Granulocytic sarcoma after stem cell transplantation in a child with biphenotypic leukemia

Bifenotipik lösemili bir çocukta kök hücre nakli sonrası granülositik sarkom

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Abstract

Granulocytic sarcoma is an extramedullary tumor composed of leukemic blasts. Isolated granulocytic sarcoma has rarely been reported in children with leukemia undergoing allogeneic stem cell transplantation. We report a case of isolated granulocytic sarcoma arising from the pleura in an 11-year-old girl who was previously treated for biphenotypic leukemia with allogeneic stem cell transplantation. Complete resolution of the tumor was achieved after two inductions with MRC 12 protocol; however, she died of sepsis during the neutropenic period. The unusual presentation, immunophenotypic differences at diagnosis and relapse, and the management options are discussed. *(Turk J Hematol 2009; 26: 151-3)*
Key words: Isolated granulocytic sarcoma, stem cell transplantation, relapse

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Özet

Granulositik sarkom, lösemik blastların oluşturduğu ekstrameduller bir tümördür. İzole granulositik sarkom, allogeneik kök hücre nakli yapılan lösemili çocuklarda nadiren bildirilmiştir. Bifenotipik lösemi relapsı nedeni ile allogeneik kök hücre nakli ile tedavi edilen ve izleminde plevra kaynaklı izole granulositik sarkom gelişen 11 yaşındaki kız olgu sunulmuştur. MRC 12 protokolüne göre iki indüksiyon tedavisi sonrası granulositik sarkomu tamamen kaybolan olgu, nötropenik dönemde gelişen sepsis nedeni ile kaybedilmiştir. Granulositik sarkomlu bu olguda olağandışı yerleşim, tanı ve relapsta immunfenotipik farklılık ve tedavi yaklaşımları tartışılmıştır. *(Turk J Hematol 2009; 26: 151-3)*
Anahtar kelimeler: İzole granulositik sarkom, kök hücre nakli, relaps

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Introduction

Granulocytic sarcoma (GS) is a solid tumor composed of leukemic myeloblasts and partially matured granulocytes [1]. GS may be the initial manifestation of myeloproliferative disorders, and the appearance of the disease in the marrow and blood may follow weeks or months later without treatment. It usually occurs in association with acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS) at diagnosis. The lesions may be found in any location, especially skin, orbita, nasal sinuses, bone, pleura, and other sites [2]. Prognosis and treatment are poor when GS occurs after stem cell transplantation (SCT) [3].

We report a child with biphenotypic leukemia who relapsed as a GS in the pleura 12 months after allogeneic SCT.

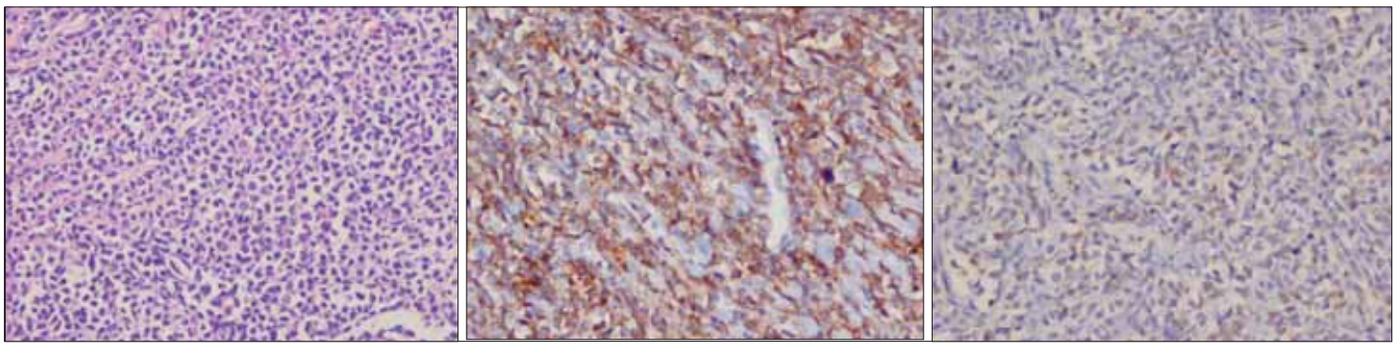
Case Report

An 11-year-old girl presented with cough, chest and bone pain of one-month duration. On physical examination, there was no other pathological finding rather than diminished breath sounds in the left lung. Laboratory investigations including blood count, urine analysis, and blood chemistry were also normal except anemia. Chest X-ray showed extensive pleural effusion filling the left lung. Histopathological analysis of the pleural specimen without immunophenotyping of the effusion material, which was performed in another center before referral to our hospital, strongly suggested infiltration predominantly by lymphoblasts. Her bone marrow also had abundant blastic infiltration. Immunophenotypic analysis was found to be positive for 67% CD13, 72% CD33, 76% CD19, 74% CD22, and 78% HLA-DR and negative for CD3, CD5, CD7, CD10 and cytoplasmic myeloperoxidase (c-MPO). Cytogenetic analysis of the marrow specimen showed normal karyotype and was negative for t (9; 22) and t (4; 11), which are the main determinants for risk classification. She was diagnosed as myeloid marker-positive acute lymphoblastic leukemia (My+ALL), and ALL-BFM 95 medium-risk protocol was started. Although pleura and bone marrow blasts had completely disappeared after induction by day 33, she developed isolated bone marrow relapse with a normal chest X-ray within one year after diagnosis. Immunophenotyping at relapse was similar to that of the diagnosis except for c-MPO positivity, which is consistent with biphenotypic leukemia. Cytogenetic markers for t (9; 22) and t (4; 11) were still negative and second remission was achieved after reinduction with ALL-BFM 95 high-risk (HR) protocol. According to the BFM-95 HR protocol, after three blocks following induction therapy she received HLA identical SCT from her sibling male donor and subsequent conditioning with busulfan, cyclophosphamide and etoposide. A bone marrow with a cellular content of CD34: 4.6 x 10^6 cell/kg was infused without any manipulation. Cyclosporine (CSA) and methotrexate were used for graft versus host disease (GVHD) prophylaxis. Neutrophil count > 0.5x10^9 /L was reached on the 17th day and platelet count > 20,000/mm^3 was reached on the 30th day. On the 40th day, she developed a stage 3 acute GVHD in skin and stage 2 in gut, which was treated by CSA and steroid for three months. The patient was not on the immunosuppressive therapy at the time of relapse. One year after transplant, she presented with isolated leukemic infiltrates in the left pleura, while her marrow showed no sign of the disease with a 100% donor chimerism. Histopathological and immunohistochemical examination revealed that the mass was a GS in which MPO, CD43, CD56, CD68, and CD117 positivity were depicted on tumor cells with no CD3 or CD20 (Figure 1 A-C). After two induction chemotherapy with MRC–12 AML protocol, the leukemic mass gradually decreased (Figure 2 A, B). However, she died of gram-negative sepsis during the neutropenic phase of the second induction therapy.

Discussion

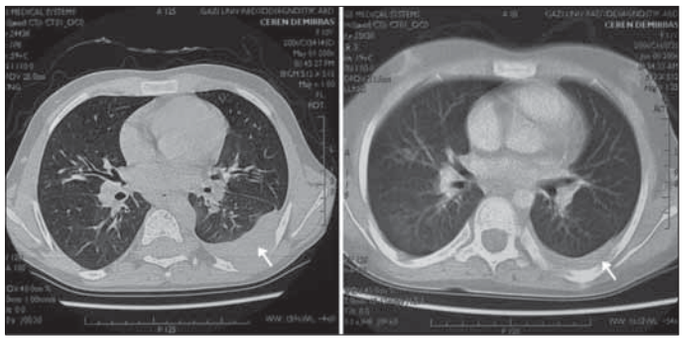
Isolated GS has rarely been reported in children undergoing allogeneic SCT for leukemia. The European Bone Marrow Transplantation (EBMT) Registry reported the incidence of GS to be 0.45% in children with myeloid malignancies, which occurred within 4 to 56 months after transplantation. It is reported to be 0.65% in AML and 0.22% in CML and MDS [3]. In children, although GS mostly accompanies myeloid malignancies, limited data are available in ALL with intracranial and orbital GS [4,5]. GS may occur in almost any part of the body but is most common in the skin, lymph nodes and bone. As pleural infiltration by leukemic cells following SCT is a rare condition, little is known about the treatment and outcome of isolated extramedullary relapse [6].

Biphenotypic leukemia, which is a relatively rare type of leukemia, is characterized by the presence of both myeloid and lymphoid cell surface antigens. The scoring system proposed by the European Group for the Immunological Characterization of Leukemia (EGIL) is useful for this purpose [7]. However, it is dif-



A B C

Figure 1. A. Tumoral infiltrate composed of blastic cells with narrow cytoplasm, round to oval nuclei and prominent small nucleoli displaying open chromatin pattern (hematoxylin-eosin, x400); B. Blastic cells show CD43 positivity (CD43, x400); C. Blastic cells show focal MPO positivity (MPO, x400)



A B

Figure 2. A. Axial CT scan showing a large pleural-based soft tissue lesion with regular contours in the upper lobe of the left lung; B. Control CT examination shows a significant decrease in the size of the lesion

ficult to differentiate MPO-negative cases of biphenotypic leukemia, and a few cases may be misinterpreted. In addition, immunological changes between initial diagnosis and relapse have also been reported, which might be due to the gain or loss of aberrant markers at relapse causing clonal instability of leukemic cell [8-10]. We also found immunophenotypic differences between initial diagnosis and relapse. Though all the published cases of mediastinal GS have relapsed, immunophenotypic differences between primary leukemia with My+ALL and recurrent leukemia with GS have not been well documented in children [11]. There are also no uniform criteria or any consensus on the treatment of these cases [12].

The management of cases with GS after SCT is controversial. Although the EBMT Registry included several treatment strategies like chemotherapy, radiotherapy, surgery, donor lymphocyte infusion, and second transplant, the optimal therapeutic approach remains unclear. It is well established that the graft versus leukemia (GVL) effect plays a substantial role in the prevention of leukemia relapse after SCT. It has been reported that the GVL effect is dependent upon GVHD in the setting of HLA identical sibling SCT [13]. Despite the full chimerism and the presence of GVHD, an isolated extramedullary relapse after transplantation occurred in our case. Possible mechanisms of extramedullary relapse that have been suggested are the inefficiency of GVL or chemotherapy in extramedullary sites compared with bone marrow [14,15]. Moreover, a full chimerism status may not be predictive of absence of minimal residual disease and it also does not appear to protect from extramedullary relapse [16].

In summary, although pleural GS with or without concurrent myeloid malignancy is well described, similar clinical findings in the presence of My+ALL or biphenotypic leukemia are not known. Immunophenotypic changes during the progression of leukemia could well be a marker of more resistant disease. In our case, GS disappeared after two induction chemotherapy regimens; we could not determine the long-term prognosis because the patient died of sepsis. Long-term studies are required to ascertain the appropriate treatment and prognosis of isolated GS after SCT.

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