Isolated testicular and bone relapse in children with acute myeloblastic leukemia and chronic graft versus host disease after allogeneic BMT

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Isolated extramedullary relapse after allogeneic bone marrow transplantation (BMT) for acute myeloblastic leukemia (AML) is very unusual, particularly in patients with graft versus host disease (GVHD) known to be associated with decreased incidence of leukemic relapses. However, these rare occasions have been suggested to result from the escape of leukemic cells at the immune-privileged sites. Here we report two unusual post-transplant cases with AML: the first developed testicular relapse during the treatment of chronic GVHD (cGVHD) and bronchiolitis obliterans and the second relapsed as granulocytic sarcoma in the proximal tibia two years after BMT.

Key words: extramedullary relapse, acute myeloblastic leukemia, bone marrow transplantation, graft versus host disease, bronchiolitis obliterans.

Allogenic bone marrow transplantation (alloBMT) is an effective and widely used treatment option for leukemia. Antileukemia efficacy of the transplant results from conditioning regimen and graft mediated immune activity against leukemic cells – so-called graft versus leukemia (GVL) effect[1,2]. Thus, graft versus host disease (GVHD) is associated with decreased incidence of relapses in leukemic patients. Extramedullary relapses frequently occur in the central nervous system (CNS) and the skin in patients with AML, and leukemic recurrence at other sites is rarely reported [3-7]. Moreover, isolated relapse without bone marrow infiltration and in association with chronic GVHD (cGVHD) is quite rare[8]. Here, two such cases are described.

Case Reports

Case 1

An 18-year-old male diagnosed as acute myeloblastic leukemia (AML) (M2) underwent alloBMT in second remission after a bone marrow relapse from his HLA 6/6 matched ABO compatible brother. BMT conditioning included cyclophosphamide (200 mg/kg) / total body radiation (1250 cGy), and cyclosporin A (CsA)/short course of methotrexate (MTX) were used for GVHD prophylaxis. Immediate posttransplant course was uneventful except for acute GVHD (grade 2-3 skin involvement) which responded very well to steroid treatment that was stopped by day +65. Following discontinuation of CsA at day +161, he presented with sudden onset of dyspnea on exertion, dry cough, hypoxemia and severe obstructive lung disease with no response to bronchodilators. Physical examination revealed occasional wheezing and rales. Breath sounds were markedly diminished. Chest X-ray showed hyperinflation and bronchoscopic examination was unremarkable. The bronchoalveolar lavage fluid was negative for bacterial and fungal cultures, Pneumocystis carinii and viral work-up including cytomegalovirus cytology and polymerase chain reaction (PCR). High-resolution chest computerized tomography revealed non-specific findings of consolidation, bronchial dilatation, vascular attenuation, and hypo-attenuated areas in the parenchyma consistent with bronchiolitis

obliterans. Transbronchial biopsy revealed few macrophages, lymphocytes and some increase in hyalin tissue in the alveoli. The subsequent clinical course was characterized by cGVHD affecting the skin and the liver. He received immunosuppressive treatment consisting of high dose steroid (10 mg/kg/day), CsA, and azathioprine and supportive treatment with intravenous immunoglobulin, and antifungal, antiviral and antibacterial agents. Since patient consent was not obtained, thalidomide was not used as an immunomodulatory agent. Although the pulmonary symptoms showed partial response to high dose steroid treatment, he often presented with exacerbations. He developed steroid-induced myopathy, osteoporosis, hyperglycemia and infection during the prolonged course of steroid treatment. His performance status gradually worsened, particularly following development of polyneuropathy which was attributed to cGVHD. Eighteen months after BMT, while in hematologic remission and in a somewhat improved state of pulmonary status, the patient presented with swelling and redness of the left testicle that was initially suggestive of epididymitis. However, histological examination revealed infiltration with myeloid blast cells. Local radiotherapy was given. Systemic chemotherapy was not administered due to the highly immunosuppressive state and poor pulmonary status of the patient. Unfortunately two months later, he suffered from marrow relapse and died in a pancytopenic state following consolidation therapy consisting of high-dose cytosine arabinoside (Ara-C) and daunorubicin.

Case 2

A 13-year-old female was diagnosed as AML-M1 and relapsed in 13 months while on maintenance treatment. She then underwent BMT from her HLA 6/6 identical ABO compatible sister in remission after receiving an MDR-modifier protocol consisting of CsA, granulocyte-colony stimulating factor, idarubicin and high-dose Ara-C. The pre-transplant course was complicated with persistent fevers, suspected fungal infections, and multiple hypoechoic nodules in the liver, spleen and kidneys. The ultrasound-guided liver biopsy was unremarkable and ruled out active fungal infection or primary disease. The conditioning regimen involved busulfan (16 mg/kg) and cyclophosphamide (120 mg/kg) and GVHD prophylaxis consisted of CsA and two doses of MTX. The early post-transplant course was uncomplicated except for catheter-related thrombosis of the jugular vein. At +5 months, she presented with elevation of liver enzymes two months after discontinuation of CsA, and was diagnosed as cGVHD involving the liver, mucocutaneous sites and the lungs. Steroid treatment was followed by complete resolution of her symptoms and was continued for eight months. At +23 months the patient presented with right-sided knee pain. The X-ray (Fig. 1a)

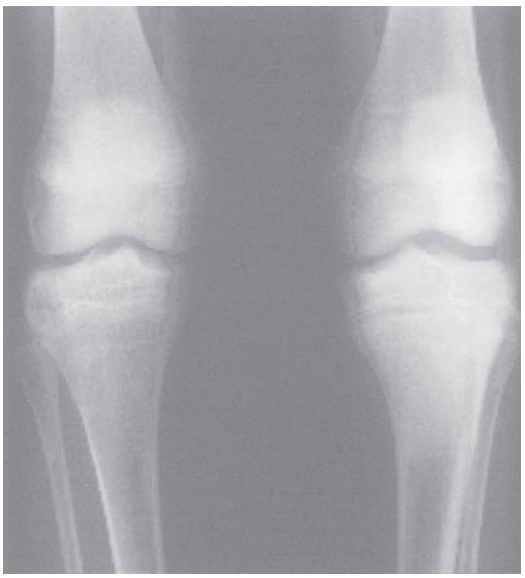

Fig. 1a. X-ray reveals osteoporosis and irregularities of epiphysis at the proximal tibia bilaterally.

revealed osteoporosis and irregularities of the epiphysis at the proximal tibia bilaterally. Magnetic resonance imaging (MRI) (Fig. 1b) showed bone infarcts in the proximal epiphysis of both tibias and an infiltrative lesion with hemorrhagic and cystic components in the proximal metadiaphysis of the right tibia. The biopsy revealed leukemic infiltration with no bone marrow involvement. Unfortunately, two months later she developed bone marrow relapse and died in sepsis three months after initiation of chemotherapy. The chimerism analysis of leukemic cells by investigation of recipient/donor short tandem repeats was consistent with leukemia of recipient origin.

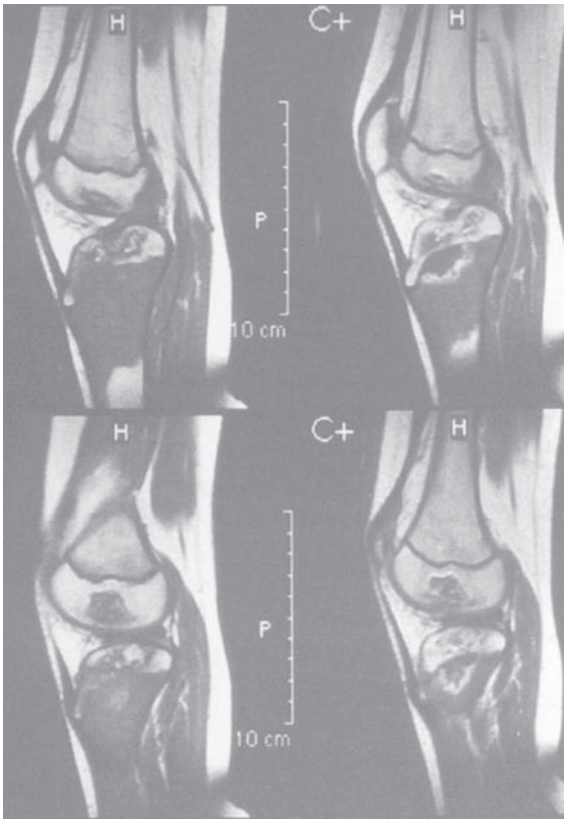

Fig. 1b. MRI shows bone infarcts in the proximal epiphysis of both tibias and an infiltrative lesion with hemorrhagic and cystic components in the proximal metadiaphysis of the right tibia.

Discussion

Extramedullary infiltration can be the presenting feature in children with AML and myelodysplastic syndrome or can develop during the course of the disease[9,10]. However, extramedullary relapse in AML after BMT is quite unusual and has been described to occur often in the skin, gum and soft tissue[4,11]. Isolated extramedullary relapse excluding CNS is only described in a number of cases, occurring in about 0.65% of patients allo-grafted for AML and 3.7% of patients allo-grafted for AML or chronic myeloid leukemia[4,11]. Isolated testicular relapse of AML is distinctly unusual and monocytic morphology is described in these cases[3,6]. Bone marrow relapse generally develops in 1-12 months after extramedullary relapse and rare cases might be cured by local treatment[4,7].

In BMT patients, lymphocytes of donor origin can mediate a powerful immune reaction towards leukemic cells upon recognition of leukemic host antigens (GVL). This immunological reaction has frequently been shown to be associated with GVHD and decreased incidence of leukemic relapses. Unfortunately, the immune-privileged sites may not be accessible to the GVHD/GVL reactions and isolated relapses at these sanctuary sites may occur[1]. To our knowledge, isolated testicular relapse in a leukemic patient during cGVHD has been reported in one case alone in whom donor lymphocyte infusion was followed by hematological remission but testicular relapse was not prevented[8]. In the first case of the present report, development of relapse was a surprising finding considering the extensive cGVHD clinical features associated with severe bronchiolitis obliterans, which is suggestive of a powerful immune reaction. Despite cGVHD, development of isolated testicular relapse suggests that GVHD/GVL is unable to control disease recurrence in immunologically privileged sites due to the immune escape of leukemic cells from donor lymphocyte attack. Alternatively, over-treatment of cGVHD might have played a role in the loss of immune anti-leukemic effect and contributed to leukemic relapse. In the second case, although the involved site at relapse was the bone, not known as an immune-privileged site, the GVH reaction was still not protective. However, the patient was free of GVHD symptoms at the time of relapse.

In conclusion, the report of these two cases of extramedullary relapses during GVHD underlines that one symptom or physical finding may be suggestive of disease recurrence and needs consideration. A false feeling of security against relapse in patients with GVHD may result in delayed diagnosis. Thus, testicular examination in patients with AML must be included in the physical exam as routinely done in patients with ALL. Additionally, this report also suggests that immunosuppressive treatments during GVHD may perhaps interfere with immune-mediated anti-leukemic reactions. Therefore, the point where the treatment of GVHD starts and where it ends may affect the outcome.

REFERENCES

1. Goldberg SL, Mangan KF, Klumpp TR, Cropper TM, Schnall SF, Macdonald JS. Lack of a graft-versus-leukemia effect in an immunologically privileged sanctuary site. Bone Marrow Transplant 1994; 14: 180-181.
2. Dermime S, Mavroudis D, Jiang YZ, Hensel N, Molldrem J, Barrett AJ. Immune escape from a graft-versus-leukemia effect may play a role in the relapse of myeloid leukemias following allogeneic bone marrow transplantation. Bone Marrow Transplant 1997; 19: 989-999.

3. Byrd JC, Edenfield WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. J Clin Oncol 1995; 13: 1800-1816.
4. Bekassy AN, Hermans J, Gorin NC, Gratwohl A. Granulocytic sarcoma after bone marrow transplantation: a retrospective European multicenter survey. Acute and Chronic Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1996; 17: 801-808.
5. Forrest DL, Dalal BI, Naiman SC, et al. Testicular relapse of acute promyelocytic leukemia after allogeneic BMT. Bone Marrow Transplant 1997; 20: 689-690.
6. Shaffer DW, Burris HA, O'Rourke TJ. Testicular relapse in adult acute myelogenous leukemia. Cancer 1992; 70: 1541-1544.
7. Au WY, Chan AC, Lie AK, Chen FE, Liang R, Kwong YL. Recurrent isolated extramedullary relapses as granulocytic sarcomas following allogeneic bone marrow transplantation for acute myeloid leukemia. Bone Marrow Transplant 1998; 21: 205-208.
8. Tringali S, Vasta S, Scime R, Catania P, Cavallaro AM, Majolino I. Testicular relapse of AML during chronic graft-versus-host disease induced by donor leukocyte infusion. Haematologica 1996; 81: 339-342.
9. Jenkin RD, Al-Shabanah M, Al-Nasser A, et al. Extramedullary myeloid tumors in children: the limited value of local treatment. J Pediatr Hematol Oncol 2000; 22: 34-40.
10. Hiçsönmez G, Cetin M, Yenicesu I, et al. Evaluation of children with myelodysplastic syndrome: importance of extramedullary disease as a presenting symptom. Leuk Lymphoma 2001; 42: 665-674.
11. Koç Y, Miller KB, Schenkein DP, et al. Extramedullary tumors of myeloid blasts in adults as a pattern of relapse following allogeneic bone marrow transplantation. Cancer 1999; 85: 608-615.