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LYMPHOMA AND HYPERCALCEMIA IN A PEDIATRIC ORTHOTOPIC LIVER TRANSPLANT PATIENT

PAUL NAKAZATO,[1] CARLOS O. ESQUIVEL, ANDREW H. URBACH,[2] LEONARD MAKOWKA,[2] VELMA SCANTLEBURY,[2] RONALD JAFFE,[2] AND THOMAS E. STARZL,[2]

We present a case report of a pediatric orthotopic liver transplant recipient who developed lymphoma with hypercalcemia on cyclosporine and prednisone immunosuppression. This is the first reported posttransplant lymphoproliferative disorder complicated by hypercalcemia, with a finding of an elevated 1,25 dihydroxyl vitamin D state, suggesting that it has a role in the pathophysiology of this B cell lymphoma hypercalcemia. The clinical course and management of this disorder with a 31-month follow-up are described.

One unfortunate sequel of transplantation has been posttransplantation Epstein-Barr virus–mediated lymphoproliferative disease (*1–3*). It has been observed that these tumors are dissimilar from other lymphomas in that they are triggered by immunosuppression and may be reversible with discontinuation or tapering of immunosuppressive agents (*4*).

Hypercalcemia as a complication of pediatric lymphoma is uncommon and has an incidence of about 2.5%, as reported by Le Blanc (*5*). A similar incidence of hypercalcemia complicating adult lymphomas, shown by Cancellos, was 1.8% (4/217) (*6*). The pathogenesis leading to malignancy-associated hypercalcemia has been inadequately elucidated, although a variety of mechanisms have been implicated, including direct bone involvement, osteoclastic-activating factor, prostaglandins, parathyroid hormone, and vitamin D metabolites (*7–11*).

We describe a pediatric orthotopic liver transplant recipient who developed lymphoma with hypercalcemia on cyclosporine and prednisone immunosuppression.

MATERIALS AND METHODS

In December 1983, a 2¼ year-old boy with biliary atresia cirrhosis, but no previous history of hypercalcemia, underwent orthotopic liver transplantation. Postoperatively, his course was uneventful and he was discharged with normal liver function tests and normal serum calcium (Fig. 1).

At 27 months after transplantation, this patient was evaluated for abdominal pain consistent with acute appendicitis. Laparotomy revealed a distal jejunoileal small bowel obstruction secondary to tumor, and right colectomy and enterocolostomy were performed. Pathology revealed a B cell lymphoproliferative, monotypic IgM lambda-secreting tumor by routine hematoxylin-eosin and combined fluorescence and ABC-peroxidase techniques. Postoperatively, the patient's maintenance immunosuppression was continued (Fig. 1). During this admission, the serum calcium and phosphorus remained normal.

RESULTS

At 28 months after transplantation, an abdominal computerized axial tomography scan showed an abdominal tumor mass, approximately 8 cm, located in the midabdomen. Immunosuppression was altered by discontinuing cyclosporine but continuing prednisone (Fig. 1).

[1] Address reprint requests to Paul Nakazato, M.D., Transplant Service, P.O. Box 7999, San Francisco, CA 94120.
[2] University of Pittsburgh School of Medicine.

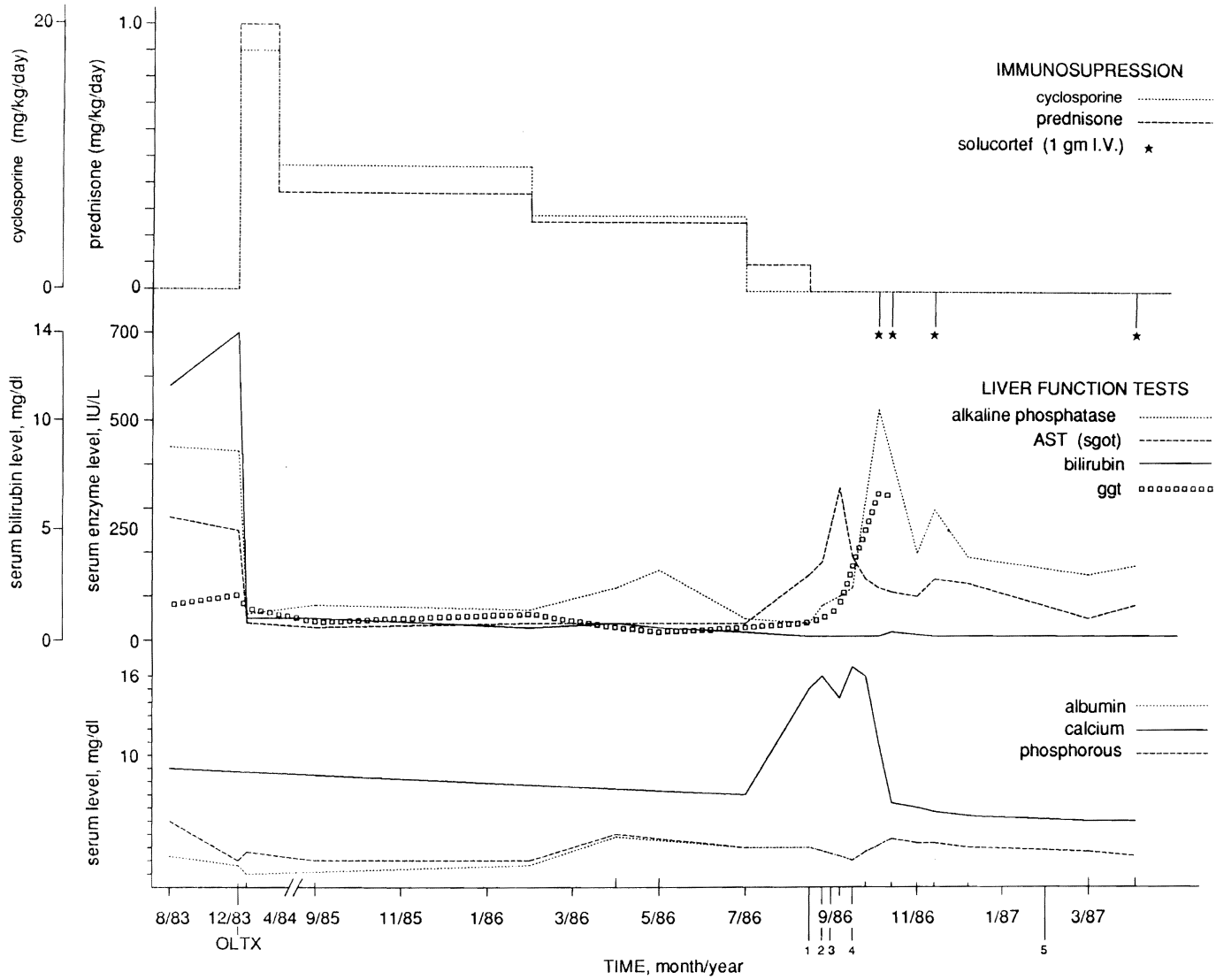

FIGURE 1. Immunosuppression and biochemical tests of a liver transplant recipient with lymphoproliferative disease. Note the normalization of serum calcium following debulking of the tumor. Slight elevation of the hepatic enzymes followed discontinuation of daily immunosuppression, consistent with mild rejection. (OLTX) orthotopic liver transplantation; (1) saline-Lasix therapy; (2) calcitonin therapy; (3) mithramycin therapy; (4) surgical debulking; and (5) surgical debulking.

At 29½ months after transplantation, abdominal CAT scan continued to show a large mesenteric mass unchanged in size. A CAT scan–directed percutaneous needle biopsy and bone marrow aspirate showed recurrent lymphoproliferative B cell, monomorphic, and lambda light chain–producing tumor without bone marrow involvement. Prednisone was discontinued and the patient was now totally off immunosuppressive agents. Calcium and phosphate serum levels were normal.

At 31 months after transplantation, still totally off immunosuppression, the patient was evaluated in our clinic and found to have hypercalcemia (15 mg/dl). Over the next several weeks, the patient was worked-up for his hypercalcemia. It was found by percutaneous liver biopsy and bone marrow aspirate that there was significant active cellular rejection in the liver transplant but no tumor present in the marrow. In the extensive hypercalcemia workup there were abnormal findings of an increased activity of serum angiotensin-converting enzyme, a normal 25-hydroxyl vitamin D level, and a markedly elevated 1,25 dihydroxy vitamin D (calcitriol) level. Management of hypercalcemia was difficult. Initially we attempted aggressive hydration and intravenous furosemide therapy but the hypercalcemia persisted. Persistent hypercalcemia refractory to calcitonin therapy (4 IU/kg subcutaneously), prompted a single dose of mithramycin (25 μg/kg i.v.). Further usage of this medication was discarded because of hepatic toxicity. Finally, because the hypercalcemia was refractory to medical therapy with persistent abdominal pain and progressive lethargy, an exploratory laparotomy was performed, with mesenteric and omental tumor debulking and liver transplant biopsy. Pathology again documented the same lymphoproliferative tumor, and the liver biopsy showed acute cellular rejection. At 9 days after operation, the patient was discharged with a calcium level of 12.5 mg/dl (Fig. 1), and without immunosuppression. Two weeks after debulking, the patient had normal serum calcium, phosphorus, 25-hydroxyl, and 1.25 dihydroxy vitamin D levels.

The patient's course after debulking was compounded by

problems of tumor recurrence. Partial small bowel obstruction prompted exploratory laparotomy and debulking at 38 months posttransplantation. Due to recurrence, chemotherapy trials consisting of cytoxan (40 mg/kg i.v.), vincristine (0.06 mg/kg i.v.), and prednisone (2.2 mg/kg p.o.) were attempted from the period of 43 months to 53 months posttransplantation. Carcinomatosis with partial small bowel obstruction occurred again, at 62 months after transplantation; this required laparotomy, small bowel resection, and further debulking. At that time, liver biopsy showed portal fibrosis, chronic inflammatory infiltrate in the portal triads, and intact bile ductules. Liver function tests were normal except for slightly elevated alkaline phosphatase. After the initial debulking at 31 months posttransplantation, serum calcium and phosphorus levels were normal until the patient died 64 months after transplantation from mediastinal, pleural, and intraabdominal disease.

DISCUSSION

Our patient is unique for three reasons: this is the first reported case of posttransplantation lymphoproliferative disorder complicated by hypercalcemia; there is a possible correlation between hypercalcemia and a lymphoproliferative tumor; associated with hypervitaminosis D; and the clinical course and management are unique.

The literature on hypercalcemia and posttransplant lymphoproliferative disease has revealed no previous report of this association. It is an uncommon complication even in the nontransplant lymphoma population, with a 1.3%–4.0% occurrence. Our transplant experience in Pittsburgh shows an estimated 1.6% incidence of posttransplant lymphoproliferative disorder—thus lymphoproliferative disease complicated by hypercalcemia occurs in 0.1% of the total transplant population.

In general, hypercalcemia and lymphomas usually become manifest with rampant disease—i.e., osteolytic lesions and bone marrow metastases (*13*). In reviewing the literature, these lymphomas are usually T cell lymphomas rather than B cell lymphomas. In our case study, there was no evidence of any direct bone involvement, as suggested by a normal marrow, skeletal survey, and a bone scan. Our hypercalcemia workup excluded vitamin D, hypervitaminosis A, hyperthyroidism, parathyroid hormone–induced hypercalcemias, and sarcoidosis as causes of secondary hypercalcemia.

De Remee and Banks (*14*) reported an association between non-Hodgkin's lymphoma hypercalcemia and an increased activity of serum angiotensin-converting enzyme. Although our child did not have sarcoidosis, a similar association was found with an elevated serum angiotensin-converting enzyme, hypercalcemia, and abnormal vitamin D metabolism. At the time of the hypercalcemia, the patient had a normal 25-hydroxy vitamin D level, which represents the precursor of the active metabolite 1,25 dihydroxy vitamin D (calcitriol); however, the latter was markedly elevated in our patient.

Because the hypercalcitriol state did not appear to be governed by the usual physiologic mechanisms, and because debulking the tumor caused normal calcemia and a precipitous decrease in the serum calcitriol level, we believe that his B cell lymphoma had the capacity to maintain a hypercalcitriol state. By developing cell cultures from the tumor, we hope to investigate whether this B cell lymphoma has a capacity similar to the renal 25(OH) D_3 1-alpha-hydroxylase enzyme to synthesize hypercalcitriol, or a role in controlling degradation.

The clinical course was interesting. After detection and debulking of the hypercalcemic lymphoproliferative disorder, the hypercalcemia and hypercalcitriol stage never recurred. Unfortunately, the tumor never did regress with termination of maintenance immunosuppression, and even with chemotherapy treatment. Finally, 31 months after maintenance immunosuppression was terminated, the patient had not undergone fatal transplant rejection, but instead had a viable graft. It may be that the calcitriol levels present in our patient are comparable to results of in vitro experiments demonstrating the inhibitory effects of calcitriol on T helper cell proliferation (*15*). The possible interference of this with graft rejection may or may not be relevant, and further investigation will be required to determine whether calcitriol or sterol-like substances are causes of this phenomenon.

REFERENCES

1. Hanto DW, Gajl-Peczalska KJ, Frizzera G, et al. Epstein-Barr virus (EBV) induced polyclonal and monoclonal B-cell lymphoproliferative diseases occurring after renal transplantation. Ann Surg 1983; 198: 356.
2. Bieber CP, Heberling RL, Jamieson SW, et al. Lymphoma in cardiac transplant recipients associated with cyclosporine A, prednisone and antithymocyte globulin (ATG). In: Purtilo DT, ed. Immune deficiency and cancer. New York: Plenum, 1984: 309.
3. Schubach WH, Hackman R, Neiman PE, Miller G, Thomas ED. A monoclonal immunoblastic sarcoma in donor cells bearing Epstein-Barr virus genomes following allogeneic marrow grafting for acute lymphoblastic leukemia. Blood 1982; 60: 180.
4. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporine-steroid therapy. Lancet 1984; 1: 583.
5. Canellos GP. Hypercalcemia in malignant lymphoma and leukemia. Ann NY Acad Sci 1974; 230: 240.
6. Le Blanc A, Caillaud JM, Hartman O, et al. Hypercalcemia preferentially occurs in unusual forms of childhood non-Hodgkin's lymphoma, rhabdomyosarcoma, and Wilms' tumor. Cancer 1984; 54: 2132.
7. Moses AM, Spencer H. Hypercalcemia in patients with malignant lymphoma. Ann Intern Med 1963; 59: 531.
8. Mundy GR. Bone resorbing activity in supernatants from lymphoid cell lines. N Engl J Med; 1974: 290; 867.
9. Klein DC. Prostaglandins: stimulation of bone resorption in tissue culture. Endocrinology 1970; 86: 1436.
10. Powell D, Singer FR, Murray TM, Minkin C, Potts JT. Nonparathyroid hormonal hypercalcemia in patients with neoplastic diseases. N Engl J Med 1973; 289: 176.
11. Breslau NA, McGuire J, Zerwekh J, et al. Hypercalcemia associated with increased serum calcitriol levels in three patients with lymphoma. Ann Intern Med 1984; 100: 1.
12. Hanto DW, Simmons RL. Lymphoproliferative disease in immunosuppressed patients. In: Morris PJ, Tilney NL, eds. Progress in transplantation. Edinburgh: Churchill/Livingston, 1984: 186.
13. Walker IR. Lymphoma with hypercalcemia. Can Med Assoc J 1974; 111: 928.
14. De Remee RA, Banks PM. Non-Hodgkin's lymphoma associated with hypercalcemia and increased activity of serum angtiotensin-converting enzyme. Mayo Clin Proc 1986; 61: 714.
15. Jordan SC, Lemire JM, Sakai RS, et al. 1,25 dihydroxyvitamin D_3-induced changes in human lymphocyte responses to interleukin-2. Transplant Proc 1986; 4: 901.
16. Abboud SL, Gordeuk V, Schacter AP. Well-differentiated lymphocytic lymphoma with peripheral blood involvement, osteolytic bone lesions and hypercalcemia. *Cancer 1985; 56: 2508.*
17. Spiegel A, Greene M, Magrath I. Hypercalcemia with suppressed

parathyroid hormone in Burkitt's lymphoma. Am J Med 1978; 64: 691.
18. Zaloga GP, Eil C, Medbery CA. Humoral hypercalcemia in Hodgkin's disease. Arch Intern Med 1985; 145: 155.
19. Rosenthal N, Insogna KL, Godsall IJ, et al. Elevations in circulating 1,25 dihydroxyvitamin D in three patients with lymphoma-associated hypercalcemia. J Clin Endocrin Metab 1985; 60: 29.

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