Textiloma-Induced 1,25-Dihydroxyvitamin D–Mediated Hypercalcemia: A Case Report and Literature Study

Julie de Bellefroid,[1] Stefaan Vandecasteele,[2] Sebastiaan Van Cauwenberge,[3] Roger Bouillon,[4] and Annick Van den Bruel[1]

[1]Department of Internal Medicine, Endocrinology, AZ Sint-Jan Brugge-Oostende, 8000 Bruges, Belgium; [2]Department of Internal Medicine, Nephrology, AZ Sint-Jan Brugge-Oostende, 8000 Bruges, Belgium; [3]Department of General, Paediatric and Vascular Surgery, AZ Sint-Jan Brugge-Oostende, 8000 Bruges, Belgium; and [4]Laboratory of Clinical and Experimental Endocrinology, Department of Chronic Diseases, Metabolism and Ageing, KU Leuven, 3000 Leuven, Belgium

ORCiD numbers: 0000-0002-6623-688X (S. Vandecasteele); 0000-0002-6446-3763 (R. Bouillon); 0000-0003-0529-7256 (A. Van den Bruel).

Foreign body causing 1,25-dihydroxyvitamin D [1,25(OH)2D]-induced hypercalcemia is an uncommon yet clinically significant cause of hypercalcemia. We report an unusual case of hypercalcemia due to a textiloma (a surgical gauze inadvertently left in place during surgery). A PubMed search for (HYPERCALCEMIA) and (FOREIGN BODY) was performed. A foreign body (surgical gauze) left over after removal of a kidney transplant caused 1,25(OH)2D-induced hypercalcemia. The diagnosis was complicated by end-stage renal disease, low PTH, and high 1,25(OH)2D.

Freeform/Key Words: 1,25-dihydroxyvitamin D, CYP27B1, foreign body, hypercalcemia

Hypercalcemia is a common clinical problem in hospital and community practice. Primary hyperparathyroidism and malignancy are the most common causes of hypercalcemia, accounting for >90% of cases. Excessive extrarenal production of 1,25-dihydroxyvitamin D [1,25(OH)2D] is a less common cause of hypercalcemia. Well-recognized etiologies of such extrarenal CYP27B1 (or 1α-hydroxylase) activation include sarcoidosis, tuberculosis, and tumors such as lymphomas [1, 2]. Also, many diseases not known to generate inflammatory granulomas have been implicated [3, 4].

1. Clinical Case

A 61-year-old man with Alport syndrome who had progressed to end-stage renal disease (ESRD) presented with recurrent and progressive hypercalcemia. His medical history included kidney transplantation and eventual removal of the kidney transplant because of graft failure after recurrent pyelonephritis, refractory to prolonged antibiotic treatment (Fig. 1). Thereafter, hemodialysis was resumed. Because of hypercalcemia and high PTH levels, a partial parathyroidectomy (with resection of two hyperplastic parathyroid glands) was performed, followed by a 14-month episode of normocalcemia and secondary hyperparathyroidism. However, routine biochemistry drawn before a dialysis session demonstrated

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; ESRD, end-stage renal disease; FDG, fluorodeoxyglucose; FGF-23, fibroblast growth factor 23; PET, positron emission tomography.

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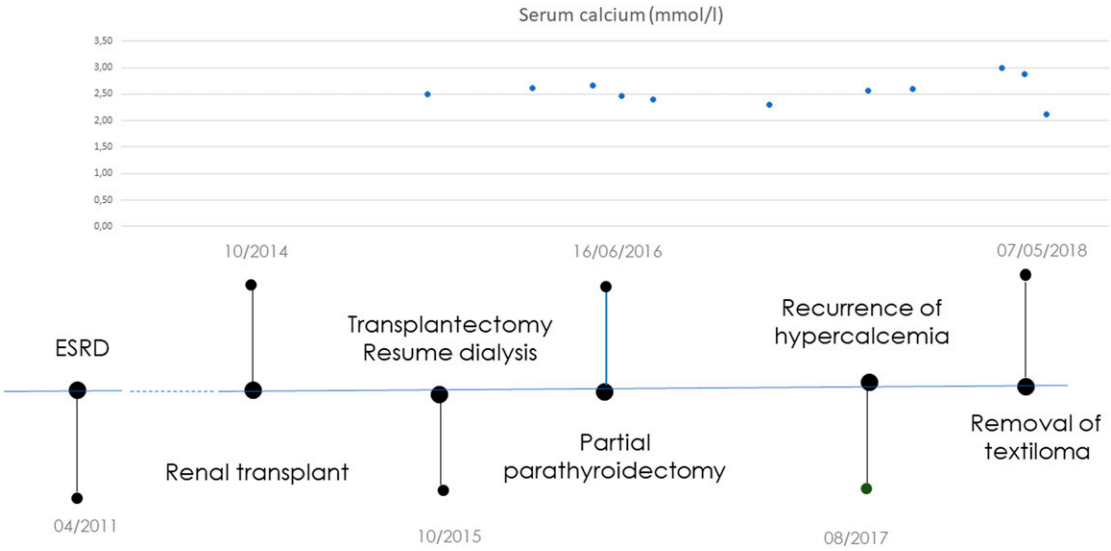

Figure 1. Timeline of events and trajectory of serum calcium.

recurrent and progressive hypercalcemia. His major complaint was increasing fatigue. Vital signs and heart and lung auscultation were unremarkable, and there were no palpable masses or lymphadenopathies. Laboratory evaluation showed marked hypercalcemia (3 mmol/L, 12 mg/dL), normal serum electrophoresis, an adequate 25(OH)D, and a PTH value at the lower end of the reference range (Table 1). This PTH concentration was much lower than expected for ESRD, and was only one-tenth of a previous value obtained during normocalcemia 1 year before (Table 1). A non–PTH-mediated cause of hypercalcemia was suspected, 1,25(OH)2D concentration was measured (iSYS chemiluminescence immunoassay; Immunodiagnostic Systems, Frankfurt am Main, Germany). ^{18}F fluorodeoxyglucose (FDG) positron emission tomography (PET) did not show mediastinal or lung uptake suggestive of sarcoidosis or tuberculosis, nor was there uptake in bone suggestive of bone metastasis, but an abdominal mass with an ^{18}F FDG avid border was detected (Fig. 2). CT scans of the chest and bone were normal. Four days later the patient was admitted to the hospital because of increasing fatigue and abdominal discomfort. Additional biochemical testing revealed mild anemia and a normal white blood cell count and formula, but C-reactive protein was very high (141 mg/L). Despite antibiotic therapy (ceftriaxone), inflammatory parameters further increased, and the patient complained of progressive abdominal pain. Diagnostic laparotomy was performed and revealed a textiloma (a surgical gauze inadvertently lost during transplantectomy two and a half years before) (Fig. 3). In retrospect one can appreciate foci of very-high CT density suggestive of metallic material in the abdominal mass on the ^{18}F FDG PET CT scan (Fig. 2).

After removal of the textiloma, the serum calcium concentration rapidly normalized. Serum 1,25(OH)2D, close to the upper limit of normal before surgery, decreased toward a low normal value (Table 1). Additional analyses with isotope dilution liquid chromatography mass spectrometry, validated for accuracy with National Institute of Standards and Technology (NIST) samples, confirmed these findings: 25(OH)D, 1,25(OH)2D, 24,25(OH)2D, fibroblast growth factor 23 (FGF-23), C-terminal EIA (Immunotopics, International, San Clemente, CA), and vitamin D binding protein (Radial Immunodiffusion) were determined in stored serum samples obtained before and after removal of the textiloma (Table 2). 1,25(OH)2 D was close to the upper limit of normal before surgery and was low after surgery. FGF-23 concentration was higher than expected for ESRD, probably related to the high 1,25(OH)2 concentration. After surgical removal of the textiloma, it decreased toward a concentration expected in a patient with ESRD.

The patient signed an informed consent for the publication of his clinical data and photographs.

Table 1. Laboratory Results

Laboratory Values	Before Parathyroid Exploration 03-2016	After Parathyroid Exploration 08-2016	03-2017	06-2017	08-2017	03-2018	At Presentation 04-2018	After Resection of Textiloma 05-2018	Reference Value	Expected Value for ESRD
Calcium	2.62 mmol/L	2.47 mmol/L	2.3 mmol/L	2.38 mmol/L	2.56 mmol/L	3 mmol/L	2.88 mmol/L	2.12 mmol/L	2.2–2.55 mmol/L	Low normal
Phosphate	2.16 mmol/L	3.19 mmol/L	1.6 mmol/L			1.9 mmol/L	1.88 mmol/L	2.48 mmol/L	0.81–1.45 mmol/L	High normal
Albumin	37 g/L	39 g/L	39 g/L				38 g/L	29 g/L	34.00–48.00 g/L	
Ca++	1.31 mmol/L		1.2 mmol/L			1.5 mmol/L			1.10–1.30 mmol/L	Low normal
Serum creatinine	11 mg/dL	14 mg/dL	14 mg/dL			14 mg/dL	13 mg/dL	11.3 mg/dL	0.6–1.2 mg/dL	High
PTH	492 ng/L	297 ng/L	291 ng/L			21 ng/L	23 ng/L	246 ng/L	15–65 ng/L	100–451 ng/L
25(OH)D						47 ng/mL			>20 ng/mL	Low–low normal
1,25(OH)2D							172 pmol/L	45 pmol/L	36–216 pmol/L	Low–low normal

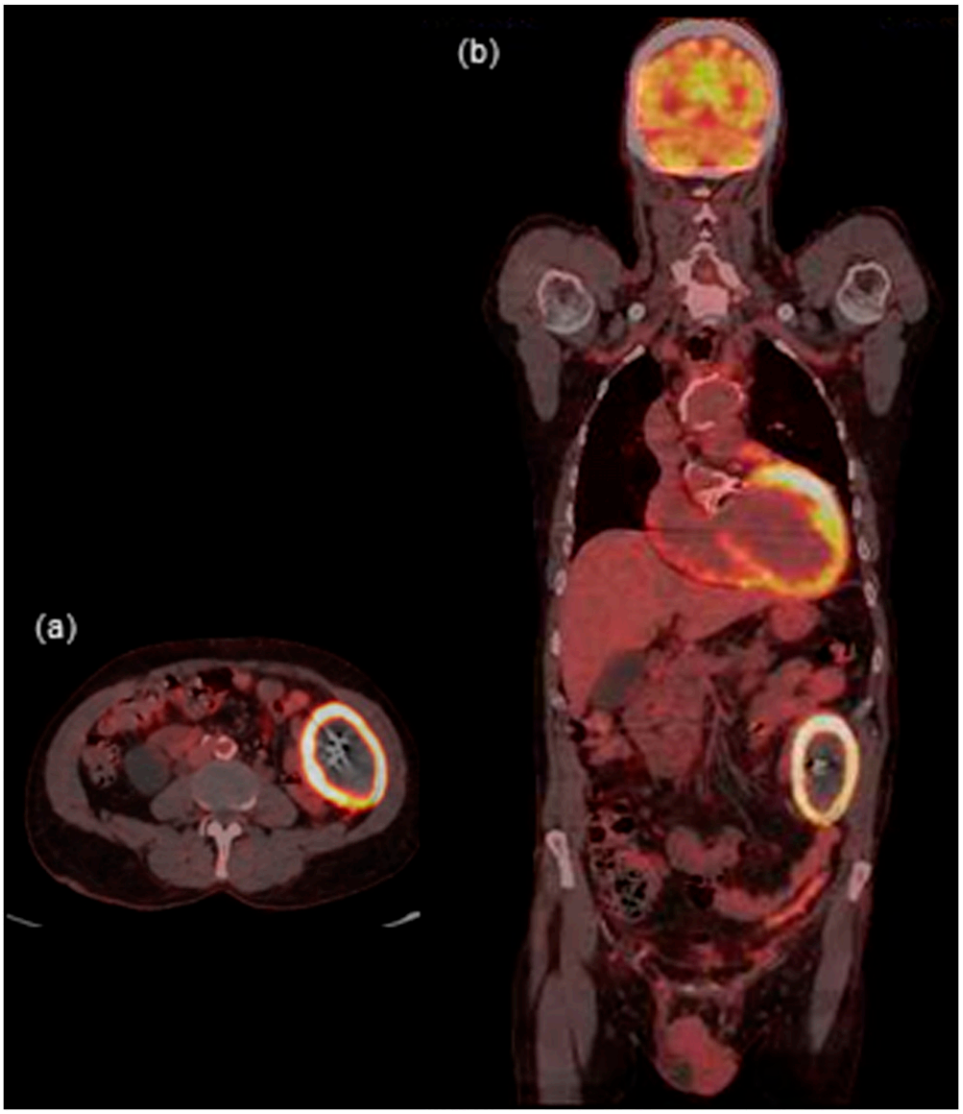

Figure 2. The ^{18}F FDG PET CT did not show any chest uptake; however, it was remarkable for an abdominal mass with an ^{18}F FDG avid border [(a) axial (b) and coronal slices].

2. Discussion

We report an unusual case of 1,25(OH)2D-mediated hypercalcemia caused by a foreign body textiloma in a patient on dialysis.

Hypercalcemia occurs in 0.2% to 4% of the population [4, 5]. If the most common causes, hyperparathyroidism and malignancy, are ruled out, less common causes such as 1,25(OH)2D or PTH-related peptide–mediated hypercalcemia must be investigated. When 1,25(OH)2D-mediated hypercalcemia is suspected, a broad spectrum of causes are possible [3]. Donovan *et al.* [4] published a hospital-based registry study (from 1999 to 2009) including 101 patients diagnosed with 1,25(OH)2D-mediated hypercalcemia and reported that the most prevalent causes were sarcoidosis (49%) and hematological malignancy (17%), followed by infectious diseases such as tuberculosis (8%). Foreign body granulomatosis accounted for only 2% of cases.

A PubMed literature search for (HYPERCALCEMIA) and (FOREIGN BODY) (accessed 2 March 2019) confirmed a low incidence, and up to 2010 only a handful of case reports had been published. The first manuscripts by Kozeny *et al.* [6] and Altmann *et al.* [7] reported on

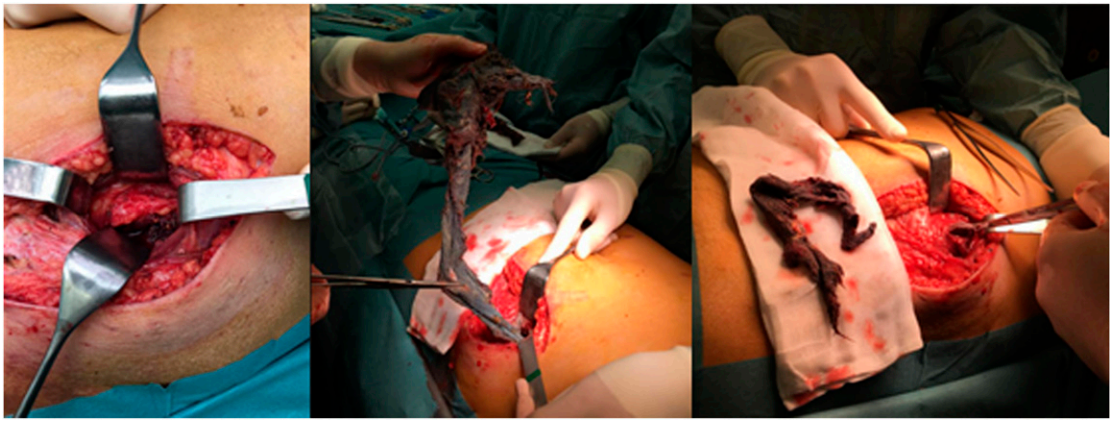

Figure 3. Photographs taken during surgery and showing removal of a textiloma.

hypercalcemia and silicone-induced granuloma probably derived from cosmetic injections and silicone spallation from inserts in dialysis blood lines, respectively. Talc pleurodesis, occupational talc inhalation, and lipoid inhalation pneumonia have been found causative [3, 8, 9]. More recently, numerous cases of hypercalcemia associated with cosmetic body contouring (dermal or intramuscular) injection of silicone, paraffin oil, or methyl methacrylate have been published as cause of 1,25(OH)2D-meditated hypercalcemia according to a systematic literature review [10]. Hypercalcemia can develop at any time after exposure (mean duration of 7.8 ± 7.2 years) to such foreign bodies, with often severe hypercalcemia complicated by renal failure. 25(OH)D and PTH were low in the majority of these cases. Serum 1,25(OH)2D concentration was elevated in only 65%, but even high normal 1,25(OH)2 concentrations are inappropriate in patients with hypercalcemia, low PTH levels, or renal failure. Biopsy of involved skin or lymph node was performed in 20 of 23 cases and revealed foreign body granulomatous reaction in 19 of 20 cases and strong CYP27B1 expression in histiocytes surrounding the foreign body in three of three cases studied [10]. A recent case series of 12 bodybuilders with nonparathyroid hypercalcemia showed similar findings [11]. Prospectively, of 60 men who injected 500 to 10,000 mL paraffin oil, one-third developed hypercalcemia, one-third had normocalcemia and suppressed PTH, and only one-third had normal calcium and PTH concentrations. All developed high urinary calcium concentrations [12]. The underlying mechanism of hypercalcemia is an overactive extrarenal CYP27B1 expression causing excessive 1,25(OH)2D production by activated histiocytes. This enzyme is resistant to normal negative feedback control by 1,25(OH)2D and FGF-23, unlike the normal renal enzyme, and therefore causes high intestinal calcium absorption and increased bone resorption [11, 13].

Our case illustrates the caveats in interpreting calcium, PTH, and 1,25(OH)2D concentrations for patients with combined hypercalcemia and renal failure. Although PTH was within the normal reference range, it was low compared with values expected in ESRD and one-tenth of a value obtained during the normocalcemic episode. 1,25(OH)2D was within the stated reference range but inappropriate considering ESRD, low PTH status, and very high

Table 2. Additional Analyses in Reference Laboratory (Validated for Accuracy With NIST)

	Before Removal of Textiloma	After Removal of Textiloma	Reference Value
1,25(OH)2D	67.8 pg/mL	15.6 pg/mL	20–80 pg/mL
25(OH)D	52.9 ng/mL	37.8 ng/mL	20–50 ng/mL
24,25(OH)2D	0.6 ng/mL	0.3 ng/mL	1–4 ng/mL
FGF-23	14,750 RU/mL	7361 RU/mL	<125 RU/mL
Vitamin D binding protein	318 mg/L	318 mg/L	250–400 mg/L

FGF-23. In each of these circumstances one would expect a decreased or very low 1,25(OH)2D concentration. The often normal 1,25(OH)2D concentration in 1,25(OH)2D-mediated hypercalcemia has been found by other authors and is a notable pitfall in the differential diagnosis of hypercalcemia [4, 10, 11]. The biochemical diagnosis was complicated, but imaging revealed the origin and the location of the cause of the disease. As in other cases and case series, ^{18}F FDG PET CT reflecting high glucose uptake located the source of 1,25(OH)2D-mediated hypercalcemia. CT scan showed high densities due to the metallic material in surgical gauzes. Unfortunately, we did not obtain CYP27B1 staining in our case because the textiloma and its surrounding scar tissue were not kept for pathologic examination after removal. The rapid normalization of serum calcium, 1,25(OH)2D and PTH and the decrease in FGF-23 after surgery demonstrate the foreign body reaction from the textiloma as the cause of the 1,25(OH)2D-mediated hypercalcemia. Although a foreign body is perceived as a rare event, systematic assessment in a health care quality study showed its presence in a mean of 7 per 100,000 discharges (range 4.1 to 12.3) in high-income countries [14]. It may be wise to consider textiloma as cause of hypercalcemia or low PTH levels in patients with previous surgery.

3. Conclusion

Well-recognized etiologies of 1,25(OH)2D-mediated hypercalcemia are sarcoidosis, lymphomas, and infectious disease such as tuberculosis. A foreign body reaction is a rare cause. We describe here a case of 1,25(OH)2D-mediated hypercalcemia with resolution of clinical symptoms and all biochemical abnormalities after removal of a textiloma. As previously recognized, 1,25(OH)2D-mediated hypercalcemia may present with high-normal 1,25(OH)2D concentrations and thereby is a notable pitfall in the differential diagnosis of non–PTH-mediated hypercalcemia. We now add textiloma or surgical gauze left after surgery as a possible cause of non–PTH-related hypercalcemia.

Additional Information

Correspondence: Annick Van den Bruel, MD, Department of Internal Medicine, Endocrinology, AZ Sint-Jan Brugge-Oostende, Ruddershove 10, 8000 Bruges, Belgium. E-mail: annick.vandenbruel@azsintjan.be.

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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