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Chronic Granulocytic Leukemia After Renal Transplantation

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• Chronic granulocytic leukemia (CGL) developed in a 31-year-old man after he underwent a third renal transplant. The leukemia was initially controlled with azathioprine sodium and prednisone therapy, but eventually it entered blast cell crisis. This was controlled with an adult acute lymphocytic leukemia protocol with an excellent response. Despite discontinuing treatment with azathioprine and with the use of busulfan to control the peripheral WBC count, the patient maintained stable renal function for one year following treatment of the blast cell crisis and subsequently died of sepsis. We suggest that CGL after renal transplantation is similar to that observed in the general population and can be treated with the usual chemotherapeutic agents for the disorder without sacrificing renal function.

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Lymphoproliferative disorders occur at a greater frequency in organ transplant recipients and may relate to the prolonged suppression of cell-mediated immunity required to maintain viability of the transplanted organ.[1] Although lymphomas are the most common of the hematologic malignant neoplasms, myelogenous leukemias have also been encountered.[2] While several articles have documented the occurrence of these disorders, information on the course and response to therapy of these disorders is difficult to ascertain.[3-5] We describe herein the development of chronic granulocytic leukemia (CGL) in a renal transplant recipient. While he was treated with multiple chemotherapeutic agents and eventually a blast cell crisis developed, he survived with stable renal function for 30 months after the onset of CGL.

REPORT OF A CASE

A 31-year-old man was initially referred to us in 1969 for azotemia and hypertension. In 1971, the patient received a cadaveric renal transplant that was lost to chronic rejection in 1973. A second renal transplant was performed in 1974, but it also was

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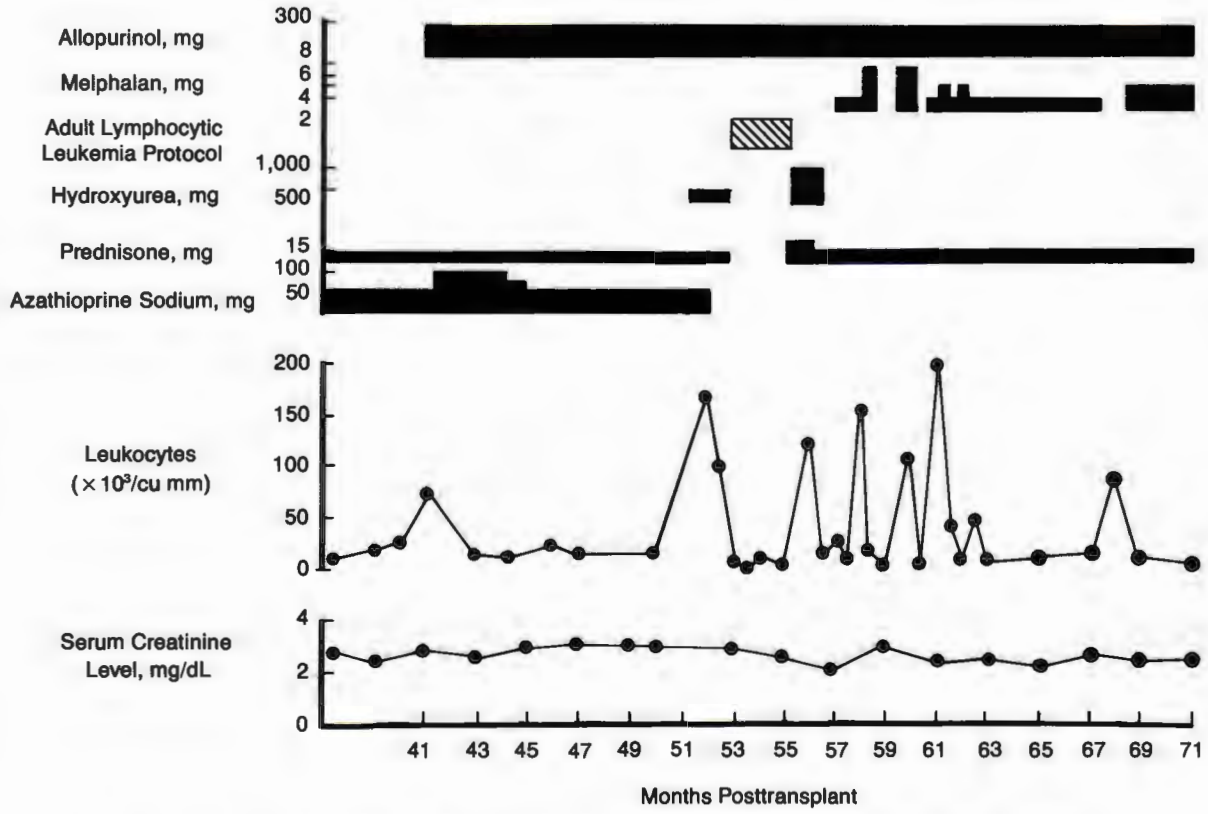

Fig 1.—Clinical course and effect of chemotherapeutic agents used to treat lymphocytic leukemia. See text for details of adult lymphocytic leukemia protocol.

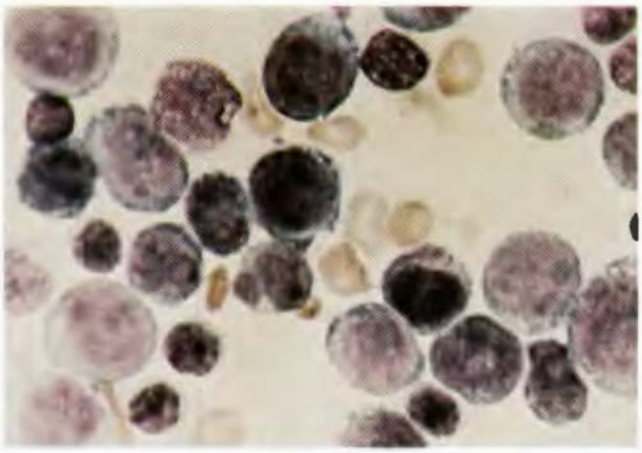

Fig 2.—Photomicrograph of bone marrow from patient at time fever and adenopathy developed. Marrow showed few erythroid elements and greater than 50% blasts (Wright's stain, ×100).

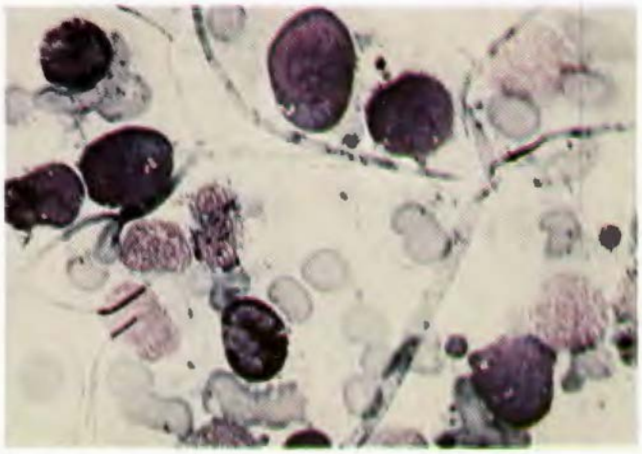

Fig 3.—Vacuolated blasts are negative for granular staining. Positive neutrophils are seen also (Sudan black, ×100).

rejected. In 1975, he received a third cadaveric kidney. The donor had no evidence of malignant neoplasms. Although the patient required both drug and radiation therapy for the control of rejection, he was eventually discharged from the hospital with a serum creatinine level of 1.4 mg/dL. The kidney continued to function well and the immunosuppressive therapy was eventually tapered to 50 mg/day of azathioprine sodium and 15 mg/day of prednisone.

Routine follow-up hematologic values were normal until 42 months posttransplantation when the patient was noted to have an increase in the peripheral WBC count to 73,000/cu mm (Fig 1). Physical examination showed no evidence of lymphadenopathy or hepatomegaly. His hematocrit was 40%, with a platelet count of 300,000/cu mm. A peripheral WBC smear demonstrated 48% segments, 19% band cells, 20% myelocytes, 12% lymphocytes, and 1% monocytes. A bone marrow biopsy showed notable hypercellularity with myeloid hyperplasia. The leukocyte alkaline phosphatase (LAP) score was zero. A Philadelphia chromosome was present. Human leukocyte antigen genotype of the malignant cells was identical to those of the patient. Therapy with allopurinol was begun and the patient's azathioprine dose was increased to 100 mg/day. Subsequent adjustments of the azathioprine dosage

were performed to maintain a peripheral WBC count of 20,000/cu mm.

Eleven months after CGL was discovered, the patient was hospitalized for fever and hypotension. At that time, his WBC count had increased to 171,000/cu mm, with 55% segments, 24% band cells, 12% myelocytes, 5% metamyelocytes, 3% blasts, and 1% lymphocytes. Cultures of his blood, urine, sputum, and CSF were negative. Because of the severe increase in the peripheral WBC count, treatment with azathioprine was discontinued and therapy with hydroxyurea was started.

One month later, the patient was readmitted to the hospital for recurrent fever and progressive inguinal and cervical adenopathy. A repeated bone marrow biopsy showed few erythroid elements, few megakaryocytes, and greater than 50% blasts (Fig 2). The blasts had a lymphoblastic morphology and failed to stain with Sudan black (Fig 3). Because of the adenopathy, morphologic features of the blasts, and negative Sudan black stain, the patient was treated for adult lymphocytic leukemia (ALL) using a standard induction protocol. This protocol consisted of 60 mg/sq m of prednisone on days 1 through 36; 2 mg/sq m of vincristine sulfate on days 1, 8, 15, 22, and 29; 20 mg/sq m of doxorubicin hydrochloride on days 17 to 19; and 600 mg/sq m of cyclophosamide and 30 mg/sq m of doxorubicin hydrochloride on day 36. During the initial two weeks of induction therapy, when the patient was receiving only vincristine and prednisone, the blasts rapidly disappeared from the marrow, the adenopathy regressed, and the platelet count increased to 100,000/cu mm. Remission was obtained in less than six weeks and the peripheral WBC smear again demonstrated the typical picture of CGL. Renal function remained stable and treatment with hydroxyurea and prednisone was restarted. The hydroxyurea therapy was eventually discontinued and melphalan therapy was initiated to gain better control of the peripheral WBCs.

Five months after completion of the ALL protocol, a bone marrow biopsy showed less than 5% blasts. An LAP score was again zero and the Philadelphia chromosome was present. Although there was a progressive increase in peripheral eosinophilia, the patient continued to do well clinically for a subsequent ten months, until progressive thrombocytopenia developed. Discontinuing the use of melphalan resulted only in an increase in WBCs, with no improvement in the platelet count. The melphalan therapy was, therefore, reinstituted and platelet transfusions begun as necessary. Two months after thrombocytopenia developed, the patient was readmitted to the hospital with fever, chills, and hypotension. The hematocrit was 20%, the platelet count was 231,000/cu mm, and the WBC count was 93,000/cu mm, with a differential cell count consisting of 2% lymphocytes, 28% segments, 3% myelocytes, 2% promyelocytes, 62% eosinophils, and 3% basophils. There were three nucleated RBCs per 100 WBCs. A bone marrow biopsy demonstrated a hypoproliferative and fibrotic marrow, with 100% of the cellular elements being eosinophils. He subsequently died of thrombocytopenia and disseminated sepsis 30 months after the onset of CGL. Serum creatinine concentration at the time of death was 2.9 mg/dL.

COMMENT

Chronic granulocytic leukemia is the most common leukemia observed after organ transplantation.[2] Although this disorder occurs at an earlier age in organ transplant recipients than in the general population, the overall incidence of CGL is only slightly increased. The extent to which immunosuppressive therapy predisposes to the development of CGL is difficult to determine. In the general population, CGL has been associated with leukemogenic factors, eg, ionizing radiation,[6] benzene exposure,[7] or viral infections.[8] Furthermore, azathioprine has been associated with chromosomal abnormalities and has been implicated in producing the Philadelphia chromosome in one previously reported case of CGL after renal transplantation.[3,9] Azathioprine has also been implicated in the development of acute myelogenous leukemia during immunosuppressive therapy for nonmalignant diseases.[10,11] Although our patient had no history of benzene exposure and no clinically apparent viral infections, he did receive considerable amounts of radiation and azathioprine during the course of his three renal transplants. Whether these factors were important in the development of CGL, however, is undetermined.

Chronic granulocytic leukemia in the transplant population seems to develop rapidly. In both this case and the previous case described by Adler et al,[3] routine hematologic studies obtained between the time of transplantation and the onset of leukemia failed to demonstrate preleukemic abnormalities. This is in contradistinction to acute granulocytic leukemia in organ transplant recipients, which seems to evolve slowly through a preleukemic state.[10,11] Little information is available on the course of CGL in transplant recipients and considerable controversy exists in the management of malignant neoplasms in the organ transplant population. Cessation of immunosuppressive therapy has produced destruction of tumors in persons in whom the tumor was inadvertently transferred with the transplanted organ.[12,13]

However, there is no evidence such strategy would be useful in the management of de novo malignant neoplasms. Three previous articles have suggested that CGL after renal transplantation may be controlled by altering the dose of immunosuppressive therapy. Adler et al[3] treated CGL in a 22-year-old man simply by increasing the dose of azathioprine. Although hydroxyurea and allopurinol therapy were eventually required for adequate control of the peripheral leukocyte count, the patient did well for the ten-month follow-up reported. Mooy et al[4] treated a case of CGL after renal transplantation by reducing the azathioprine dose and adding cyclophosphamide. Busulfan therapy, however, was eventually substituted for the cyclophosphamide and the latter agent caused hemorrhagic cystitis. This patient eventually died of sepsis five months after CGL was first diagnosed. Lubynski et al[5] obtained adequate control of the peripheral leukocyte count in a transplant patient with CGL merely by the addition of allopurinol to his usual immunosuppressive regimen. This patient apparently did well for the 19 months on which their article was based. Although the CGL in our patient was also initially well controlled by addition of allopurinol, adjustment of azathioprine, and subsequently hydroxyurea, the leukemia eventually entered a blastic phase. Remission was fortunately induced with an ALL protocol. This is consistent with the observations of Rosenthal et al[14] that lymphoblastic morphology during blast crisis imports a better prognosis and good response to combination therapy with vincristine and prednisone. Thus, markers that suggest response to a specific form of chemotherapy in granulocytic leukemia occurring in the general population may have the same prognosis in CGL that occurs after renal transplantation. Furthermore, neither the ALL protocol nor cessation of azathioprine therapy impaired renal function. Once the blast crisis had resolved, the alkalating agents both controlled the peripheral WBC count and prevented rejection.

These observations suggest that CGL after renal transplantation follows a similar course and responds to similar therapies as CGL in the general population. Furthermore, markers that suggest a more favorable prognosis in CGL in blast crisis may also apply to the transplant group. Finally, appropriate therapy for CGL may be successfully undertaken without adversely affecting the transplanted kidney.

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