Fifteen patients with lymphoma and hypercalcemia (≥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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cochromatographs with authentic 1,25-(OH)2-D and competes with chromatography in diverse solvent systems for sample purification, followed by chromatography on a silica (normal-phase) Sep-Pak cartridge before competitive protein binding assay.

The interassay coefficient of variation for all serum tested in this assay was 8.1% and 15.0% for consecutive-day samples from the same patient; 6.9% and 12.0% of human PTH. The coefficient of variation for values from the same sample was 12.2%.

The stippled areas represent the range of normal values in a population of normocalcemic patients.

**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 in 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 1) 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 1) 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-

---

**Table 1. Clinical and Biochemical Features of Lymphoma Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Type</th>
<th>Stage HIV-1¢</th>
<th>HTLV-1¢</th>
<th>Ca2+ (mg/dL)</th>
<th>Caμ</th>
<th>Hypercalcemic patients</th>
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<tr>
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<td>57</td>
<td>LNC-FCC</td>
<td>III</td>
<td>ND</td>
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<td>2</td>
<td>F</td>
<td>63</td>
<td>SNC</td>
<td>IV</td>
<td>ND</td>
<td>ND</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>SC-FCC</td>
<td>IV</td>
<td>ND</td>
<td>ND</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>75</td>
<td>SC-FCC</td>
<td>IV</td>
<td>ND</td>
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<td>16.1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>62</td>
<td>Hodgkin’s</td>
<td>IV</td>
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<td>ND</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>48</td>
<td>LNC-FCC</td>
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<td>—</td>
<td>12.2</td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
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<td>B-IBS</td>
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<td>+</td>
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<td>8</td>
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<td>14.6</td>
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<td>47</td>
<td>ATCL</td>
<td>IV</td>
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<tr>
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<td>B-IBS</td>
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<td>32</td>
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<tr>
<th>Hypercalciuric patients</th>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Type</th>
<th>Stage HIV-1¢</th>
<th>HTLV-1¢</th>
<th>Caμ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>F</td>
<td>63</td>
<td>LNC-FCC</td>
<td>III</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>9.1</td>
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<td>+</td>
<td>+</td>
<td>10.2</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*LNC-FCC, large noncleaved follicular center cell; SNC-B, small noncleaved B cell; SC-FCC, small cleaved follicular center cell; B-IBS, B-cell immunoblastic sarcoma; ATCL, adult T-cell lymphoma/leukemia.

¢ND, virus screening not performed.

1 Corrected for the serum albumin concentration: serum calcium (mg/dL) − serum albumin (g/dL) + 4.

2 Fractional urinary calcium excretion rate; normal, <0.16 mg calcium/100 mL GF.

3 Bone marrow involvement by tumor.

---

*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.*
therapy. In patient 8, a young man with AIDS-associated lymphoma, 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 3 weeks after initiation of chemotherapy. The rapidity of the response was more pronounced in patient 10. Within ten days of the 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 ± 0.3 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 in 23 normocalcemic patients with lymphoma, either associated (open squares) or not associated with AIDS (closed squares, panel A), and in 18 normocalcemic patients with AIDS not associated with lymphoma (panel B). The stippled area depicts the normal range of values for both tests. Correlation of the two parameters was ascertained by the method of least squares.

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-
tons are altering the normal production and/or catabolism of extrarenal site has been established in the human granulocytic lymphoma patients are not subject to control by those accompanying increase in the serum iPTH concentration the vitamin D metabolite-mediated hypercalcemia. In this of the host antitumor chemotherapeutic regimens and silicone-induced granulomatous disease.32 In the current (Fig 2). These results demonstrate that circulating concentrations of the active vitamin D metabolite in some hypercalcemic patients are not subject to control by those factors that normally regulate the renal 25-OH-D-l-a-hydroxylase22 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 sarcoidosis23; the sarcoid macrophage has related metabolite is extrarenal. Precedent for the inappro- ximation that was below the range of normal. Furthermore, studies from our laboratory,27 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 hypercalcemia 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 hypercalcemia (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 hypercalcemia may be the forerunner of vitamin D metabolite-mediated hypercalcemia in patients with lymphoma.

Among the nine hypercalcemic/hypercalcicuric 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.5 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 patients in this study, five of whom had an adrenal mass or other tumor-derived cytokine could induce pathologic bone resorption. However, previous histo- morphometric 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.58 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 hypercalcicuria 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.

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HYPERCALCEMIA IN PATIENTS WITH LYMPHOMA

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Vitamin D metabolite-mediated hypercalcemia and hypercalciuria patients with AIDS- and non-AIDS-associated lymphoma

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