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Exacerbated hypercalcemia, nephrolithiasis, and renal impairment after vitamin D supplementation in granulomatous disease: a case report

S. Theilade[1,3*], S. Kafai Yahyavi[4], M. Blomberg Jensen[2,4,5] and E. Eldrup[3]

Abstract

Background The cosmetic industry is booming with unorthodox therapies aimed at improving the appearance of beauty and strength. One such therapy is self-administered, intramuscular injections of paraffin oil for the purpose of increasing presumed muscular size. Paraffin oil injections are becoming frequent among younger male individuals, who inject up to several liters in (primarily) the upper extremities. However, paraffin oil leads to the formation of granulomas, which are rich in macrophages with an upregulated extrarenal 1-hydroxylation. These macrophages will rapidly and unimpededly convert inactive vitamin D ($25OHD_2$) to active vitamin D ($1,25OH_2D_3$), thereby causing significant hypercalcemia and derivative disease.

Case presentation In 2007, a Scandinavian male individual in his 20s had self-injected 1200 ml of paraffin oil into both biceps. Within 5 years, the oil had migrated and was then widely dispersed in his biceps and surrounding tissues, causing swelling and pain. By 2015, granulomas had formed at injection sites, and he was admitted to a hospital with severe hypercalcemia, which was managed with fluid therapy and slowly resolved. From 2015 to 2020, his calcium levels were intermittently elevated, and he experienced two episodes of nephrolithiasis requiring surgical intervention. In 2020, he was prescribed one dose oral vitamin D (6000 µg cholecalciferol) for suspected vitamin D deficiency based on a low serum $25OHD_2$. His episodic hypercalcemia increased, and he developed nephrolithiasis and exacerbated renal impairment.

Conclusion Unlike most other patients with low $25(OH)D_2$, patients with granulomatous disease should not routinely receive vitamin D supplementation, as this may aggravate hypercalcemia and hypercalcuria, causing nephrolithiasis and renal impairment.

Keywords Paraffin oil, Granulomatous disease, Vitamin D, Hypercalcemia, Nephrolithiasis

*Correspondence:
S. Theilade
karen.simone.theilade.01@regionh.dk
Full list of author information is available at the end of the article

Background

In recent years, an increasing number of men aged 20–45 years have been seen in primary and secondary care centers with granulomatous disease following self-injection of paraffin oil. The oil is injected into muscular regions for the purpose of enhancing muscular size. However, paraffin oil injections may induce foreign body reactions and granuloma formation, which in turn leads to increased extrarenal vitamin D activation, and subsequently, hypercalciuria and hypercalcemia. Affected individuals are primarily treated with prednisolone, which inhibits inflammation, vitamin D activation, gastrointestinal calcium absorption, and osteoclast activity. It seems to be imperative that patients with paraffin oil-induced granulomatous disease (POGD) abstain from sun exposure, vitamin D supplementation, and high dietary calcium intake.

Normally, cutaneous production or orally absorbed vitamin D (cholecalciferol) needs activation before it can bind to the vitamin D receptor and exert its actions [1]. This activation occurs through hydroxylation—first by the enzyme CYP2R1, mainly in the liver—creating 25-hydroxyvitamin D ($25OHD_2$), and subsequently, by CYP27B1 in the kidneys, creating active calcitriol ($1,25OH_2D_3$) [2]. CYP27B1 is the rate-limiting step in calcitriol synthesis and is tightly regulated under physiologic conditions. Downregulation of high calcitriol is achieved by a feedback system, where calcitriol stimulates CYP24A1, which in turn hydroxylates calcitriol to the inactive $1,24,25OH_2D_3$ [3, 4]. Several other players, for example, parathyroid hormone (PTH), fibroblast growth factor 23, and others, regulate calcium homeostasis [5].

However, in macrophages, CYP27B1 is upregulated by interleukin 2, and the inhibiting enzyme CYP24A1 is nonfunctional. Therefore, granulomas can produce large amounts of calcitriol unopposed by the otherwise tight regulatory mechanisms present in the kidneys. Unimpeded, calcitriol increases intestinal calcium absorption, renal reabsorption, and to some extent, probably calcium release from bones, all leading to hypercalcemia [6, 7]. Hypercalcemia is a late feature of accelerated vitamin D activation, as several counterregulatory mechanisms attempt to maintain normocalcemia. For example, increased urinary calcium excretion (UCE) and reduced PTH secretion lower plasma calcium levels, enabling normocalcemia, probably even with pronounced relatively high calcitriol levels. However, in advanced disease, these regulatory mechanisms become saturated, and hypercalcemia develops.

In healthy people and most patients, measurement of $25OHD_2$ is a valid measure for vitamin D status. However, in patients with granulomatous disease, the unregulated 1-hydoxylation (CYP27B1) seems to quickly hydroxylate $25OHD_2$ and create calcitriol. Hence, men with POGD have low $25OHD_2$ and high (although within normal range) calcitriol [8]. In these patients, $25OHD_2$ is an unreliable measure of vitamin D status, and low $25OHD_2$ levels do not warrant vitamin D supplementation.

Case presentation

During his teens in the 2000s, a Scandinavian male individual commenced an ongoing abuse of anabolic steroids (AS) and occasional use of erythropoietin (EPO). In 2007, when in his 20s, he injected 1200 ml of paraffin oil into both arms' biceps muscles and surrounding tissues for cosmetic reasons.

In 2011, he suffered from feelings of heaviness and altered skin sensation of both arms. Magnetic resonance imaging (MRI) scan of the upper extremities revealed inoperable, widely dispersed paraffin oil deposits in the muscles and surrounding tissues (see Fig. 1).

In 2014, the patient had developed polycythemia (hemoglobin 11–12 mmol/L; normal range: 8.3–10.5 mmol/L) and increased hematocrit (52–56%; normal range:40–50%). This was believed to be caused by his AS and/or EPO use, as a bone marrow biopsy was normal, and genetic testing ruled out mutations in the Janus kinase or calreticulin genes. He was offered venesection and recommended vitamin D supplements owing to low levels of $25OHD_2$, but he failed to attend appointments and was discontinued from the clinic.

In 2015, he was admitted to a hospital with severe hypercalcemia (ionized calcium: 1.76 mmol/L; normal range:1.15–1.35 mmol/L). A positron emission

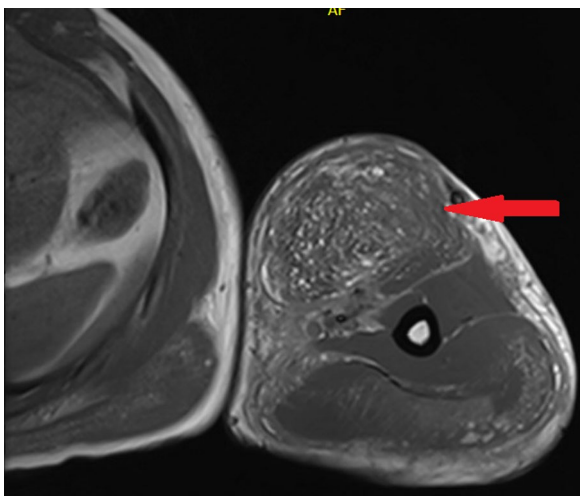

Fig. 1 Magnetic resonance imaging of the upper extremities (2011). The arrow indicates widely dispersed and inoperable paraffin oil deposits in the muscles and surrounding tissues

tomography and computed tomography (PET-CT) of chest, abdomen, and upper arms showed large granulomatous masses in the biceps and calcifications of the renal papils (Figs. 2 and 3), but it was otherwise with normal findings. He was treated with intravenous fluids for 2 weeks, recommended vitamin D supplements, and discharged with mild hypercalcemia (ionized calcium: 1.45 mmol/L), but without further treatment. He failed to attend follow-up appointments and was discontinued from the clinic.

In 2017, the patient had his first admission with nephrolithiasis with reduced renal function on the right side (38%) and was treated with a right-sided JJ catheter.

In September 2018, he was referred to the Endocrinology Department of the Herlev-Gentofte Hospital for treatment of hypercalcemia. Intermittent hypercalcemia had been present since October 2015 (1.27–1.76 mmol/L), but he had never received any outpatient therapy. At referral, he had: ionized calcium: 1.34 mmol/L; $25OHD_2$: 45 nmol/L (normal range: 50–160 nmol/L); calcitriol: 130 pmol/L (normal range: 60–180 pmol/L); PTH: < 0.4 pmol/L (normal range: 1.2–8.3 pmol/L); creatinine: 124 umol/L (normal range: 60–105 umol/L); UCE: 9.6 mmol/24 hours (normal range: 2.5–8.1 mmol/24 hours); and urine calcium/creatinine ratio (UCCR): 0.51 (normal range: < 0.14). He was advised to avoid D vitamin supplementation and sun exposure and to reduce dietary calcium intake, but was otherwise monitored without treatment.

In October 2018, he was prescribed prednisolone 25 µg/daily owing to hypercalcemia (1.47 mmol/L), which quickly normalized (1.17–1.35 pmol/L). He was tapered out of prednisolone by April 2019 and remained eucalcemic afterwards.

In February 2019, despite eucalcemia, he was again admitted with nephrolithiasis and treated with endoscopic nefrolithotomy with a temporary left nephrostomy catheter and left ureter stent. Later that year, he underwent right sided percutaneous stone removal.

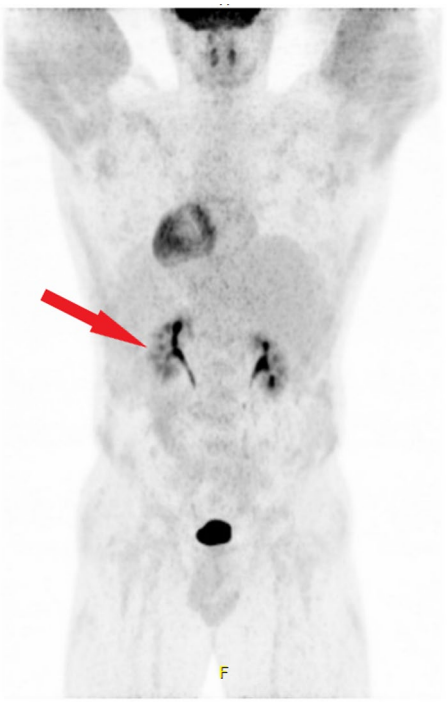

Fig. 3 Positron emission tomography and computed tomography of chest, abdomen, and upper arms (2015). The arrow indicates calcifications of the renal papils

From June 2020, he discontinued AS/EPO abuse entirely despite ongoing testosterone deficiency.

In August 2020, he was untreated and eucalcemic (ionized calcium: 1.28 mmol/L), but with low PTH (0.6 pmol/L) and high UCCR (0.43). He was again referred to a local hospital for venesection with an elevated hematocrit (53%). On the basis of a low $25OHD_2$ (27 nmol/L), but with a normal calcitriol (132 pmol/L),

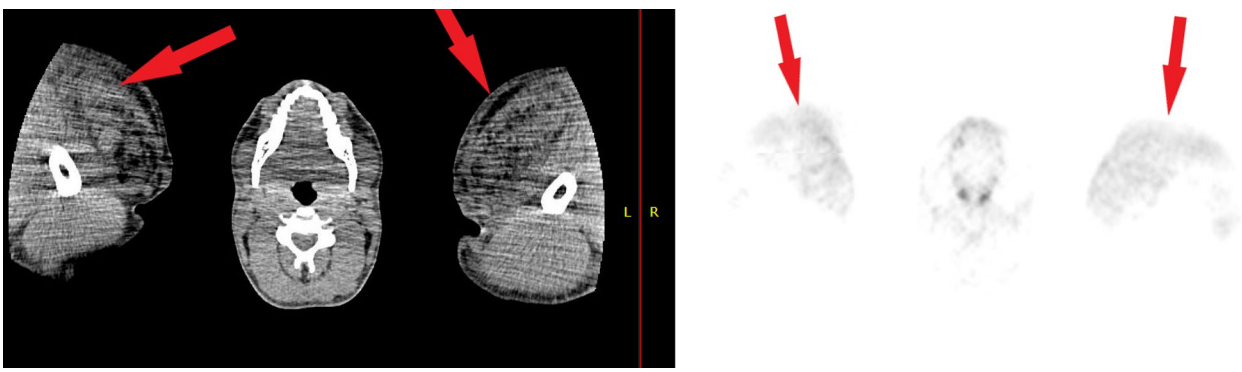

Fig. 2 Positron emission tomography and computed tomography of chest, abdomen, and upper arms (2015). The arrows indicate the presence of large granulomatous masses in the biceps

he was prescribed one dose of Dekristol® 240,000 IU, equivalent to 6000 µg cholecalciferol. A total of 2 weeks later he developed hypoparathyroid hypercalcemia (ionized calcium: 1.43 pmol/L; PTH 0 pmol/L) and renal impairment (estimated glomerular filtration rate, eGFR, decreased from 73 to 57 ml/minute/1.73 m^2), and 6 weeks later, he again developed nephrolithiasis, which was initially managed medically. However, by December 2020 he had ongoing pain and was scheduled for a nephron-ureteroscopic stone removal. The procedure was postponed owing to the coronavirus disease 2019 (COVID-19) pandemic, which delayed many elective procedures in Denmark. In May 2021, he finally underwent renewed endoscopic nefrolithotomy. Without medical treatment, the patient's hypercalcemia had resolved (ionized calcium: 1.25–1.29 pmol/L; PTH 1.6 pmol/L) and renal function had normalized.

The patient had previously been denied debulking surgery through the public health system, as the diseased tissue was so widely dispersed, and the risks of complications were thought to override potential benefits. However, in March 2022, he underwent bulk resection of paraffin oil and granuloma tissue from the right upper and lower arm at a private clinic. We have no data on the surgical procedure or amount of tissue resected, but he has ongoing postoperative wound healing complications and persistent pain and swelling of both arms.

The patient has residual renal stones, not requiring removal now, but he will be followed up with regular consults and computed tomography (CT) scans, and as of June 2022, he remains eucalcemic (ionized calcium: 1.22 mmol/L).

Discussion

This case demonstrates an important exception to the general medical belief that people with low $25OHD_2$ levels are vitamin D deficient and should receive vitamin D supplementation. No previous documentation of hypercalcemia and nephrolithiasis caused by vitamin D supplementation in patients with POGD has been published. Recently, we showed that uncontrolled vitamin D activation is an important player in POGD [9, 10]. Others have shown that both vitamin D supplementation and $25OHD_2$ levels in the higher (although normal) ranges may increase UCE and kidney stone formation in predisposed individuals [11].

Given the novelty of POGD, long-term treatment recommendations have not yet been formulated. It is generally believed that prednisolone effectively reduces hypercalcemia in these and in other patients with granulomatous disease of different origins [12, 13]. However, for patients without hypercalcemia, there is no evidence-based treatment regimens available. We have previously presented a cohort of approximately 90 male patients with the condition, of which approximately one-third have manifest hypercalcemia, one-third have altered calcium homeostasis (reduced PTH and/or increased calcium clearance), and one-third have normal calcium homeostasis [9, 10]. Only patients with hypercalcemia have thus far been offered medical treatment. However, we fear that with time, most patients will develop calcium disturbances and ultimately require medical therapy, and we wonder whether medical treatment prior to development of hypercalcemia is warranted.

Several of our patients have undergone debulking surgery to relieve pain and local discomfort, and we recently found debulking surgery to improve not only inflammation and subjective symptoms, but also to improve calcium homeostasis in hypercalcemic individuals with POGD [14].

For this patient, we have considered long-term prednisolone treatment—even as his ionized calcium is currently within normal range. This is to inhibit the inflammatory process in the granulomas, thereby delaying potential granuloma progression. However, it inhibits calcium extraction from the gut and bone, as well as granulomatous vitamin D activation. However, corticosteroid therapy increases the risk of the development of secondary osteoporosis [15], with higher doses and longer treatment—which patients with POGD are likely to receive—further increasing fracture risk [16].

The bone mineral status of patients who suffer from POGD is widely unknown, but needs to be considered when prescribing corticosteroid treatment. We are currently collecting data on bone mineral status in our POGD cohort.

It is unknown whether low $25OHD_2$ with normal calcitriol harms bone mineral content, as well as whether patients with granulomatous disease with low $25OHD_2$ and low calcitriol, should receive D vitamin supplementation.

Conclusion

Patients with POGD have low $25OHD_2$ owing to unregulated extrarenal D vitamin activation. These patients should not routinely receive vitamin D supplementation, as this may aggravate hypercalcemia and hypercalcuria, causing nephrolithiasis and renal impairment.

Abbreviations

$1,25OH_2D_3$	Calcitriol
$25OHD_2$	25-Hydroxyvitamin D
AS	Anabolic steroids
EPO	Erythropoietin
PET-CT	Positron emission tomography and computed tomography
POGD	Paraffin oil-induced granulomatous disease
PTH	Parathyroid hormone
UCE	Urine calcium excretion
UCCR	Urine calcium/creatinine ratio

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None.

Author contributions
EE followed the patient in clinic and collected the data. ST drafted the manuscript. SK, MBJ, and EE made critical revisions of the manuscript for key intellectual content. ST is the guarantor of this work, had full access to all the data on the case report, and takes responsibility for the integrity of the data and accuracy of the data analyses.

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Availability of data and material
The case report is based on information from the patient's electronic health records.

Declarations

Ethics approval and consent to participate
The patient gave written and oral consent for treatment in our clinic and for publication of the case report.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
None of the authors have competing interests.

Author details
[1]Steno Diabetes Center Copenhagen, Herlev, Denmark. [2]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. [3]Department of Medicine, Herlev-Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark. [4]Group of Skeletal, Mineral, and Gonadal Endocrinology, Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark. [5]Division of Bone and Mineral Research, HSDM/HMS, Harvard University, Boston, MA, USA.

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