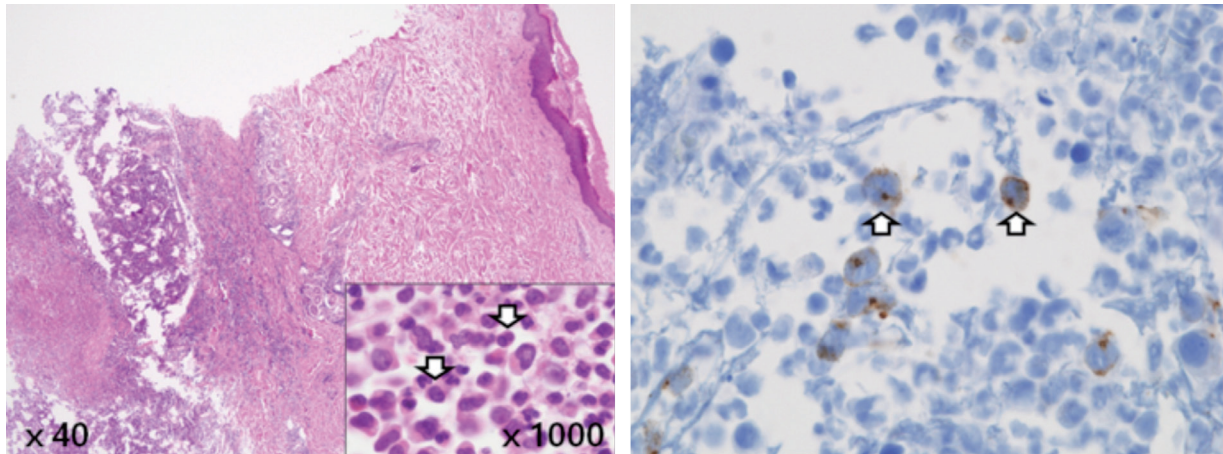


Fig. 5. Skin biopsy revealed atypical hematopoietic cell infiltration and positive myeloperoxidase staining (arrow).

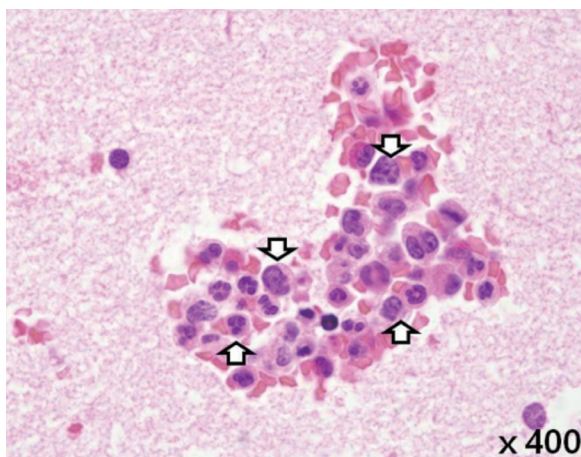


Fig. 6. Right inferior frontal gyrus brain biopsy shows patchy infiltration of immature myeloid cells (arrow) in the brain parenchyme.

mass via neuronavigation, which showed similar infiltration of immature myeloid cells. It also showed myeloperoxidase positivity in same line with the blasts from the bone marrow aspiration and possibly to get a diagnosis of granulocytic sarcoma (Fig. 6).

Since she suffered from a severe leukocyte stagnancy, performed leukapheresis a total of five times within 5 days after admission. Furthermore, 2 g of hydroxyurea was administered for 14 days to

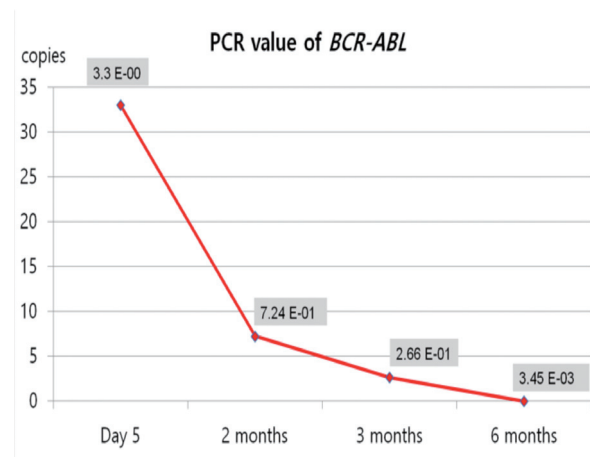


Fig. 7. After 6 months of dasatinib treatment, the patient entered a major molecular response state of *BCR-ABL* rearrangement. PCR, polymerase chain reaction.

reduce tumor expansion. After confirming of CML, the administration of 600 mg of imatinib was done, but the patient experienced hypoesthesia and hypokinesia of the left upper and lower limbs accompanied by cerebellar symptoms. Therefore, we concluded that imatinib did not affect a significant impact on the tumors and switched to 140 mg of dasatinib. The 16th day of dasatinib treatment, platelet count was reduced to $23 \times 10^9/\mu\text{L}$, so discontinued.

On the 15th day after discontinuation, the platelet count was increased to $44 \times 10^3/\mu\text{L}$ and 50 mg of dasatinib was readministered. The patient achieved hematological remission within 1 week after dasatinib administration and achieved a partial cytogenetic response after 3 months medication. After 6 months of dasatinib treatment, she gained a major molecular response state (Fig. 7). The multiple chloromas in brain and skin also completely disappeared (Fig. 2B). The patient is currently on a daily dose of 100 mg of dasatinib and remains in major molecular response state after 39 months of treatment.

Discussion

Granulocytic sarcoma, an extramedullary mass composed of undifferentiated granulocytes, is also called chloroma since it frequently represents green color due to exposure of myeloperoxidase to oxygen [4]. However, about 30% of chloromas appears as a different color; it is most accurately and commonly referred to as “granulocytic sarcoma”, a term coined by Rappaport in 1966. Recently, the World Health Organization characterized them into two categories—granulocytic sarcoma and monoblastic sarcoma—under the umbrella term of myeloid sarcoma [5].

Dock [6] described a correlation between acute leukemia and granulocytic sarcoma, and it is currently known that granulocytic sarcoma can occur in 3% of patients with myeloid leukemia, and presented common systemic symptoms of acute myeloid leukemia. It can also accompany in myelodysplastic syndrome, myeloproliferative disease, and CML [7]. Granulocytic sarcoma occurs in the throughout of all body tissues, organs and most commonly affect the bones. It also appeared in the skin, lymph nodes, soft tissues, and gastrointestinal tract but invasion of central nervous system seldom occurs [1]. The symptoms of granulocytic sarcoma depend on its

location, and in sometimes discovered coincidentally during examination for leukemia since they usually represent no symptom. According to the analysis of Neiman *et al.* [7], the development of granulocytic sarcoma can occur in a patient without hematological disease, and be an acute phase symptom of CML, contribute to the transformation of myeloproliferative diseases into leukemia, or be a clinical manifestation of acute myeloid leukemia. Since its manifestation in CML may occur as a symptom of transformation into blast crisis, the prognosis is known to quite poor. Also, according to Paydas *et al.* [8], 32 cases of granulocytic sarcoma, arisen from CML were 11 cases, of which, 6 were in the chronic phase, 3 were in the accelerated phase, and 2 were in blast crisis. But it is rare to discover and diagnose CML from presenting symptoms of granulocytic sarcoma as shown in this case. The first symptom of patient was dizziness caused by granulocytic sarcoma located inside of the brain, followed by neurological symptoms such as hypoesthesia and hypokinesia of the left upper and lower extremities. While characteristics of the chronic phase were observed in the bone marrow study, but the possibility of its transformation into blast crisis could not be eliminated, so it required prompt histochemical diagnosis and appropriate treatment in a condition that is predicted to have a poor prognosis.

Since it is difficult to diagnose granulocytic sarcoma by solely evaluating its forms, a tissue biopsy was required. A diagnosis may be possible if myeloblasts or immature granulocytes are observed on conventional staining with hematoxylin and eosin. However, it is often difficult to distinguish from other diseases such as malignant lymphoma; hence, misdiagnosis occurs somewhat frequently when patients do not have a history of hematological diseases [9]. Differential diagnosis is generally difficult because distinguishing it from malignant lymphoma, Ewing's sarcoma, thymic carcinoma, and multiple myeloma by histological or radiological

methods is not easy and moreover its incidence is low. Therefore, conducting cytogenetic/molecular tests and immunohistochemical staining is absolutely necessary when the diagnosis is questionable. Bone marrow study needs to find a evidence of increased myeloblasts, and cytogenetics demonstrate an chromosomal abnormality, t(9;22)(q34;q11) that is the Philadelphia chromosome pathognomic finding of chronic myeloid leukemia. Florescent in-situ hybridization (FISH) investigation with specific fluorescently labeled DNA probes is helpful for diagnosis. The probe hybridizes with the patient's DNA and the signal, *BCR-ABL* translocation fusion product, is detected by a fluorescent microscope [2]. Also, to confirm the diagnosis, the use of naphthol-ASD-chloroacetate esterase which stains granulocytes, or immunohistochemistry staining of CD34, CD117, and myeloperoxidase are required [7]. Staining with anti-lysozyme antibody or observing the microstructure of the electron-dense specific granules that had accumulated inside the granulocytes under electron microscopy may help with the diagnosis [10].

Granulocytic sarcoma accompanying CML is thought to be a sign of blast crisis and, hence, an indication for systemic chemotherapy. Furthermore, as shown in this case, when granulocytic sarcoma invades the central nervous system and the patient experiences symptoms of paralysis or a dramatic deterioration of neurologic symptoms, surgical resection or radiotherapy should be considered. Since granulocytic sarcoma is very sensitive to radiotherapy, it can be preferentially conducted when the sarcoma invades the central nervous system. However, granulocytic sarcoma should be considered as a systemic disease, rather than local disease, the treatment have to be approached accordingly. A delay in diagnosis or treatment or treating only locally through surgery will lead to deterioration of leukemia or the development of systemic diseases.

This case showed granulocytic sarcoma

accompanying Philadelphia chromosome-positive CML, and the recently developed tyrosine kinase inhibitors allowed for the determination of a treatment option. Imatinib mesylate currently displays a prominent effect as an oral target agent of CML that developed due to a genetic abnormality of *BCR-ABL*. However, since imatinib mesylate does not easily cross the blood-brain barrier, its effect on CML granulocytic sarcoma invading the central nervous system may be limited and the risk of relapse is also predicted.

Porkka *et al.* [11] proved the effectiveness of dasatinib in the treatment of leukemia that occurs in the central nervous system in an animal study that compared imatinib and dasatinib. In their study, imatinib and dasatinib were administered to the brain of mice with CML. Disease that occurred in the central nervous system could not be stabilized or reduced in size in a group treated with imatinib, whereas the tumor sizes were markedly decreased and the survival rate was significantly increased in a dasatinib group. In addition, a daily dose of 140 mg of dasatinib given to the patients with leukemia achieved favorable effect on the majority cases and showed more than partial remission [11]. In this case, she obtained complete remission in brain chloromas after the administration of dasatinib. She currently showed no evidence of relapse and continued taking dasatinib without any troublesome adverse effect. Although the occurrence of granulocytic sarcoma in the patients with CML is rare and an indication for poor prognosis when it occurs in the central nervous system, its treatment, specifically the effect of tyrosine kinase inhibitors on relapse and prognosis, has not been clearly documented. Dasatinib, second-generation tyrosine kinase inhibitor, easily crosses the blood brain barrier and suggested to make a significant contribution in the treatment of leukemia occurred within the central nervous system. Usual survival period of blast crisis in CML are short, but this

patient survives over 3 years after diagnosis of CML with systemic, extramedullary involvement.

Here, we reported acquisition of complete remission in a patient with CML that manifested as a granulocytic sarcoma in the central nervous system when she was treated with dasatinib, the second-generation tyrosine kinase inhibitor and reviewed the literature.

Conclusion

Granulocytic sarcoma, often called a chloroma, is an extramedullary mass composed of undifferentiated granulocytes that may occur during the clinical course of CML. Its occurrence suggests progress toward blast crisis and, therefore, poor prognosis. In particular, the occurrence of granulocytic sarcoma in the central nervous system may have an even poorer prognosis, and the effect of a second-generation tyrosine kinase inhibitor upon it has not been concretely established. Here we reported a case and a literature review and experienced a major molecular response using the second-generation tyrosine kinase dasatinib in a patient with CML that manifested as a granulocytic sarcoma in the central nervous system.

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