HYPERCALCEMIA ASSOCIATED WITH ADULT T-CELL LEUKEMIA/LYMPHOMA (ATL)

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Hypercalcemia is a frequent manifestation of human T-cell lymphotrophic virus type I (HTLV-I)-associated adult T-cell leukemia/lymphoma (ATL). Human T-cell lymphotrophic virus type I infection is endemic in the Caribbean, Japan, Melanesia, and Africa. This article presents two cases of ATL to increase awareness of the disease by primary care physicians. The management of hypercalcemia is discussed. (*J Natl Med Assoc.* 1995;87:746-748.)

Key words • hypercalcemia
• adult T-cell leukemia/lymphoma

Adult T-cell leukemia/lymphoma (ATL) is an aggressive and often fatal malignancy that is etiologically linked with the infection caused by the human T-cell lymphotrophic virus type I (HTLV-I). This virus belongs to the oncovirus subfamily of retroviruses and can immortalize human lymphocytes, specifically CD_4 positive T lymphocytes in ATL.[1,2]

Human T-cell lymphotrophic virus type I infection is endemic in southwestern Japan, the Caribbean, Melanesia, and parts of Africa. Prevalence rates as high as 15% have been reported in these areas in older age groups, with women being infected more frequently than men. In the United States, the seroprevalence rate among volunteer blood donors is 0.016%.

Human T-cell lymphotrophic virus type I is transmitted from mother to child, by sexual contact, blood transfusion, and the sharing of contaminated needles. Sexual transmission of HTLV-I is more efficient from males to females than from females to males. Transmission by blood transfusion occurs only with transfusion of cellular blood products. Besides ATL, HTLV-I is associated with a degenerative neurological disease. Adult T-cell leukemia/lymphoma occurs in 2% to 4% of individuals who are seropositive for HTLV-I in endemic areas where early childhood infection is common. A long latent period is likely since it occurs most frequently in persons aged 40 to 60 years.[3]

The usual clinical features of ATL are generalized lymphadenopathy, hepatosplenomegaly, skin lesions, leukemia with circulating abnormal lymphocytes (flower cells), and bone lesions with hypercalcemia and abnormal calcium metabolism. Severe hypercalcemia is a frequent complication of ATL and is one of the main causes of early death.[4] This article describes two cases of hypercalcemia associated with ATL to increase the awareness of this disease by primary care physicians serving inner-city populations. The etiology and management of the associated hypercalcemia are discussed.

CASE REPORTS

Case 1

A 41-year-old female presented with a history of syncopal episodes. The patient, who was born and living in Trinidad, West Indies, was on vacation in Brooklyn when these episodes occurred. There was no significant past medical history, and she denied promiscuity and drug abuse. Her mother had died of Hodgkin's disease. The positive findings on physical examination were pale mucous membranes, and cervical and inguinal lymphadenopathy. The liver and spleen were not palpable.

Initial laboratory values were: hemoglobin, 7.8 g; white blood cell count, 21 300 mm^3; platelets, 18 000 mm^3; and calcium, 11.7 mg/dL. Four days after admission, her calcium level was 14.7 mg/dL. Hydration with

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saline restored the calcium level to normal range. The blood smear showed polylobated lymphocytes.

A bone marrow biopsy was diagnostic of lymphocytic leukemia. Antibodies to HTLV-I were demonstrated in the patient's serum using an enzyme-linked immunoabsorbent assay (ELISA) and confirmed by Western blot. CD_4 T lymphocytes were noted to be 92.1% of peripheral lymphocytes (normal: 38% to 56%). The soluble T_{AC} protein was markedly elevated, which is consistent with HTLV-I-associated ATL. The patient received chemotherapy over a period of 11 months. She died 14 months after diagnosis.

Case 2

A 25-year-old female, who was born in Barbados, West Indies, presented with a history of generalized malaise. She gave a history of testing positive for the human immunodeficiency virus (HIV) 1 month prior to admission. The main finding on physical examination was generalized lymphadenopathy.

Initial laboratory values were: a hemoglobin, 12.1 g; white blood cell count, 8300 mm^3; platelets, 176,000 mm^3; and calcium, 12.4 mg/dL. One week after admission, the levels were: hemoglobin, 8.7 g; white blood cells, 3220 mm^3; platelets, 47,000 mm^3; and calcium, 15.5 mg/dL. Hydration with 0.9% normal saline and combination therapy with calcitonin, and pamidronate restored normocalcemia.

A bone marrow biopsy and blood smear were consistent with ATL. Antibodies to HTLV-I were demonstrated in the patient's serum by ELISA and confirmed by Western blot. The patient was started on chemotherapy but died 3 weeks after admission.

DISCUSSION

The prognosis for patients with ATL is usually poor, with the median survival being 11 months from the time of diagnosis.[2] Conventional chemotherapy is not curative, and relapses occur quickly. Hypercalcemia is one of the common causes of death in patients with ATL. There is often a rapid elevation of the serum calcium, which is refractory to therapy, toward the terminal course of the disease.[4]

Fukumoto et al[5] demonstrated that most patients with ATL, even among the normocalcemic group, manifested hypercalciuria. Proliferation of osteoclasts with extensive bone resorption has been noted at autopsy in cases with ATL.[6] This abnormal calcium metabolism initially was attributed to alteration in vitamin D metabolism.[7] However, more recent studies have shown that activated vitamin D (I-25 dihydroxy vitamin D) levels are not elevated in ATL.[5,8]

Parathyroid hormone levels have been shown to be suppressed in all cases of hypercalcemia associated with ATL. However, with the identification of parathyroid hormone-related protein, several studies have confirmed secretion of this protein by the neoplastic tissue in ATL. Prostaglandin E_1, interleukin-1, and interleukin-2 have been shown to stimulate the production of parathyroid hormone-related protein by HTLV-I infected T cells. Thus, parathyroid hormone-related protein seems to be the putative factor for the hypercalcemia associated with ATL.[9-13]

Aggressive management of hypercalcemia would improve symptoms and the quality of life in patients with ATL. Repletion of sodium and extracellular volume deficits with intravenous 0.9% saline is indicated in all cases. Saline repletion improves hypercalcemia by increasing the glomerular filtration rate and promoting a sodium-linked diuresis in the proximal renal tubule. Patients with severe hypercalcemia may require as much as 6 L of 0.9% saline to replenish the deficits. This should be given in the first 24 to 48 hours. Thereafter, saline infusion should be continued at a minimum rate of 2 L/day until calcium levels become normal. Loop diuretics should only be used if there is evidence of fluid overload. Osteoclast inhibitors will be necessary, in addition to saline repletion, to restore normocalcemia.

Calcitonin, with a rapid onset of action of less than 2 hours, should be the first osteoclast inhibitor to be used. However, it is only effective for 2 to 3 days because of an "escape" due to rapid downregulation of the calcitonin receptors on osteoclasts. As a result, pamidronate, a biphosponate (a potent osteoclast inhibitor) should be used simultaneously with calcitonin. After intravenous pamidronate is given, serum calcium values start to fall within 24 to 48 hours, reach a nadir at 5 to 7 days, and then start to rise in 15 to 30 days. Oral biphosponates, etidronate, or clodronate can be used at this stage to supplement the effect of pamidronate. Gallium nitrate, another potent osteoclast inhibitor, may be used if pamidronate therapy is unsuccessful. The somatostatin analog octreotide has been shown to be effective in the treatment of hypercalcemia of malignancy due to secretion of parathyroid hormone-related protein.[14]

Finally, primary care physicians practicing in the large metropolitan areas in the United States should be aware of ATL, since a recent report has shown that the disease is not uncommon in the inner city.[15]

Acknowledgments

The authors thank Shaunice Cabba-Gestalk for preparing the manuscript and Paul Tobin for his assistance.

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