Vitamin D Metabolite-Mediated Hypercalcemia and Hypercalciuria Patients With AIDS- and Non-AIDS-Associated Lymphoma

By John S. Adams, Manuel Fernandez, Mercedes A. Gacad, Parkash S. Gill, David B. Endres, Suraia Rasheed, and Frederick R. Singer

Fifteen patients with lymphoma and hypercalciuria (≥11.0 mg/dL) were identified by screening the serum chemistry profile obtained from patients upon admission to the Los Angeles County/USC Medical Center. Seven of the 15 (47%) possessed a frankly elevated serum concentration of 1,25-dihydroxyvitamin D [1,25-(OH)2-D]. An additional patient with severe hypercalcemia (16.2 mg/dL) had a serum 1,25-(OH)2-D concentration in the midnormal range, not a suppressed value. To examine the potential existence of hypercalciuria in absence of overt hypercalcemia, prospective screening of 23 normocalcemic patients with lymphoma was undertaken. Four of the 23 patients (17%) had increased fractional urinary calcium excretion rates (0.35 ± 0.3 mg calcium/100 mL glomerular filtrate [GF], mean ± SE; normal, <0.16 mg/100 mL GF); two of the hypercalciuric patients had a frankly elevated serum 1,25-(OH)2-D concentration. Of the 19 hypercalcemic/hypercalciuric lymphoma patients identified, none had an elevated serum immunoreactive parathyroid hormone concentration. Fourteen of the 19 hypercalcemic/hypercalciuric patients (74%) suffered from B-cell neoplasms, three had Hodgkin’s lymphoma, and two had adult T-cell leukemia/lymphoma. All hypercalcemic/hypercalciuric patients had widespread disease (stage III or IV). Six patients, four with hypercalcemia and two with hypercalciuria, had acquired immunodeficiency syndrome (AIDS). These data suggest that the deregulated synthesis of a 1,25-(OH)2-D-like metabolite is a common cause of hypercalcemia and hypercalciuria in patients with lymphoma including patients with AIDS-associated tumors.

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THE OVERALL INCIDENCE of hypercalcemia in patients with lymphoma is reported to be relatively low when compared with solid neoplasms and multiple myeloma. For this reason clinical investigation into the pathogenesis of lymphoma-associated hypercalcemia has been limited. However, interest in this problem has been recently rekindled with the recognition of human retrovirus-associated lymphoma; a high percentage of patients with human T-lymphotrophic virus, type I (HTLV-I)-induced T-cell leukemia/lymphoma develop hypercalcemia. Hypercalcemia has also been reported in patients with acquired immunodeficiency syndrome (AIDS), a human immunodeficiency virus (HIV)-induced disease that can be complicated by lymphoma. The possibility that hypercalcemia in some patients with lymphoma may develop as a consequence of disordered vitamin D metabolism has been raised by five recent reports describing nine patients with lymphoma and hypercalciuria who had unexpectedly high circulating concentrations of the active vitamin D metabolite, 1,25-dihydroxyvitamin D [1,25-(OH)2-D]. In this report we describe the calcium-regulating hormone status in two groups of lymphoma patients, those presenting with overt hypercalcemia and those with normocalcemia in whom the fractional urinary calcium excretion rate was examined; a study of normocalcemic lymphoma patients was undertaken because vitamin D metabolite-mediated hypercalcemic disorders are frequently preceded by a period of hypercalciuria. The results indicate that an inappropriate elevation in the serum 1,25-(OH)2-D concentration is a common occurrence in hypercalcemic/hypercalciuric patients with lymphoma, either associated or not associated with AIDS.

MATERIALS AND METHODS

Hypercalcemic patients. Serum was obtained from 15 lymphoma patients with hypercalcemia (Table 1) before institution of antitumor and/or antihypercalcemia therapy. Patients were identified by screening the serum chemistry profiles of hospital admissions for a serum calcium concentration ≥11.0 mg/dL. All patients but one (patient 1, Table 1) were admitted to the Los Angeles County/USC Medical Center between 1977 and 1988.

Normocalcemic patients. Fasting urine and serum samples were obtained in three groups of normocalcemic patients attending the outpatient facilities at the Los Angeles County/USC Medical Center between 1986 and 1987: (a) patients with lymphoma not associated with AIDS (n = 12), (b) patients with lymphoma and AIDS (n = 11), and (c) patients with AIDS but without known lymphoma (n = 18). Informed consent was obtained from all patients. Criteria for entrance into the study were (a) the presence of normocalcemia (range, 8.4 to 10.4 mg/dL), (b) a serum creatinine concentration ≤1.5 mg/dL, and (c) a normal serum concentration of immunoreactive parathyroid hormone (iPTH) in an amino terminal assay. The fractional urinary calcium excretion rate was determined from urine collected over a four-hour period and expressed in terms of milligrams calcium excreted per 100 mL glomerular filtrate (GF).

Serum and urine analyses. The serum and urine calcium, phosphorus, and creatinine concentrations were determined immediately by an autoanalyzer technique. Analysis of the serum concentration of lipid with 1,25-(OH)2-D receptor binding capacity was performed according to the method of Reinhardt et al. This method uses solid-phase extraction of the serum on a C-18 (reverse-phase)
cochromatographs with authentic 1,25-(OH)2-D and competes with chromatography in diverse solvent systems for sample purification."6 cartridge followed by chromatography on a silica (normal-

The interassay coefficient of variation for specific binding in extracts of calf serum samples with a mean value of 20.8 pg/mL (n = 12). The intraassay coefficient of variation for this measurement is 8.6% (n = 12). The intraassay coefficient of variation is 8.4% for human serum samples with a mean value of 20.8 pg/mL (n = 12) and 6.9% for serum samples with a mean value of 80.2 pg/mL. The assay for 1,25-(OH)2-D-like material in the serum of nine of 15 hypercalcemic patients and three of four hypercalcemic patients with lymphoma was repeated on at least one occasion. Of the 12 repeated analyses, eight were performed on the same serum sample, and four were performed on consecutive-day samples from the same patient. The coefficient of variation for values from the same sample was 8.1% and 15.0% for consecutive-day samples from the same patient; the mean coefficient of variation for all serum tested in this assay was 10.6%. The serum concentration of iPTH was assessed in an assay using one of two antisera directed toward the amino terminus of human PTH11-18; the serum of patient 1 (Table I) was also assayed for iPTH by using an antisemir that recognizes the carboxy terminus of human PTH.19 In four of the 15 hypercalcemic patients (patients 2 through 5, Table 1) the serum iPTH concentration was measured by using two different radioimmunoassays. In all but patient 1 (Table 1) the serum was assayed for iPTH within 3 months of venipuncture. All sera were stored at -70°C before assay.

Table 1. Clinical and Biochemical Features of Lymphoma Patients

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<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Type</th>
<th>Stage</th>
<th>HIV-1†</th>
<th>HTLV-1</th>
<th>CASg (mg/dL)</th>
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*BNC-FC, large noncleaved follicular center cell; SNC-B, small noncleaved B cell; SC-FC, small cleaved follicular center cell; B-IBS, B-cell immunoblastic sarcoma; ATCL, adult T-cell lymphoma/leukemia.
†ND, virus screening not performed.
‡Corrected for the serum albumin concentration: serum calcium (mg/dL) - serum albumin (g/dL) + 4.
§Fractional urinary calcium excretion rate; normal, <0.16 mg calcium/100 mL GF.
‖Bone marrow involvement by tumor.

Separation of the C13-C15 lymphoma patients was performed on the same serum sample, and four of the 15 hypercalcemic patients were tested for antibodies to both HTLV-I and HIV-1 by using an enzyme-linked immunoabsorbent assay and confirmatory immunoblot (Western blot) analysis as described previously.20

RESULTS

Hypercalcemic patients. The serum calcium, 1,25-(OH)2-D, and iPTH concentrations in the 15 hypercalcemic patients with lymphoma are depicted in Fig 1. The serum 1,25-(OH)2-D concentration was elevated above the normal range in seven of 15 lymphoma patients with hypercalcemia (47%). This degree of elevation of values in the serum assay for 1,25-(OH)2-D (85 ± 7 pg/mL [mean, ±SE]; normal range, 15 to 60 pg/mL) is clearly inappropriate in the presence of hypercalcemia (13.1 ± 0.7 mg/dL; normal range, 8.4 to 10.4 mg/dL). Values for iPTH were in the normal range or clearly suppressed in the serum of all patients examined. One severely hypercalcemic patient (patient 2, Table I) had a serum 1,25-(OH)2-D concentration that was in the midrange of normal, clearly not suppressed. In contrast, seven patients (patients 3, 7, 9, 11, 12, 13, and 15, Table I) including three of the four patients with AIDS-associated tumors and two patients with adult T-cell lymphoma had 1,25-(OH)2-D levels that were appropriately suppressed. In these seven patients the serum creatinine and phosphate concentrations (Fig 2) ranged from 0.7 to 1.7 mg/dL and 2.4 to 4.1 mg/dL, respectively, which suggests that neither severe renal insufficiency nor hyperphosphatemia were responsible for the suppression in circulating concentration of 1,25-(OH)2-D or related metabolites. Hypophosphatemia was observed in no patient, thus indicating that a decrease in the serum phosphate concentration was not the proximate cause of the elevated serum 1,25-(OH)2-D concentration observed in seven of the hypercalcemic patients.

In two patients (patients 8 and 10, Table 1), the serum calcium and 1,25-(OH)2-D concentrations were monitored after institution of a successful course of antitumor chemo-

Fig 1. Hypercalcemic lymphoma patients. Serum concentrations of calcium, 1,25-(OH)2-D and iPTH that were obtained from 16 hypercalcemic lymphoma patients before institution of antitumor and antihypercalcemic therapy. The stippled areas represent the range of normal values in a population of normocalcemic human subjects. □, AIDS-associated; ■, non-AIDS-associated.
Chemotherapy. The rapidity of the response was more pronounced in patient 10. Within ten days of institution of chemotherapy the serum calcium concentration decreased from 14.4 to 9.4 mg/dL and the serum 1,25-(OH)\(_2\)-D concentration from 129 to 22 pg/mL. Three weeks after initiation of chemotherapy. The rapidity of the response was more pronounced in patient 10. Within ten days of institution of chemotherapy the serum calcium and 1,25-(OH)\(_2\)-D concentrations decreased from 13.2 to 10.0 mg/dL and from 78 to 7 pg/mL, respectively. These data provide circumstantial evidence for the production of a renal 1,25-(OH)\(_2\)-D secretogogue or for the synthesis of a 1,25-(OH)\(_2\)-D-like sterol by the tumor.

Normocalcemic patients. Prospective evaluation of 23 normocalcemic patients with lymphoma showed four patients (17%) to be hypercalcemic (3.5 ± 0.03 mg calcium/100 mL GF) (Table 1 and Fig 3A). The mean serum calcium concentration (9.7 ± 0.2 mg/dL) and 1,25-(OH)\(_2\)-D concentration (60 ± 11 pg/mL) in these four patients was significantly greater (P < .05 and P < .01, respectively) than were the mean values for calcium (8.9 ± 0.1 mg/dL) and 1,25-(OH)\(_2\)-D (33 ± 3 pg/mL) in the remaining 19 normocalcemic patients with lymphoma. In two of the four hypercalcemic patients with lymphoma the serum 1,25-(OH)\(_2\)-D concentration was elevated above the range of normal. As depicted in Table 2, among normocalcemic lymphoma patients the serum calcium concentration, 1,25-(OH)\(_2\)-D concentration, and fractional urinary calcium excretion rate were not influenced by clinically apparent infection with HIV-1. However, normocalcemic patients with lymphoma, as a group and either associated or not associated with AIDS, exhibited a significantly greater urinary calcium excretion rate than did normocalcemic patients with AIDS not associated with lymphoma. In normocalcemic patients with lymphoma there was a positive correlation between the serum 1,25-(OH)\(_2\)-D concentration and the fractional urinary calcium excretion rate (Fig 3A), thus indicating that the circulating concentration of 1,25-(OH)\(_2\)-D may be an important factor in determining the urinary calcium excretion rate in this group of patients. By comparison, the serum 1,25-(OH)\(_2\)-D concentration in patients with AIDS but without lymphoma was not correlated with the fractional urinary calcium excretion rate (Fig 1B).

DISCUSSION

We have investigated the calcium-regulating hormone status in 15 patients with lymphoma and hypercalcemia. Seven of the 15 patients with hypercalcemia (47%), includ-
ing one patient with AIDS-associated lymphoma, had a frankly elevated serum 1,25-(OH)2-D concentration. This increase occurred in the presence of hypercalcemia without an accompanying increase in the serum iPTH concentration (Fig 1) or a decrease in the serum phosphate concentration (Fig 2). These results demonstrate that circulating concentrations of the active vitamin D metabolite in some hypercalcemic lymphoma patients are not subject to control by factors that normally regulate the renal 25-OH-D-1α-hydroxylase and suggest that tumor-related, humoral factors are altering the normal production and/or catabolism of 1,25-(OH)2-D or that synthesis of 1,25-(OH)2-D or a closely related metabolite is extrarenal. Precedent for the inappropriate synthesis and secretion of 1,25-(OH)2-D from an extrarenal site has been established in the human granulomatous disease sarcoidosis; the sarcoid macrophage has been identified as one cell capable of synthesizing 1,25-(OH)2-D in this disease. Vitamin D metabolite–mediated hypercalcemia has also been described in patients with infectious and noninfectious granulomatous diseases including tuberculosis, disseminated candidiasis, leprosy, and silicone-induced granulomatous disease. In the current study, circumstantial evidence for the potential existence of an extrarenal site of 1,25-(OH)2-D synthesis in patients with both AIDS and non-AIDS-associated lymphoma was provided by the observation that the institution of effective antitumor chemotherapeutic regimens resulted in a substantial decrease in the circulating concentration of the 1,25-(OH)2-D–like metabolite.

The finding of a high 1,25-(OH)2-D concentration in a patient with AIDS-related lymphoma suggests that infection of the host with HIV may play a role in the expression of vitamin D metabolite–mediated hypercalcemia. In this regard, experiments from our laboratory demonstrate that infection of cultured human lymphoma cells with HIV-1 can confer the capacity on infected cells to metabolize 25-OH-D3 to a more polar compound that is chromatographically identical to 1,25-(OH)2-D3. In addition, Fetchick et al and Reichel et al recently reported that transformation of normal human lymphocytes with HTLV-1 can confer 1,25-(OH)2-D3 synthetic capability on transformed cells. Although a high percentage of patients with HTLV-1–associated lymphoma/leukemia become hypercalcemic during the course of their disease, a high circulating concentration of a 1,25-(OH)2-D–like metabolite has been found in only one of these patients. In the largest series so far reported, Dodd et al found that among five patients with HTLV-1–associated adult T-cell lymphoma/leukemia and hypercalcemia all had suppressed serum 1,25-(OH)2-D concentrations. Our results confirm the observation of Dodd et al; both hypercalcemic patients with HTLV-1–associated lymphoma in our series had a serum 1,25-(OH)2-D concentration that was below the range of normal. Furthermore, studies from our laboratory, performed under a variety of conditions, show that an HTLV-1–associated lymphoma cell line established from patient 9 in our series (Table 1) does not metabolize 25-OH-D3 to a 1,25-(OH)2-D–like compound in vitro.

Because hypercalciuria frequently precedes the development of overt hypercalcemia in vitamin D metabolite–mediated disorders of calcium homeostasis, we prospectively screened a group of 23 normocalcemic lymphoma patients, both with AIDS and non-AIDS-associated disease, for hypercalciuria (Table 2, Fig 3). An increased fractional urinary calcium excretion rate was found in four of the 23 patients (17%). Two of these patients had a frankly elevated serum 1,25-(OH)2-D concentration. These results suggest that an elevated serum value for 1,25-(OH)2-D and fasting hypercalciuria may be the forerunner of vitamin D metabolite–mediated hypercalcemia in patients with lymphoma.

Among the nine hypercalcemic/hypercalciuric lymphoma patients with elevated serum 1,25-(OH)2-D concentrations reported here, none harbored a T-cell neoplasm; two patients suffered from Hodgkin’s lymphoma and the remainder from B-cell neoplasms. All nine patients with elevated serum 1,25-(OH)2-D concentrations had intermediate- or high-grade tumors and widespread disease (stage III or IV). This finding is in agreement with the observations of other investigators. Bone marrow involvement, documented by the presence of tumor cells in a marrow aspirate or biopsy specimen, was found in 12 of the 19 hypercalcemic/hypercalciuric patients in this study, five of whom had an elevated circulating 1,25-(OH)2-D metabolite concentration. It is conceivable that high local concentrations of an active vitamin D metabolite or other tumor-derived cytokine could induce pathologic bone resorption. However, previous histomorphometric analysis of the bone of one patient (patient 1, Table 1) showed increased bone-resorbing surfaces and decreased bone-forming surfaces in the absence of bone marrow invasion by tumor. This observation is consistent with a systemic effect of a 1,25-(OH)2-D–like metabolite or another humoral factor on bone cell function.

The results of this study lend further support to the concept that deranged metabolism of vitamin D by cells of the immune system may be responsible for hypercalcemia and hypercalciuria in a variety of human disorders. The potential role for local production of active vitamin D metabolites in normal skeletal physiology and the identity of other cytokines that might explain hypercalcemia in lymphoma patients with suppressed 1,25-(OH)2-D concentrations remain to be determined.

## ACKNOWLEDGMENT

We are indebted to D. Ramos, K. Johnson, M. Yuen, and S. Stover for technical assistance and to Dr G.J. Marshall for helpful discussions.

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<thead>
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<th>Patients</th>
<th>n</th>
<th>CAs (mg/dL)</th>
<th>1,25-(OH)2-D (pg/mL)</th>
<th>CAu (mg/100 mL GFE)</th>
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<td>With Lymphoma</td>
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<td>9.0 ± 0.1</td>
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<tr>
<td>− AIDSt</td>
<td>12</td>
<td>9.2 ± 0.1</td>
<td>39.5 ± 5.1</td>
<td>0.13 ± 0.04*</td>
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<tr>
<td>+ AIDS</td>
<td>11</td>
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<td>36.5 ± 6.0</td>
<td>0.10 ± 0.03*</td>
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<tr>
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<td>18</td>
<td>9.0 ± 0.1</td>
<td>31.1 ± 3.2</td>
<td>0.05 ± 0.02</td>
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*The fractional urinary calcium excretion rate significantly greater (P < .05) than in patients with AIDS not associated with lymphoma.

†HIV testing was negative in all 12 patients.

## Table 2. Calcium Homeostasis in Normocalcemic Patients

Because hypocalciuria frequently precedes the development of overt hypercalcemia in vitamin D metabolite–mediated disorders of calcium homeostasis, we prospectively screened a group of 23 normocalcemic lymphoma patients, both with AIDS and non-AIDS-associated disease, for hypercalciuria (Table 2, Fig 3). An increased fractional urinary calcium excretion rate was found in four of the 23 patients (17%). Two of these patients had a frankly elevated serum 1,25-(OH)2-D concentration. These results suggest that an elevated serum value for 1,25-(OH)2-D and fasting hypercalciuria may be the forerunner of vitamin D metabolite–mediated hypercalcemia in patients with lymphoma.

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REFERENCES


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