Leukemic Relapse 5½ Years After Allogeneic Bone Marrow Transplantation

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A 13-yr-old male with acute myelogenous leukemia was treated with various chemotherapy regimens for 3½ yr and then underwent an allogeneic bone marrow transplantation. The donor marrow was successfully engrafted, and the patient remained in remission free of all chemotherapy. Then, 5½ yr later, he developed an extramedullary relapse with a chlo-

remoma of his maxillary sinus. This case illustrates the need for prolonged followup of transplant recipients and suggests that statements proposing cure as a result of this procedure may be premature.

Over the last eight years there has been increasing interest in the possible role of allogeneic bone marrow transplantation in the treatment of patients with acute leukemia. Although initial attempts at marrow transplantation were generally unsuccessful, recent reports have suggested that results are improving. Prolonged periods of disease-free survival following transplantation have been described.

In this report we describe a patient with acute myelogenous leukemia (AML) who, after being in clinical remission for 5 yr following an allogeneic bone marrow transplantation, developed an unusual extramedullary relapse.

CASE REPORT

T.G. first presented to the NCI in January 1968 at age 13 yr with the diagnosis of AML. The initial bone marrow aspirate revealed 70%, myeloblasts with numerous Auer rods. Clinical remission was initially induced with cytosine arabinoside (ara-C), but despite maintenance chemotherapy a bone marrow relapse occurred in April 1969. Over the next 2½ yr four additional remissions and relapses occurred despite treatment with various combinations of daunomycin, vincristine, prednisone, methotrexate, 6-mercaptopurine, and L-asparaginase. By September 1971 the patient was again in relapse, and the decision was made to perform an allogeneic bone marrow transplant. The patient's brother had previously been identified as an HLA-identical and MLC (mixed leukocyte culture)-compatible donor.

Details of the transplantation procedure and subsequent complications have been previously reported. In brief, the patient was prepared for transplantation with bischloroethyl nitrosourea, ara-C, 6-thioguanine, and cytoxan given over 4 days; 24 hr later, he received an infusion of approximately $2.5 \times 10^{10}$ donor bone marrow cells. The posttransplant hospital course was complicated by multiple bacterial infections, acute graft-versus-host disease, and a gastrointestinal hemorrhage. Nevertheless, in October 1971, a bone marrow examination documented the successful engraftment of donor marrow and complete remission of the leukemia. At that point, all antileukemic chemotherapy was discontinued.

It is noteworthy that in August 1971, prior to transplantation, the patient had developed a pansinusitis and a right-sided nasopharyngeal mass, presumed to be of infectious origin. Both these processes responded to antibiotics and had resolved by the completion of the transplantation. However, in February 1972 pansinusitis redeveloped, again requiring antibiotic therapy. After 1 mo the sinusitis cleared and remained quiescent until October 1972, when symptoms recurred.

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The sinusitis persisted despite antibiotics, and in March 1973 the patient underwent bilateral maxillary antrotomies with subsequent resolution of all symptomatology. Biopsy material from both sinuses taken during surgery revealed chronic inflammatory tissue. For the next 4 yr the patient remained asymptomatic and in continuous remission. In January 1977 symptoms of nasal congestion and right maxillary tenderness developed. Antibiotic therapy was not effective, and in March 1977 a right maxillary antrotomy was performed. Biopsy samples from this procedure showed granulation tissue and hypertrophied mucosa. Despite this procedure, the symptoms persisted, and x-rays revealed continued opacification of the right maxillary sinus. Consequently, in May 1977 a second right-sided antrotomy was performed. Biopsy specimens from this procedure (Fig. 1) revealed sheets of myeloblasts. Tomograms and CT scans showed a mass eroding into the medial wall of the right maxillary sinus. All additional laboratory studies, including bone marrow aspirate and CSF examination, failed to show other evidence of leukemia.

The patient has been started on a combined treatment regimen of local radiotherapy and systemic chemotherapy. Although this treatment is still in progress, a repeat antrotomy and sinus exploration performed in September 1977 showed that a clinical remission had been established.

**DISCUSSION**

Recently, Thomas et al. reported their results with a small group of patients who had undergone successful allogeneic bone marrow transplantation. Based on the observation of disease-free survivals of 1-4.5 yr after transplantation and a flattening of the life table graph after 2 yr, it was suggested that these patients...
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had been cured of their leukemia. The latest relapse seen in this group occurred after 27 mo. The occurrence of a late relapse in the patient presented in this report suggests that the use of the term "cure" to describe patients in prolonged posttransplant disease-free periods may be premature. The extramedullary nature of the relapse also emphasizes that even in situations where marrow can be successfully transplanted and remain disease free the possibility of developing extramedullary leukemia is very real.

It is becoming increasingly apparent that extramedullary relapses are more common in the posttransplant setting than previously appreciated. In a recent review, 25% of initial relapses following transplantation occurred in extramedullary sites, and in those patients who survived for at least 1 yr before relapsing 50% suffered extramedullary relapses. In addition, granulocytic sarcomas (chloromas) are unusual in acute leukemia, although when they arise it is most often in association with AML. As in the case reported here, chloromas tend to arise in the skull, often in proximity to the orbits, and are frequently locally invasive. It is interesting that the chloroma in this patient developed in an area of chronic inflammation.

The origin of the myeloblasts in this relapse is unclear. They may have arisen from either a donor or recipient clone. This point is important, since leukemia relapses in donor marrow have been reported. However, we could not differentiate between these possibilities, since both donor and recipient had identical karyotypes. Furthermore, it was not possible to tell whether the chloroma represented a recrudescence of the original leukemia or an entirely new leukemic process in the patient's own leukocytes. This question is relevant because there have been several reports of second malignancies, including leukemia, occurring in patients who received chemotherapy.

The occurrence of leukemic relapse in this patient 5.5 yr after bone marrow transplantation is of obvious concern and points up the necessity of continued close followup for all patients with a history of leukemia.

REFERENCES


Leukemic relapse 5 1/2 years after allogeneic bone marrow transplantation

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