

CASE REPORT

# Hypercalcemia in Langerhans' Cell Granulomatosis With Elevated 1,25 Dihydroxyvitamin D (Calcitriol) Level

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A 48-year-old woman presented with a history of premature menopause, polyuria, polydipsia, fever, and diffuse bony tenderness. Her evaluation revealed central diabetes insipidus, hypothalamic amenorrhea, an elevated free calcium on multiple occasions with an elevated 1,25 dihydroxyvitamin D level, and osteoporosis by densitometry. Skeletal series revealed multiple lytic lesions involving the long bones. The diagnosis of Langerhans' cell granulomatosis was made. She was treated with hormone replacement therapy, radiotherapy, and vinblastine, with a dramatic improvement in her pain and a near normalization of her free calcium. Whereas hypercalcemia has been described in several granulomatous disorders and is secondary to unregulated extrarenal production of 1,25 dihydroxyvitamin D, it is, however, extremely rare in Langerhans' cell granulomatosis. This is the first case report of Langerhans' cell granulomatosis with hypercalcemia and documented elevated increased 1,25 dihydroxyvitamin D level that responded to the treatment of her primary disease. (Bone 30:331–334; 2002) © 2002 by Elsevier Science Inc. All rights reserved.

**Key Words:** Langerhans' cell granulomatosis; Hypercalcemia; 1,25(OH)<sub>2</sub>D.

## Introduction

Langerhans' cell granulomatosis (LCG) is a rare multisystem disease of unclear etiology that is more common in children than adults.<sup>3,10,14</sup> Although skeletal involvement is one of its commonest presenting features, the occurrence of hypercalcemia is extremely rare. Furthermore, the etiology of hypercalcemia in the two cases published in the literature was unclear. We describe the first case report of an adult with LCG with multiple skeletal involvement and hypercalcemia that was associated with elevated 1,25 dihydroxyvitamin D level and that responded to treatment of the primary disease.

## Case Summary

A 48-year-old woman presented with a history of weight loss of 15 pounds over 5 months, fever, anorexia, generalized weakness,

and irritative cough of several months' duration. The patient also complained of diffuse pain over the long bones, especially in the lower extremities, which was restricting the patient's motion, and of polyuria and polydipsia (4–5 L/day) for several months. Twenty years before admission, she was diagnosed to have ulcerative colitis by colonoscopy after presenting with bloody diarrhea. She was treated with Asacol for 10 months; it was discontinued due to development of severe glossitis and gingivitis. Ten years before admission, the patient had premature menopause that was not investigated, and she was transiently treated for few months with cyclical hormone replacement therapy (HRT). Seven years before admission, she complained of right lower limb pain, swelling, and a biopsy of a right lytic tibial lesion revealed LCG. She was treated with analgesics (Paracetamol), but the pain was progressively becoming more intense and bilateral, thus restricting the patient's ambulation.

## Physical Examination

Examination revealed a sick-looking, middle-aged woman with a temperature of 39°C. The relevant findings included a body mass index of 20 kg/m<sup>2</sup>, the presence of glossitis and gingivitis, and tenderness on pressure over the proximal left and right tibial areas.

## Laboratory Studies

Studies revealed hemoglobin (Hb) 6.3 g/dL, hematocrit (Hct) 20%, mean corpuscular volume (MCV) 60 femtoliter (fl), calcium 9.7 mg/dL (normal [nl]: 8.5–10.5), albumin 20 g/L (nl: 36–53). Corrected total calcium calculated as: measured total calcium + 0.8(4.5 – albumin) = 11.3 mg/dL. Several serial calcium measurements obtained within 1 week were equally elevated, calculated at 11.5 and 11 mg/dL using the above formula, phosphorus 4.4 mg/dL, intact parathyroid hormone (PTH) 8.7 pg/mL (nl: 8.0–76.0), alkaline phosphatase was elevated at 186 IU/L (nl: up to 120), 25 hydroxy vitamin D [25(OH)D] 12.2 ng/mL (nl: 20–60), 1,25 dihydroxy vitamin D [1,25(OH)<sub>2</sub>D] 89.3 pg/mL (nl: 20.1–46.2), and a 24-h urine calcium 178 mg/24 h, thyroid stimulating hormone (TSH) 0.42 μU/mL (nl: 0.3–3.0), FT4 0.7 ng/dL (nl: 0.6–1.8), am cortisol level 14.00 μg/100 mL. The serum intact PTH was measured with the use of ELISA-PTH immunoradiometric assay (Cis Bio International, Gif-sur-Yvette, France) and the 25(OH)D by a competitive protein binding assay with the use of the Diasoren Incstar kit (Incstar, Stillwater, MN).

A few days after admission, she developed hypernatremia, Na 160 mEq/L, with a 24-h urine volume of 4–5.5 L. She had a low

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**Figure 1.** Lateral plain radiograph of the right knee and leg shows multiple lytic lesions in the distal femur and tibia. Endosteal scalloping is noted at the posterior tibial cortex. Sclerotic areas surround the lytic lesions. The proximal fibula shaft shows thinning of its anterior cortex and ill-defined bony rarefaction.



**Figure 2.** Anteroposterior plain radiograph of the distal left femur shows diffuse abnormal bone trabeculations involving the diaphysis, metaphysis, and epiphysis of the femur. Note both lytic and sclerotic pattern of the bony involvement in this patient with LCG.

urine osmolality (Uosm), 104, in the presence of a high serum osmolality of 291. The diagnosis of diabetes insipidus (DI) was suspected and confirmed by an increase of Uosm of more than 65% after 1  $\mu$ g of desmopressin SC (Uosm 139 at time 0, 242 at 1 h, and 369 at 2 h). The evaluation of her amenorrhea revealed an undetectable estradiol level; follicle stimulating hormone (FSH) and luteinizing hormone (LH) were inappropriately low for a menopausal state measured at 0.7 mIU/mL (nl: 9.0–75.0) and 1.6 mIU/mL (nl: 31.0–134.0), respectively. Luteinizing hormone releasing hormone (LHRH) and Thyrotropin releasing hormone (TRH) stimulation tests revealed an intact pituitary reserve with an appropriate stimulation of TSH, prolactin, FSH, and LH levels.

#### Imaging

A skeletal series revealed multiple slightly expansile lytic lesions with endosteal scalloping involving the distal shafts of both femora and proximal right tibia (Figures 1 and 2). These were surrounded by coarse trabeculae. Sclerosis with small lucent lesions were noted in the right intertrochanteric region, distal radius and ulna, and proximal ulna bilaterally. A bone scan showed faint increase uptake at the sites of bony involvement. Bone mineral density was measured with a Lunar DPX-L densitometer and revealed osteoporosis at the level of the spine, T

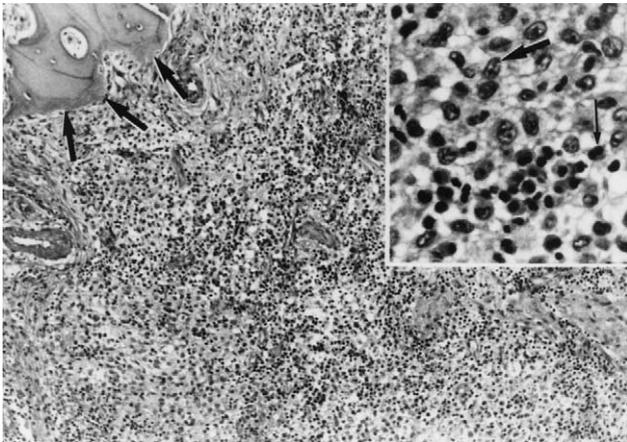
score (number of SD below peak young normal) was  $-3.08$ , and severe osteopenia at the hip, T score  $-2.20$ . Total-body bone mineral density (BMD) T score was  $-0.61$ . Computed tomography scan of abdomen, pelvis, and chest and mammogram were all normal. Pulmonary function tests were normal.

#### Pathology

Bronchial washings showed no significant pathologic abnormality. Rectosigmoid biopsies revealed nonspecific acute colitis but no evidence of LCG. Review of the previous tibial biopsy showed the classic histologic features of LCG with positive immunohistochemical staining for S-100 protein (Figures 3 and 4).

#### Hospital Course

The patient received several transfusions for her anemia. Her workup for infections was negative. She had radiation of the lesion in the right femur/tibia for a total dose of 15.4 Gy delivered in eight fractions over 10 days, and was also given vinblastine 10 mg intravenous push (IVP) once weekly. Her pain started improving several days after the start of the radiotherapy. She was started on desmopressin intranasally 10  $\mu$ g daily for her DI, and on HRT. Corticosteroids were avoided due to the low bone density. Calcium level repeated 1 month after discharge,



**Figure 3.** A section of the tibial lesion showing a dense cellular infiltrate expanding the marrow space, with a bone trabeculum seen in the left upper corner (arrows) (H&E,  $\times 40$ ). The inset shows the infiltrate to be composed mainly of Langerhans' cells (thick arrow) and eosinophils (thin arrow) (H&E,  $\times 400$ ).

after having received four cycles of vinblastine and eight sessions of radiotherapy, was 7.6 mg/dL (free calcium 5.6 mg/dL).

### Discussion

Langerhans' cell granulomatosis (or eosinophilic granuloma) is a disease of unknown etiology that encompasses a wide spectrum of clinical, pathologic, and radiologic features that is more common in children.<sup>3,10,14</sup> The hallmark of the disease is an abnormal proliferation of reticuloendothelial cells, predominantly the histiocyte. The association of LCG and hypercalcemia is extremely rare: to our knowledge, only two cases were reported so far, neither of which with a clear documentation of the etiology of the hypercalcemia. The first was a case report of a 46-year-old black woman with eosinophilic granuloma of the lung who had a calcium of 11-12 mg/dL that improved to 10.6 mg/dL after treatment with hydrocortisone 50 mg bid for 8 days.<sup>7</sup> The etiology of the hypercalcemia was unclear, as vitamin D metabolites were not measured; however, the calcium response

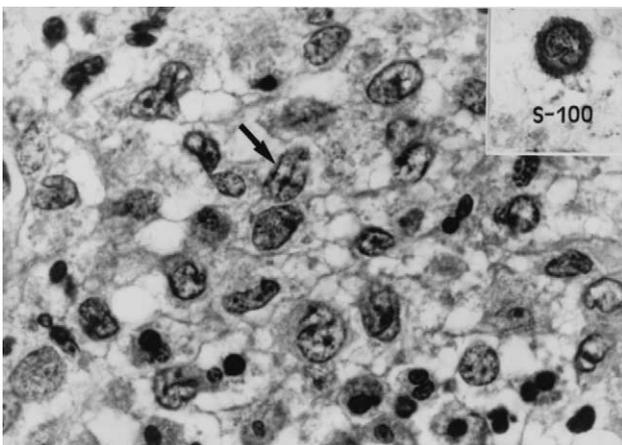
to corticosteroids suggests that it may have been mediated by vitamin D excess.<sup>7</sup> The second case, which was part of a 348-case series of LCG reported in France, had severe hypercalcemia (up to 16 mg/dL) and multiple bony lesions. The etiology of the hypercalcemia was also unclear; however, it was said to have resolved without any complications.<sup>13</sup> Our case is the first where the hypercalcemia is documented in the presence of elevated 1,25(OH)<sub>2</sub>D level. Other possible mechanisms for the hypercalcemia include production of bone-resorbing cytokines such as interleukin-1 and prostaglandin E<sub>2</sub>, both of which have been described to be secreted by the Langerhans' cells *in vitro*.<sup>2</sup> It is unlikely that the hypercalcemia in our patient was secondary to a malignancy. Indeed, in humoral hypercalcemia of malignancy (HHM), the 1,25(OH)<sub>2</sub>D level is low,<sup>12</sup> unless the malignancy is a lymphoma, for which there was no evidence in this case. Furthermore, an extensive radiologic evaluation in our patient was negative for malignancy. Elevated blood levels of 1,25(OH)<sub>2</sub>D have been described in hypercalcemic patients with several granulomatous diseases such as sarcoidosis,<sup>1,6</sup> tuberculosis,<sup>4</sup> disseminated candidiasis,<sup>8</sup> silicone-induced granuloma,<sup>9</sup> and histoplasmosis,<sup>11</sup> but have not been previously reported in LCG. In contrast to the normal situation, in which the renal conversion of circulating 25(OH)D to 1,25(OH)<sub>2</sub>D is tightly regulated, in patients with these granulomatous disorders, 1,25(OH)<sub>2</sub>D production appears to be largely, and perhaps exclusively, substrate dependent. The low 25(OH)D levels in our patient speak to that effect. It could, therefore, be argued that the 1,25(OH)<sub>2</sub>D in our patient may have been even more elevated if she did not have vitamin D insufficiency (low 25(OH)D levels), thus jeopardizing further extrarenal conversion to 1,25(OH)<sub>2</sub>D.

Hypercalcemia can be the cause of diabetes insipidus, albeit of the nephrogenic type. Our patient had documented central diabetes insipidus. The hypercalcemia in our case is most likely due to elevated 1,25(OH)<sub>2</sub>D level resulting in enhanced intestinal calcium absorption, increased bone resorption,<sup>5</sup> and possibly hypercalcemia-induced reduction in glomerular filtration. There may also have been an element of cytokine-induced bone resorption, although cytokines were not measured in our patient. The normalization of her calcium may have been due to control of her primary disease with chemotherapy and possibly radiotherapy; unfortunately, a 1,25(OH)<sub>2</sub>D level posttreatment was not available, as the patient was lost to follow-up.

In summary, this is the first reported case of LCG presenting with hypercalcemia due to elevated 1,25(OH)<sub>2</sub>D level that responded to treatment of the primary disease. It would have been possible to treat the hypercalcemia with corticosteroids; however, this was avoided because of the patient's osteoporosis, which was most severe at trabecular sites. The favorable prognostic factors in this patient are her older age and the lack of solid organ involvement; however, the multiple bone lesions put her in a worse prognostic category. The clinical course of this disease is highly variable and, therefore, the long-term evolution of her LCG in general and hypercalcemia in particular remain to be determined.

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**Figure 4.** Further magnification reveals the characteristic lobulated appearance of Langerhans' cell nuclei. The arrow shows one such cell with a longitudinal nuclear groove (H&E,  $\times 1000$ ). Positive cytoplasmic immunostaining for S-100 protein of a Langerhans' cell is seen in the inset ( $\times 1000$ ).

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*Date Received:* May 21, 2001

*Date Revised:* September 6, 2001

*Date Accepted:* September 7, 2001