Massive bone marrow necrosis in a patient with chronic myelocytic leukemia following imatinib mesylate therapy

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To date, 240 cases of bone marrow necrosis have been reported, of which only 13 were reported in association with chronic myelogenous leukemia (CML).[1-4] Imatinib mesylate is an agent which can specifically inhibit the activity of tyrosine kinase chimeric protein BCR-ABL which is caused by the balanced translocation between the short arm of chromosome 9, and the long arm of chromosome 22, and is closely related to the etiology of CML. Here we report a case of bone marrow necrosis following imatinib mesylate therapy in accelerated-phase CML. A 64-year-old woman was admitted to our hospital in February 2003 due to high fever, dyspnea, and shock. In January 2000, she was referred from another hospital because of marked leukocytosis with a leukocyte count of 113800/μL (1% blasts, 3% promyelocytes, 35% myelocytes, and 5% metamyelocytes). Because of a low alkaline phosphatase rate and ratio and the presence of Philadelphia chromosome, she was diagnosed as having chronic myelogenous leukemia (CML). She was treated with 6 MU interferon-alpha biweekly with complete hematological response until she developed eruptions in her neck and face in September 2000. She was then treated with 1000 mg hydroxycarbamide and switched to 400 mg imatinib mesylate in February 2002 because imatinib mesylate became available in our hospital. In September she began to experience eruptions, and low-grade fever and therefore imatinib mesylate was discontinued. In October 2002, she was admitted to our hospital as she developed marked leukocytosis and she was treated with 120 mg cytarabine SC infusion daily for seven days. In November 2002 she was discharged from our hospital with a fully recovered hematological index, and she was prescribed 400 mg imatinib mesylate. Her disease was stable until February 2003, when she began to suffer from general fatigue and was admitted to our hospital. The initial work-up revealed anemia, facial and lower limb edema, dry rales in the bilateral lower lung field, and mild splenomegaly. Hematuria and elevated blood urea nitrogen and creatinine were also observed. Peripheral blood analysis revealed anemia (red blood cell count was 192×10^4/μL), decreased platelet count (3.7×10^4/μL), and increased leukocytes (35,700/μL) with an increased immature myeloid series. Coagulation studies showed prolonged prothrombin time, increased fibrin degradation products and D-dimer, and decreased anti-thrombin III and plasminogen, which indicated the presence of disseminated intravascular coagulopathy (DIC).Bone marrow aspiration revealed hypercellular marrow but the differential was unclear because of massive necrosis. Chest x-ray revealed pneumonia in the lower lung field of both lungs. A diagnosis of bone marrow necrosis, DIC, acute renal failure, and pneumonia was made, and antibiotics and gabexate mesilate were administered. The patient died three days after admission due to hemorrhagic pneumonia.

Previously, reported bone marrow necrosis cases with CML showed an association between bone marrow necrosis and the blastic transformation of the disease.[3] The differential of bone marrow of our case was not clear because of the necrosis, most of the cells could be identified as being rather immature of presumably myeloid origin. Therefore, although our patient did not show any sign of blastic transformation of CML during her whole history, blastic transformation might took place at the point bone marrow necrosis occurred. Most CML cases terminate in blastic transformation, but only 13 cases has been reported to develop bone marrow necrosis.[1-4] Therefore, there is a possibility that imatinib mesylate played a role in bone marrow necrosis occurred in our case, even our case was in blast crisis. Recently, Burton et al. reported bone marrow necrosis in a patient with accelerated-phase CML treated with imatinib mesylate which was not related to disease progression.[4] Imatinib mesylate was developed to inhibit BCR-ABL fusion protein as an effective treatment for CML. Mitochondria are frequently the target of injury after stress, leading to necrotic and apoptotic cell death. By modifying an anti-apoptotic member of the Bcl-2 family, BCR-ABL provides a cytoplasmic *umbrella*, protecting mitochondria from the *rain* of apoptotic signals, thus death preventing cell death.[5] BCR-ABL exhibits an anti-apoptotic function, and inhibition of BCR-ABL activity by imatinib mesylate may be expected to induce apoptosis in this setting. Overgrowth of leukemic cells during blast crisis of CML may cause stress which might lead leukemic cells toward necrosis, imatinib mesylate might inhibited the anti-apoptotic capability of BCR-ABL in our case. Necrosis caused by imatinib mesylate has also been reported in the liver and skin,[6,7] suggesting that cell death caused by imatinib mesylate is not limited to Philadelphia chromosome-positive leukemia cells. Platelet-derived growth factor (PDGF) receptor is a known target of imatinib mesylate. Recently, Pietras et al. showed that the inhibition of PDGF signaling by imatinib mesylate in tumor stroma increased antitumor effects,[8] which may also have a possibility to be involved in the mechanism of bone marrow necrosis in our case.

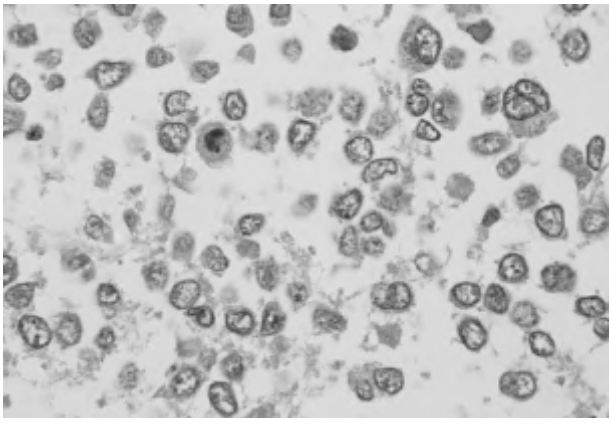

Figure 1. Bone marrow (May-Giemsa staining, original X 400). Shows necrotic cells with ill-defined cytoplasmic borders within an amorphous background.

Takahiro Tamura,[1] Taizo Tasaka,[2] Miharu Fujimoto,[1] Yoshiko Matsuhashi,[2] Tetsuya Fukumot,[2] Shohei Mano,[3] Minoru Kuwajima,[3] Masami Nagai[2]

[1]Department of Medicine, Kagawa Prefectural Central Hospital
[2]Kagawa University, First Department of Internal Medicine
[3]Department of Laboratory Medicine, Kagawa Prefectural Central Hospital

Correspondence: Taizo Tasaka, M.D.
First Department of Internal Medicine Kagawa University1750-1 Ikenobe, Miki-cho Kagawa 761-0793 JAPAN
Phone: 81-87-891-2145 Fax: 81-87-891-2147

References

1. Janssens AM, Offner FC, Van Hove WZ. Bone marrow necrosis. Cancer 2000; 88:1769-1780.
2. Vesterby A, Myhre Jensen O. Aseptic bone/bone marrow necrosis in leukaemia. Scand J Haematol 1985; 35 :354-357
3. Chim CS, Ma SK, Lam CK. Bone marrow necrosis masquerading as interferon toxicity in chronic myeloid leukemia. Leuk Lymphoma 1999, 33(3-4):385-388
4. Burton C, Azzi A, Kerridge I. Adverse events after imatinib mesylate therapy. N Engl J Med 2002; 346 :712-713
5. Skorski T. BCR/ABL regulates response to DNA damage: the role in resistance to genotoxic treatment and in genomic instability. Oncogene. 2002; 21:8591-8604.
6. Vidal D, Puig L, Sureda A, Alomar A. Sti571-induced Stevens-Johnson Syndrome. Br J Haematol 2002; 119: 274-275.
7. Ohyashiki K, Kuriyama Y, Nakajima A, Tauchi T, Ito Y, Miyazawa H, Kimura Y, Serizawa H, Ebihara Y. Imatinib mesylate-induced hepato-toxicity in chronic myeloid leukemia demonstrated focal necrosis resembling acute viral hepatitis. Leukemia 2002; 16 :2160-2161.
8. Pietras K, Rubin K, Sjoblom T, Buchdunger E, Sjoquist M, Heldin CH, Ostman A. Inhibition of PDGF receptor signaling in tumor stroma enhances antitumor effect of chemotherapy. Cancer Res 2002; 62: 5476-5484.