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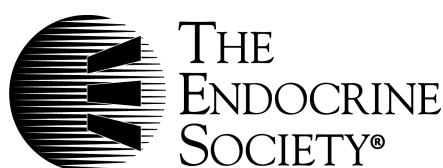
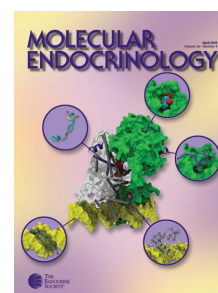
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Rare Causes of Calcitriol-Mediated Hypercalcemia: A Case Report and Literature Review

Melissa Kallas, Francis Green, Martin Hewison, Christopher White,
and Gregory Kline

Department of Medicine (M.K., G.K.), University of Calgary, Calgary, Alberta, Canada T2N 4J8; Department of Pathology and Laboratory Medicine (F.G.), University of Calgary, Calgary, Alberta, Canada T2N 2N1; Department of Orthopaedic Surgery (M.H.), University of California, Los Angeles, California 90095-7358; and Department of Clinical Neurosciences (C.W.), University of Calgary, Calgary, Alberta, Canada T2N 2T9

Context: Calcitriol-mediated hypercalcemia resulting from elevated extrarenal 25-hydroxyvitamin D-1 α -hydroxylase (1 α -hydroxylase) activity has not previously been described in giant cell polymyositis.

Case: We report an unusual case of hypercalcemia due to disseminated granulomatous disease in a 62-yr-old woman with profound proximal muscle weakness and weight loss. She was initially diagnosed with vitamin D deficiency myopathy with a low serum 25-hydroxyvitamin D; serum calcium at this time was low-normal. Vitamin D₃ 3000 IU daily was prescribed. One month later, blood work showed new hypercalcemia and hypercalciuria with normalized 25-hydroxyvitamin D. 1,25-dihydroxyvitamin D was high-normal, despite a suppressed PTH, undetectable PTHrP, and essentially normal renal function. Her hypercalcemia resolved, and her strength improved only after prednisone was added to bisphosphonate therapy. Two weeks later, she died from acute congestive heart failure.

Methods and Results: Autopsy revealed a disseminated giant cell myositis affecting skeletal, cardiac, and gastrointestinal smooth muscle. Immunohistochemistry localized 1 α -hydroxylase to the inflammatory infiltrates in skeletal and cardiac muscle.

Evidence: A review of English publications in Medline and Embase, including a reference search of retrieved articles, revealed that calcitriol-mediated hypercalcemia has been described in over 30 conditions, most of which are granulomatous in nature, ranging from inflammatory conditions and foreign body exposures to infections and neoplasms.

Conclusions: Hypercalcemia resulting from autonomous 1 α -hydroxylase activity may be unmasked by low-dose vitamin D supplementation and should not be excluded from the differential diagnosis of nonparathyroid causes if the serum calcitriol is inappropriately normal, rather than frankly elevated. (*J Clin Endocrinol Metab* 95: 3111–3117, 2010)

Along with awareness of the importance of vitamin D in calcium homeostasis, inappropriately elevated 1,25-dihydroxyvitamin D [1,25(OH)₂D] in granulomatous, neoplastic, and other diseases is increasingly implicated as a cause of hypercalcemia. In sarcoidosis, the well-known prototype, hypercalcemia is common, with an estimated incidence of 11% (1). However, in other con-

ditions, including inflammatory diseases [*e.g.* Crohn's disease (2, 3)], infections [*e.g.* disseminated candidiasis (4)], and foreign body granulomas [*e.g.* from silicone (5)], hypercalcemia is extremely rare and is described only on the basis of a few case reports. The unifying mechanism, as exemplified in sarcoidosis, is attributed to elevated extrarenal 25-hydroxyvitamin D-1 α -hydroxylase (1 α -hydrox-

ylase) activity in tissue macrophages (6), leading to increased serum $1,25(\text{OH})_2\text{D}$ levels. Unlike the native renal enzyme, macrophage 1α -hydroxylase activity is resistant to normal feedback controls (7) but is sensitive to suppression with corticosteroids (8).

Here, we present the first report of hypercalcemia associated with giant cell polymyositis (GCP), an idiopathic systemic granulomatous disease. The hypercalcemia was unmasked by correction of nutritional vitamin D deficiency and was associated with inappropriately high-normal, rather than elevated, serum calcitriol. We review the literature describing unusual causes of calcitriol-mediated hypercalcemia and suggest that GCP should be added to this broad differential diagnosis.

Patient and Methods

Patient

A 62-yr-old woman presented to an outpatient neurology clinic with a 2-yr history of painless progressive proximal leg and arm weakness and a 30-pound weight loss. She could only ambulate two blocks with a walker and had difficulty with overhead arm movement. Review of systems was significant for chronic diarrhea and a leg rash, and she had recently undergone investigation for incidental splenomegaly. She was a smoker and had a history of excess alcohol use and possible rheumatoid arthritis. Her only medications were acetaminophen, pancreatic lipase, and zopiclone. There was no unusual travel and no occupational, animal, or drug exposures, nor any risk factors for tuberculosis.

On examination, she was normotensive and afebrile, but appeared cachectic. Neurological abnormalities included Medical Research Council grade 3/5 motor strength in the shoulders, elbows, and knees with only 2/5 strength on hip flexion. She had a scaly macular rash on her torso and limbs, axillary adenopathy, and splenomegaly. The rest of her general examination was unremarkable.

Initial investigations suggested vitamin D deficiency myopathy with a serum 25-hydroxyvitamin D [$25(\text{OH})\text{D}$] of 9.9 nmol/liter (normal, 40–130 nmol/liter; RIA; DiaSorin Inc., Stillwater, MN) and needle electromyography showing voluntary motor unit potentials consistent with a myopathy with segmental necrosis. Serum calcium at presentation was low-normal (2.16 mmol/liter; normal, 2.10–2.55) with a normal albumin at 33 g/liter (normal, 33–48 g/liter). Vitamin D_3 3000 IU daily was prescribed, and a rehabilitation program was instituted.

One month later, routine blood work demonstrated new-onset hypercalcemia (3.84 mmol/liter; albumin, 29 g/liter) and hypercalciuria (9.63 mmol/d) in the context of normalized $25(\text{OH})\text{D}$ (122 nmol/liter; normal, 80–200; LIAISON chemiluminescence assay; DiaSorin Inc.). At this time her $1,25(\text{OH})_2\text{D}$ was high-normal at 156 pmol/liter (normal, 55–190; RIA; DiaSorin Inc.), despite a suppressed intact PTH (8 ng/liter; normal, 13–54; LIAISON automated immunoassay; DiaSorin Inc.) and undetectable PTHrP (<2 pmol/liter; normal, <4; Quest Diagnostics, Madison, NJ). Remaining blood work showed the following: hemoglobin, 117 g/liter (normal, 120–160); creatinine kinase, 19 U/liter (0–170); creatinine, 101 $\mu\text{mol/liter}$ (35–100; estimated glomerular filtration rate, 51 ml/min/1.73 m^2); phos-

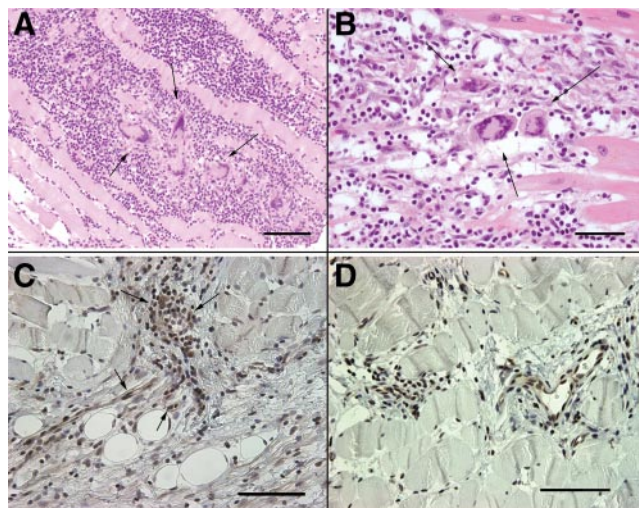


FIG. 1. A, Antemortem skeletal muscle biopsy showing granulomatous inflammation with multinucleate giant cells (arrows). The inflammatory infiltrate is both perimysial and endomysial in distribution. There is variation of muscle fiber size, and the myopathy was accompanied by mild denervation. Hematoxylin and eosin; scale bar = 100 μm . B, Postmortem cardiac muscle with giant cell (arrows) granulomas and inflammatory infiltrates similar to those seen in the skeletal muscle. Hematoxylin and eosin; scale bar = 50 μm . C, Expression of 1α -hydroxylase (brown) in histiocytes (tissue macrophages) in antemortem skeletal muscle biopsy using a previously characterized (9) polyclonal antiserum (1:1000 dilution). The secondary antibody was visualized with 3,3'-diaminobenzidine, and sections were counterstained with Mayer's hematoxylin. There is strong expression in histiocytes (arrows) and low level expression in muscle tissue. Scale bar = 50 μm . D, Negative control using 1α -hydroxylase antiserum preabsorbed with immunizing peptide as previously reported (9). Scale bar = 50 μm .

phate, 1.57 mmol/liter (0.80–1.50); TSH, 2.14 mU/liter (0.20–6.00); and morning cortisol, 450 nmol/liter. Her white blood cell count, rheumatoid factor, antinuclear antibody, celiac screen, lactate dehydrogenase, and serum protein electrophoresis were normal. A computed tomography scan of the chest, abdomen, and pelvis demonstrated bilateral axillary and periaortic adenopathy as well as splenomegaly. Axillary lymph node biopsy, bone marrow examination, and nuclear medicine bone scan were nondiagnostic with no evidence for malignancy. The patient was bedridden by her weakness. Initial therapy in hospital with iv fluids and bisphosphonate (pamidronate, 90 mg iv) resulted in only modest improvement in her serum calcium to the 2.80 to 3.08 mmol/liter range, despite normalized renal function. When a muscle biopsy (Fig. 1A) showed granulomatous myositis, corticosteroids (prednisone, 50 mg daily) were commenced. The hypercalcemia rapidly decreased to 2.46 mmol/liter (albumin, 27 g/liter), and her muscle strength improved to such a degree that she was able to walk again. Two weeks later, she died at home in acute congestive heart failure.

A full autopsy revealed a disseminated giant cell granulomatous process affecting skeletal, cardiac (Fig. 1B), and gastrointestinal smooth muscle. Massive involvement of the heart was the immediate cause of death. Pulmonary edema was present, as well as hepatosplenomegaly attributable to congestion (no inflammation or infiltration). In the skeletal muscle and lymph nodes, the numbers of histiocytes (tissue macrophages) and giant cells were decreased compared with the biopsies before receiving prednisone. The inflammatory infiltrates were similar in appear-

ance to a skin rash biopsy that had been performed 7 yr earlier. The histopathology and distribution of the granulomatous disease was not characteristic of sarcoidosis or Langerhans cell histiocytosis. There was no evidence of a malignancy (including lympho-proliferative disorders), vasculitis, or small bowel mucosal ulceration (Crohn's disease). Stains (Gram, Grocott, ZN, and Fite) were negative for infectious agents.

Immunohistochemistry

Immunohistochemistry was used to characterize the inflammatory cell infiltrates in and around the granulomas. The histiocytic cells (including giant cells) were CD68 positive; only scarce S100-positive cells and even rarer CD1a-positive cells were detected. The small number of these cells, their normal nuclear morphology, and absence of eosinophils ruled out a diagnosis of Langerhans cell histiocytosis. The surrounding inflammatory cell infiltrate was predominantly composed of CD3/CD4 positive T lymphocytes. Almost no B (CD20) lymphocytes were seen in the lesions.

Immunohistochemical analysis of 1α -hydroxylase protein expression in paraffin-embedded tissue sections was carried out using methods described previously (9). Extensive positive 1α -hydroxylase staining of histiocytic cells was seen in antemortem (Fig. 1, C and D) and postmortem samples of voluntary muscle.

Discussion

Our case is the first report of hypercalcemia associated with GCP. GCP is an extremely rare idiopathic granulomatous process affecting multiple muscle groups (10, 11). Our patient's condition was significant for having not only striated voluntary muscle involvement but also cardiac and intestinal smooth muscle. An association with thymoma or autoimmune conditions has been reported (10). The typical presentation depends on involved areas but may include proximal muscle weakness and fatal cardiac involvement. GCP appears to be a clinical entity distinct from giant cell myocarditis, which is generally confined to the myocardium (12, 13). Key pathological features for distinguishing giant cell myocarditis from sarcoid inflammation in the heart have been described (13), and our patient had no features of disseminated sarcoidosis at autopsy. Evidence of other systemic diseases, including malignancies or vasculitis, was absent. The same inflammation was seen in the lymph nodes as in the muscles, and the hepatosplenomegaly was congestive rather than inflammatory or infiltrative. The patient's weight loss was most likely a combination of poor baseline nutritional status, systemic inflammation, and small bowel involvement with chronic diarrhea. Her hypercalcemia was a result of autonomous extrarenal 1α -hydroxylase, provoked by exogenous vitamin D supplementation and exacerbated by calcium-induced diuresis, hypovolemia, and mild acute renal insufficiency. A high-normal $1,25(\text{OH})_2\text{D}$ is not consistent with malignancy- or immobilization-associated hypercalcemia, and bisphosphonates would have effectively treated any

concurrent immobilization hypercalcemia. Her calcium normalized, and she regained her mobility only after corticosteroid introduction suppressed extrarenal 1α -hydroxylase (8), presumably lowering her $1,25(\text{OH})_2\text{D}$ and thereby reducing calcium absorption from the intestine.

Our review demonstrated over 30 conditions with suspected calcitriol-mediated hypercalcemia, including infections, foreign body exposures, autoimmune diseases, and neoplasms (Table 1). In several cases of calcitriol-mediated hypercalcemia, a distinct disease entity was not found despite extensive investigations (14, 15). At the heart of these associations appears to be overexpression of 1α -hydroxylase by tissue macrophages, identified in non-Hodgkin's lymphoma (16), dysgerminoma (17), and granulomatous slack skin disease (18), and the case of GCP presented here. In addition to sarcoidosis (19), calcitriol-mediated hypercalcemia has been described in association with Crohn's disease, where serum calcium and $1,25(\text{OH})_2\text{D}$ levels parallel disease activity (2, 3), as well as Wegener's granulomatosis (20–22), Langerhans cell granulomatosis (23), liver granulomas in chronic dialysis patients (24), and subcutaneous fat necrosis of the newborn (25). Rheumatoid arthritis (26) and severe osteoarthritis (27) may have a similar mechanism, supported by observations that synovial fluid macrophages in inflammatory arthritides may produce $1,25(\text{OH})_2\text{D}$ (28).

Infectious causes of calcitriol-mediated hypercalcemia should be considered particularly in immunocompromised patients, including those with HIV or transplant recipients. Mycobacterial infections such as tuberculosis (29–31) are a well-known cause of calcitriol-mediated hypercalcemia. Alveolar immune cells in bronchoalveolar lavage samples from patients with tuberculosis have been shown to produce $1,25(\text{OH})_2\text{D}$ *in vitro* (32), but the extent to which it contributes to hypercalcemia depends partly on clinical characteristics (33). Hypercalcemia has also been reported in leprosy (34–36) and in a patient with transitional cell carcinoma of the bladder who was treated with intravesical bacillus Calmette-Guerin (BCG), complicated by BCG sepsis (37). Disseminated *Mycobacterium avium* complex infection (38, 39) and *Pneumocystis jirovecii* pneumonia (40) have both been implicated as additional causes of calcitriol-mediated hypercalcemia in patients with AIDS. Similarly, hypercalcemia has been found in a variety of fungal infections including disseminated candidiasis in a patient with acute lymphocytic leukemia (4), histoplasmosis associated with subacute hand tenosynovitis (41), and paracoccidioidomycosis [South American blastomycosis (42)]. Coccidioidomycosis has been associated with hypercalcemia in a heart transplant patient with concurrent thyroiditis (43) but also in conjunction with cryptococcal pneumonia (44). Reports of hypercalcemia with cryptococcus include patients with end-stage renal disease (45) and AIDS (46). All of these infection-related dis-

TABLE 1. Reported causes of calcitriol-mediated hypercalcemia

Disease	Clinical clues	Ref.
Crohn's disease	Chronic diarrhea with crampy abdominal pain; fistulae and perianal disease; skin, eye, joint involvement	2, 3
Hepatic granulomatosis in chronic dialysis	Cholestasis without cholelithiasis in chronic hemodialysis patients	24
Langerhans cell histiocytosis (formerly eosinophilic granuloma)	Systemic disorder that may include interstitial lung disease, diabetes insipidus and/or hypopituitarism, rash, or bone pain	23
Osteoarthritis	Severe degenerative arthritis	27
Rheumatoid arthritis	Symmetric polyarticular inflammatory arthritis including small joints; possible pleuropericarditis, vasculitis, neuropathy, sc nodules, renal and eye disease	26
Sarcoidosis	Lung disease with hilar adenopathy; also skin, bone, muscle, cardiac, eye, or neurological involvement	19
Slack skin disease	Lymphoproliferative skin disorder with indurated plaques that progress to drooping masses of skin	18
Subcutaneous fat necrosis of the newborn	Erythematous, distinct sc nodules involving sites with thick fat deposits, appearing within weeks of birth, and often related to fetal distress	25
Wegener's granulomatosis	Upper and lower respiratory tract disease and acute renal failure; eye, skin, joint, or nerve involvement	20–22
Foreign substance reactions		
8-Cl-cAMP therapy	Experimental chemotherapy agent	50
Lipoid pneumonia	Pulmonary infiltrates from aspiration or inhalation of fat-like material, e.g. oil-based laxatives or nasal preparations	48, 49
Silicone granulomatosis	Silicone injections, implants, or contamination	5
Talc granulomatosis	Lung disease from occupational or industrial exposure to pharmaceuticals, cosmetics, lubricating or dusting agents; also injection drug users (filler agents in tablets)	47
Infectious causes		
BCG therapy/sepsis	Adjunctive therapy for superficial bladder cancer	37
Candidiasis	Immunocompromised or critical care patient with fever; may have skin pustules or nodules, eye lesions (chorioretinitis, endophthalmitis), muscle abscesses	4
Cat-scratch fever	Self-limited regional lymphadenopathy after cat scratch or bite (<i>Bartonella henselae</i>)	64
Coccidioidomycosis	Lung infection possibly with cutaneous manifestations (erythema nodosum and multiforme); risk of disseminated disease in immunocompromised hosts to central nervous system, soft tissue, or skeleton	43
Cryptococcosis	Immunocompromised patient with lung infection or meningoencephalitis; may have skin lesions resembling molluscum contagiosum	45, 46; in combination with coccidioidomycosis, 44
Histoplasmosis	Endemic in central and southern USA; acute to chronic lung infection, arthritis/arthralgias, erythema nodosum or multiforme, with local involvement oropharynx, skin, gastrointestinal tract, brain, or adrenals	41
Leprosy	Developing countries; skin lesions may be accompanied by sensory or motor loss	34–36
Mycobacterium avium complex	Lung disease; superficial lymphadenitis; or disseminated disease (lung or gastrointestinal) in immunocompromised patients	38, 39
Paracoccidioidomycosis (formerly South American blastomycosis)	Chronically progressive lung infection with male gender bias and Latin American distribution; also skin (ulcers or vegetations), lymph node, mucous membrane, or adrenal involvement	42
<i>Pneumocystis carinii</i> (<i>P. jirovecii</i>)	Indolent (HIV+) or fulminant (other immunocompromised states) lung infection	40
Tuberculosis	Pulmonary and extrapulmonary disease (pleura, lymph nodes, meningitis, pericarditis, bone marrow, genitourinary); immunocompromised or from endemic area	29–31

(Continued)

TABLE 1. Continued

Disease	Clinical clues	Ref.
Neoplastic causes		
Dysgerminoma	Ovarian tumor with predilection for young women	17, 52
Hodgkin lymphoma	Lymphadenopathy spreading in a contiguous fashion, especially cervical or mediastinal; may have pruritus	51
Leiomyoblastoma (gastrointestinal stromal tumor)	Mesenchymal tumors, especially of the stomach or small intestine, presenting with pain, obstruction, or bleeding	54
Lymphomatoid granulomatosis/angiocentric lymphoma	Lymphoproliferative disorder with blood vessel involvement	55
Non-Hodgkin's lymphoma	Lymphadenopathy with diverse presentations depending on site, increased risk in certain chronic diseases (e.g. HIV)	16, 51
Plasma cell granuloma	Primary lung tumor, found more commonly in children and young adults	57
Seminoma	Painless testicular mass	53
Squamous cell bronchogenic carcinoma	Non-small cell lung cancer with tendency to involve central airways	56

eases are associated with granulomatous inflammation, in which tissue macrophages predominate.

Other rare causes of calcitriol-mediated hypercalcemia include foreign substance reactions, such as to talc in a former mold maker (47). Two cases of hypercalcemia with lipoid pneumonia have been described after exposure to paraffin laxatives (48) and vaporizing ointment (49). Silicone has been implicated with cosmetic injections (5) and possibly to a case of liver granulomatosis in a chronic dialysis patient (24). Most of these reactions are granulomatous in nature, but occasionally the connection is less clear, as in a series of patients with solid cancers receiving 8-chloro-cAMP therapy (50).

Hypercalcemia of malignancy has multiple possible etiologies, which are by no means mutually exclusive, including osteolysis as well as inappropriate secretion of PTHrP and calcitriol. Among malignancies, elevated $1,25(\text{OH})_2\text{D}$ production is most widely described in Hodgkin's disease, and to a lesser extent non-Hodgkin's lymphoma (51). However, it has also been reported in dysgerminoma (17, 52), seminoma (53), leiomyoblastoma (54), lymphomatoid granulomatosis/angiocentric lymphoma (55), squamous cell bronchogenic carcinoma (56), and plasma cell granuloma (57). Some of these nonhematopoietic tumors may be associated with a granulomatous inflammatory response surrounding the tumor and/or in adjacent lymph nodes, implicating tissue macrophages rather than the tumor itself in the elevated $1,25(\text{OH})_2\text{D}$ production (56). Tissue from a pulmonary plasma cell granuloma as well as lymphoma tissue has been shown to convert $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$ *in vitro* (57, 58); in the latter, immunohistochemistry localized 1α -hydroxylase to the macrophages, not the lymphoma cells (16). However, 1α -hydroxylase was expressed by both tumor cells and macrophages in 12 samples of dysgerminomas (17). There-

fore, extrarenal 1α -hydroxylase function in malignancy may reflect the inflammatory response, as well as the innate properties of tumors, particularly in high-grade lymphomas (17, 59).

Although calcitriol-mediated hypercalcemia is classically associated with an elevated $1,25(\text{OH})_2\text{D}$, ours is among a handful of reported cases in patients with an "inappropriately high-normal" $1,25(\text{OH})_2\text{D}$. In all cases, including patients with Wegener's granulomatosis (20, 21), fungal or mycobacterial infections (35, 36, 42–44), osteoarthritis (27), or sarcoidosis (60), PTH was suppressed and there was no hypophosphatemia. The extent of $1,25(\text{OH})_2\text{D}$ elevation may be a function of the type of assay used, including whether both $1,25(\text{OH})_2\text{D}_2$ and $1,25(\text{OH})_2\text{D}_3$ are detected. Also, the degree of hypoproteinemia and thus association with serum vitamin D-binding protein may play a role (21). About 85% of $1,25(\text{OH})_2\text{D}$ is bound to vitamin D binding protein, 0.4% is free, and the remainder is bound to albumin (61). Our patient, in particular, had borderline hypoalbuminemia, possibly increasing the free portion of $1,25(\text{OH})_2\text{D}$. Serum $1,25(\text{OH})_2\text{D}$ levels may also not accurately reflect tissue concentrations, and the specific end-organ responsiveness to a given $1,25(\text{OH})_2\text{D}$ level has not yet been described. Nevertheless, a normal $1,25(\text{OH})_2\text{D}$ despite suppressed PTH in our patient and others is inappropriately high and likely pathological.

The ability of sunlight or even low-dose vitamin D_3 supplementation to precipitate hypercalcemia in sarcoidosis has long been recognized, and also witnessed in other conditions such as histoplasmosis (62), candidiasis (4), and rheumatoid arthritis (26). Our patient was initially vitamin D deficient, which may have resulted from a combination of decreased dietary or environmental supply and/or increased consumption from up-regulated 1α -hydroxylase activity. When she received supplemental vita-

min D₃, she subsequently developed hypercalcemia with normal, not toxic, 25(OH)D levels. Granulomatous hypercalcemia seems particularly sensitive to vitamin D exposure. However, once the underlying cause has been treated, vitamin D supplementation can be reinstituted without recurrence of the hypercalcemia (29, 39).

If a calcitriol-mediated cause of hypercalcemia is suspected, the most effective therapy is one that is targeted toward the underlying cause. According to case reports, treatment of GCP with corticosteroids or azathioprine may offer a partial response, although prognosis is guarded (10, 11). Activity of 1 α -hydroxylase appears to be sensitive to corticosteroids (8), which have specifically been shown to reduce both 1,25(OH)₂D and serum calcium levels in sarcoidosis (8, 60, 63), paracoccidioidomycosis (42), *Mycobacterium avium complex* infection (39), Crohn's disease (2), liver granulomas (24), subcutaneous fat necrosis of the newborn (25), and tuberculosis (19). Corticosteroids are also useful as an adjunct to primary disease treatment (18, 34, 35, 44). Rarely, corticosteroid therapy fails until specific therapy for the underlying disease is instituted (22). Other options may include chloroquine or hydroxychloroquine (19, 20).

Conclusion

The differential diagnosis of calcitriol-mediated hypercalcemia is broad, but is thought to have a common mechanism through autonomous 1 α -hydroxylase activity in tissue macrophages. We have reported the first case of hypercalcemia in GCP, which was associated with an inappropriately high-normal 1,25(OH)₂D after vitamin D supplementation and 25(OH)D repletion. Our patient's hypercalcemia resolved only when a granulomatous cause was suspected and corticosteroid therapy was instituted. Physicians should not necessarily exclude granulomatous diseases in the investigation of non-parathyroid hypercalcemia when the calcitriol level is within a normal range.

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Address all correspondence and requests for reprints to: Dr. Gregory Kline, Department of Medicine, University of Calgary, 1403 29 Street NW, Calgary, Alberta, Canada T2N 4J8. E-mail: gakline@ucalgary.ca.

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