

Calcitriol-mediated hypercalcemia secondary to granulomatous disease caused by soft-tissue filler injection: a case report

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Summary

Soft-tissue filler (STF) injections have been used worldwide for cosmetic reasons. In most cases, they are not approved by the United States Food and Drug Administration (FDA). Regulatory boards in Latin American countries do not allow the medical use of STF injections; however, these injections are still widely used. A case of calcitriol-mediated hypercalcemia with ectopic calcifications, chronic kidney disease, nephrolithiasis and calcinosis is presented. The reported case highlights the consequences of STF use, including calcitriol-mediated hypercalcemia secondary to granulomatous reactions years after an esthetic procedure.

KEY WORDS: hypercalcemia; granulomatous disorders; calcinosis; soft-tissue filler; calcitriol.

Introduction

Hypercalcemia is a common condition in clinical practice (1). Most cases are secondary to malignancy or primary hyperparathyroidism. Once both conditions have been ruled out, hypercalcemia becomes a clinical challenge (2), and uncommon causes such as granulomatous disorders should be considered (3). These diseases are associated with high or high-normal levels of 1,25-dihydroxyvitamin-D₃ (calcitriol). Increased calcitriol is secondary to an increase in the activity and number of macrophages with 1- α -hydroxylase activity, which transforms 25-hydroxyvitamin-D (25-OH-D) into calcitriol, leading to hypercalcemia by increased intestinal calcium absorption and reduction in renal calcium and phosphate excretion, but also to accelerated bone resorption with subsequent higher calcium levels, saturating renal calcium reabsorption mechanism, leading also to hypercalciuria (4).

Calcitriol-mediated hypercalcemia is an uncommon entity (3), and few reports have been published on this condition. Although the pathophysiology behind this uncommon entity has been described (5), the management can be quite difficult, and there are no established guidelines supporting the current treatment.

Some soft-tissue filler (STF) injections can induce an inflammatory granulomatous effect of varying severity. In some cases, this reaction can lead to symptomatic, life-threatening hypercalcemia (6-15). Additionally, STFs are difficult to remove and may be associated with infectious complications such as cellulitis and even sepsis.

This report summarizes the clinical findings and therapeutic approach in a patient with calcitriol-mediated hypercalcemia secondary to STF injections.

Case report

A 40-year-old woman presented to our hospital after five years of multiple complications due to hypercalcemia. Her past medical history included a cosmetic procedure involving the injection of an unknown STF for gluteal augmentation 10 years prior.

The patient had experienced several complications associated with STF, including hypercalcemia, nephrocalcinosis, microcytic anemia, stage 3 chronic kidney disease (CKD), recurrent buttock cellulitis, hyperphosphatemia, and calcinosis cutis.

The patient was admitted after experiencing several weeks of weight loss, buttock ulcers with bacterial superinfection, hypoacusia and major depression. A laboratory examination showed the following: calcium (Ca), 13 mg/dL (8.2 – 10.2 mg/dL); 25-hydroxy vitamin D, 12.7 ng/mL (30 – 40 ng/mL); creatinine (Cr), 2.18 mg/dL (0.5 – 1.1 mg/dL); albumin (Alb), 3.2 g/dL (3.5 – 5 g/dL); phosphorus, 5.5 mg/dL (2.5 – 4.7

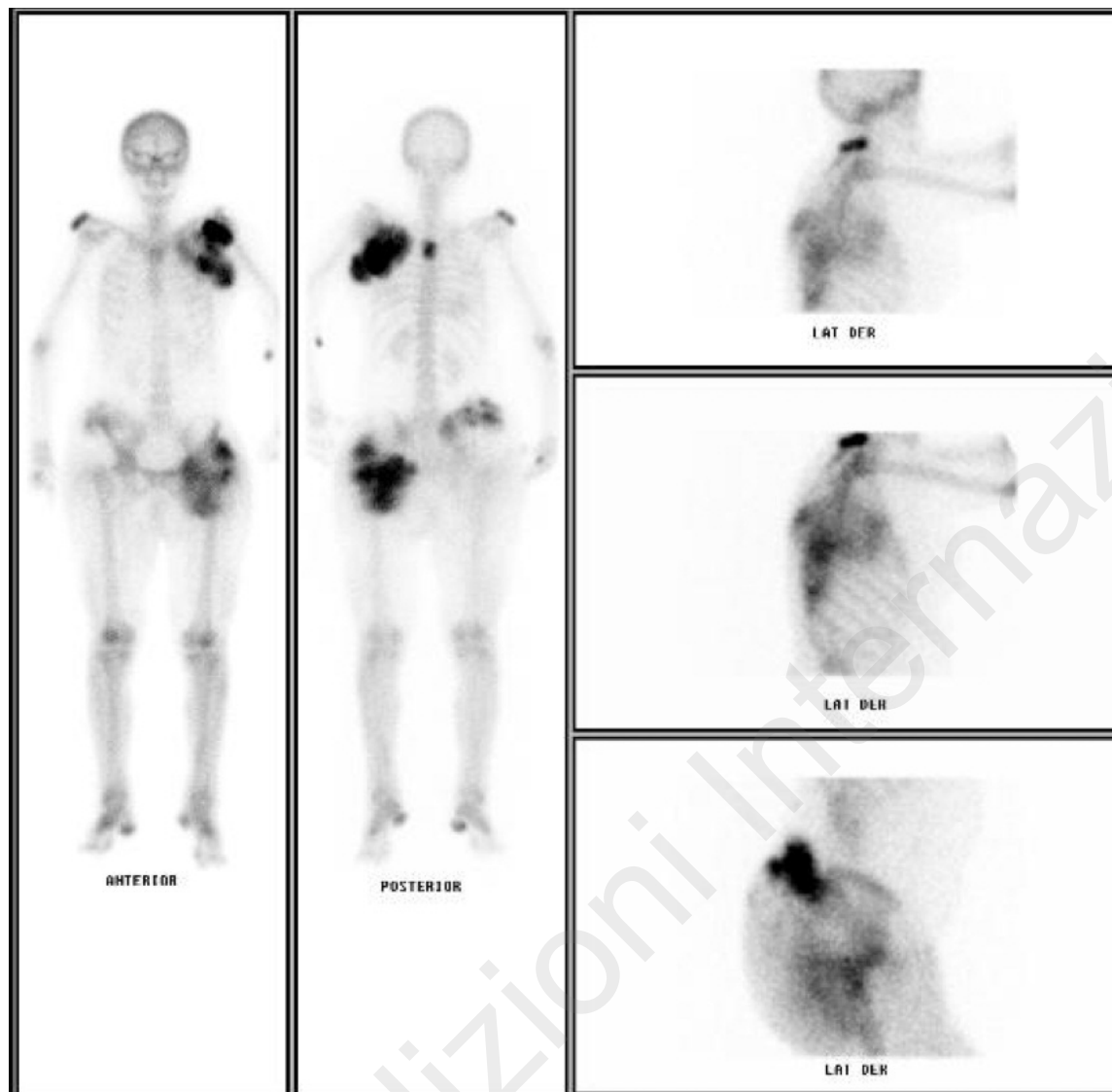


Figure 1 - ^{99m}Tc bone scintigraphy showing calcinosis in the right acromioclavicular joint, bilateral heels and soft tissues of the left shoulder area, right buttock and left hip.

mg/dL); 24-hour calciuria, 237 mg/24 hours (100 – 300 mg/24 hours); parathyroid hormone (PTH) 1.27 pg/mL (15 – 68.3 pg/mL); and inappropriately normal calcitriol, 69.1 pg/mL (25 - 86.5 pg/mL). Management in the emergency room included the administration of intravenous (IV) fluids and IV furosemide.

The patient had multiple subcutaneous nodules on the knees, toes, elbows, and metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints (Figure 1). Additionally, nephrolithiasis, calcinosis of the left hemithorax (Figure 2) and paravertebral region, microcalcifications around the ankle, and subcutaneous calcification of the heels, right hand, left wrist, right forearm and sclerae were documented. A pelvic MRI showed inflammation and chronic fibrosis due to a foreign body reaction of the gluteus maximus muscles and perianal region, as well as dystrophic calcified masses that suggested soft tissue calcinosis. An audiometric study showed conductive hearing loss. Calcinosis was documented using the ^{99m}Tc bone scintigraphy (Figure 1) in the right acromioclavicular joint, bilateral

heels and soft tissues of the left shoulder area, right buttock and left hip. The patient underwent resection of calcified masses in the gluteal areas, and the postoperative period was uneventful. A biopsy of the gluteal tissue showed chronic granulomatous inflammation with a foreign-body giant-cell reaction and calcinosis.

The management of hypercalcemia in this patient was challenging. Given the severity of the hypercalcemia, and prior to the confirmation of calcitriol-induced hypercalcemia, 4 mg of IV zoledronic acid was administered; the calcium levels did not decrease. Then, high-dose oral steroids were administered (prednisone 30 mg/day); however, the calcium level did not improve (before prednisolone, 13 mg/dL; after, 12.8 mg/dL). Treatment with sevelamer (800 mg PO daily) and chloroquine (250 mg PO daily) was initiated but did not adequately control the hypercalcemia. The patient had several admissions to the emergency department for relapse of hypercalcemia and acute kidney injury, which responded to the administration of intravenous fluids. The patient was on periodic follow-up by our service and was treated with pred-

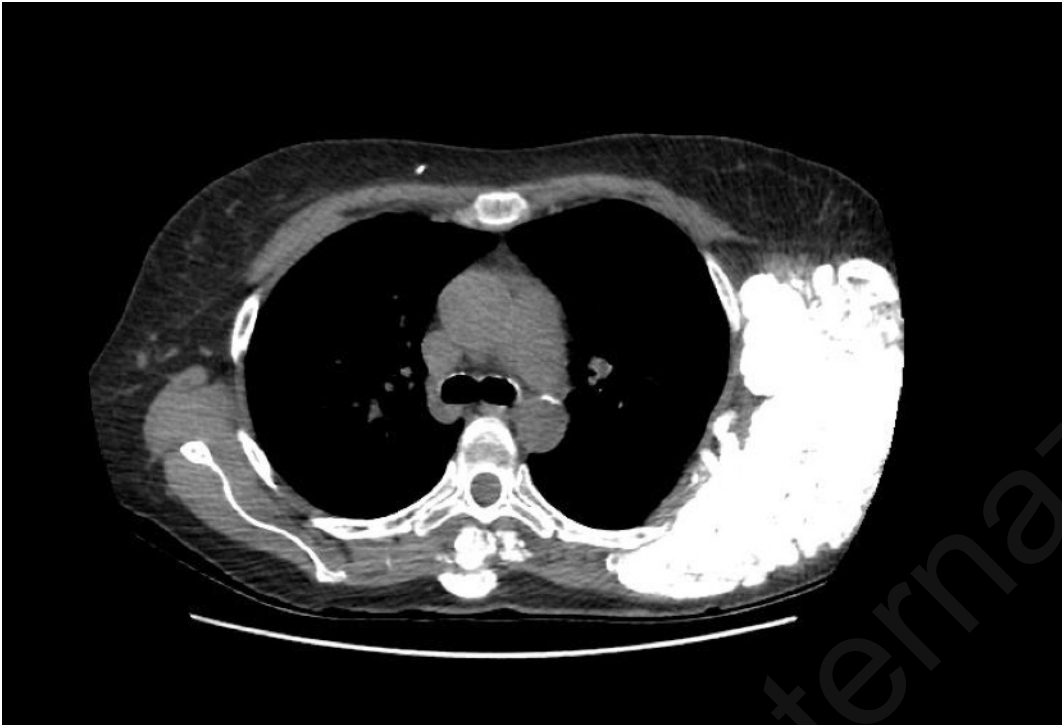


Figure 2 - CT scan: calcified mass of the left hemithorax.

nisolone 5 mg daily without a clear improvement in calcium levels. She passed away due to complications of hypercalcemia.

Discussion

The patient arrived at the emergency room with signs and symptoms suggestive of a severe and longstanding calcium disorder. Initial management with IV fluids and zoledronic acid without a successful response suggested that the hypercalcemia had an uncommon etiology and posed a challenging case for our clinical practice.

The findings of reduced PTH and high phosphorus levels excluded a diagnosis of primary hyperparathyroidism. A thorough imaging study ruled out malignancy. PTH-related peptide assays are not routinely available in our country, and blood samples must be sent overseas for this test. Additionally, most patients with malignancy-associated hypercalcemia already have a cancer diagnosis at the time of presentation, suggesting that the patient's hypercalcemia was not related to cancer. The patient's history of STF injection led us to suspect a calcitriol-mediated cause associated with a granulomatous reaction.

Inappropriately normal calcitriol levels confirmed our suspicion. Low 25-OH-D levels due to increased conversion to calcitriol supported this diagnosis. PTH has three main roles as follows: to increase bone resorption by secondary activation of the osteoclasts, to increase renal calcium absorption and to reduce phosphate absorption. In the kidney, PTH exerts its action by activating 1-alpha-hydroxylase, transforming 25-OH-D to calcitriol. Under normal circumstances, a high calcium level will suppress PTH and thereby reduce calcitriol production as well as kidney phosphate re-absorption. In granulomatous disorders, the calcitriol level is not sup-

pressed due to an atypical production of 1-alpha-hydroxylase by macrophages. For example, the calcitriol levels in this patient and in previous case reports were "inappropriately" normal (Table 1) (7-18). In this regard, normal calcitriol levels (25 – 86,5 pg/mL) do not exclude calcitriol-mediated hypercalcemia. Some malignancies, such as Non-Hodgkin's lymphoma, can also have increased 1-alpha-hydroxylase activity, leading to increased calcitriol levels (16).

One of the most severe and interesting findings was the presence of multiple calcified lesions in the joints, left hemithorax and buttocks, correlating with the imaging findings of the affected areas. Additionally, the patient had subcutaneous nodules on the knees, toes, elbows, and metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints. All these manifestations are an example of the complexity of this disease with an increased calcium phosphorus product (calcium: 13 mg/dL, phosphorus: 5.5 mg/dL, product 71.5 NV: < 55) (17). Additionally, nephrolithiasis, calcinosis of the left hemithorax (Figure 2) and paravertebral region, microcalcifications around the ankle, and subcutaneous calcification of the heels, right hand, left wrist, right forearm and sclerae were documented and affected the quality of life of the patient. A pelvic MRI showed inflammation and chronic fibrosis due to a foreign-body reaction of the gluteus maximus muscles and perianal region that was associated with dystrophic calcified masses suggestive of soft-tissue calcinosis. Audiometry showed conductive hearing loss. Calcinosis was documented using ^{99m}Tc bone scintigraphy (Figure 1) in the right acromioclavicular joint, bilateral heels and soft tissues of the left shoulder area, right buttock and left hip. A computed tomography scan showed an enormous calcification of the left hemithorax, and the calcification of both sclerae was an interesting additional finding. A ^{99m}Tc bone scintigraphy study was consistent with the clinical findings and demonstrated the exten-

Table 1 - Reports of calcitriol-mediated hypercalcemia in the literature

Author	Patient	Material of injection	Clinical presentation	Laboratories	Imaging
Hindi SM, et al. (28)	45-year-old man, HIV (+) and HBV (+).	PMMA for HIV lipodystrophy in gluteus and deltoids.	Fatigue / polyuria / weight loss.	Ca 14.6 mg/dL, Cr 2.02 mg/dL, calcitriol 128 pg/mL.	Nodular soft tissue densities in both buttocks without evidence of sarcoïd or malignancy.
Negri AL, et al. (12, 14)	53-year-old woman.	PMMA in gluteus.	Fatigue / Asthenia.	Ca 15.2 mg/dL, iPTH 3.5 pg/mL and calcitriol 55.5 pg/mL	N.A.
	29-year-old woman.	PMMA in gluteus and thighs.	AKI / Anemia.	Ca 12 mg/dL, iPTH 11.6 pg/mL, calcitriol 88.3 pg/mL, Cr 5.62 mg/dL	Multiple nodular hypointense images in subcutaneous tissue and in both glutei.
	50-year-old woman.	PMMA in legs.	AKI / Hypercalcemia.	Ca 13.2 mg/dL, iPTH 15 pg/mL, calcitriol 53.6 pg/mL and Cr 2.2 mg/dL	Nodular images in the subcutaneous tissue compatible with granulomas.
	39-year-old woman and HIV (+).	PMMA in lower extremities.	AKI	Ca 12 mg/dL, iPTH 16 pg/mL, 25-D 9 ng/dL and calcitriol 94 pg/mL	Increased activity in the gluteus and thighs. Infiltrates around methacrylate deposits.
Rados DV, et al. (27)	82-year-old woman.	PMMA in gluteus.	Recurrent episodes of confusion, delirium, and somnolence or stupor.	Ca 13.7 mg/dL, phosphorus (PO4) 2.5 mg/dL, PTH 2.8 pg/mL, calcitriol 34 pg/mL.	Extensive and symmetric increased metabolic activity in the glutei regions in whole body 18F-FDG PET-CT. Hard nodules were identified by palpation.
Agrawal N, et al. (6)	45-year-old man and HIV (+).	Silicone in gluteus and cheeks.	Fatigue and abdominal pain.	Ca 13.1 mg/dL, Cr 3.0 mg/dL, PO4 3.6 mg/dL, PTH undetectable	Extensive high-density reticulonodular densities in buttocks and gluteal muscles extending to the lower back, consistent with body-sculpting silicone injections, along with prominent external iliac and inguinal nodes.
Camuzard O, et al. (7)	63-year-old woman	Liquid injectable silicone in gluteus.	Buttock pain, nausea, constipation, abdominal pain, dehydration. CKD and anemia were reported.	Calcitriol 65 pg/mL, Ca 12 mg/dL.	Major nodular infiltrate of subcutaneous soft tissues in buttock and hips. Diffuse nodular calcifications and advanced nephrocalcinosis. Increased uptake in buttock and hip regions.
Moraitis AG, et al. (8)	45-year-old man.	Mineral oil in breasts, gluteus, thighs and calves.	Severe, persistent skin and subcutaneous reactions, recurrent cellulitis in both lower limbs. Symptomatic hypercalcemia.	Ca 15.6 mg/dL, 24-h urine calcium (uCa) 880 mg/24 h, calcitriol elevated.	ND.
Schanz J, et al. (9)	72-year-old woman	Topical silicone-lipid. Injectable silicone use was denied.	Fatigue, appetite loss, weight loss.	Ca 12.1 mg/dL, 24-h uCa 196.2 mg/24 h. Normal PTH, PO4 and calcitriol.	Scintigraphy of the bone, whole body computed tomography were normal.
Gould-Simon A, et al. (10)	56-year-old man and HIV (+).	Liquid silicone in face and gluteus.	Unexplained hypercalcemia and elevated calcitriol.	Sarcoïdosis and tuberculosis were excluded.	Increased radiotracer accumulation in face and gluteal region.

to be continue

Continue from Table 1.

Gyldenløve M, et al. (11)	23-year-old man.	Paraffin oil in chest, arms, and back.	24-hour scrotal pain. Inflammation in the region of injection, dyspnea.	iCa 2.29, low 25-D, high calcitriol, suppressed PTH.	Increased metabolic activity in the subcutaneous area of the anterior thorax and arms. Diffuse pulmonary infiltration, lipid pneumonia and foreign-body inflammatory reaction.
Loke SC, et al. (13)	78-year-old woman	Silicone in chest and abdomen.	Progressive cognitive function loss, dehydration, multiple firm subcutaneous lumps on anterior chest wall, upper abdomen, and extremities	Ca 14.24 mg/dL, PO4 4.53 mg/dL, Cr 1.35 mg/dL	Numerous calcifications throughout subcutaneous fat and muscle layers on the anterior chest wall and abdomen.
Visnvei K, et al. (15)	40-year-old man, African American male-to-female transgender patient, HIV (+).	Industry-grade silicone in gluteus and thighs.	Malaise, dysuria, abdominal pain, increased thirst and blurred vision. Bilateral subcutaneous deposits in gluteal and thigh area.	Ca 12.3 mg/dL, Cr 1.56 mg/dL, calcitriol 47 pg/mL and decreased PTH.	Large amounts of diffusely infiltrating granulomatous tissue.

PMMA: Polymethylmethacrylate, AKI: Acute kidney injury, CKD: Chronic kidney disease, Ca: Calcium, iCa: Ionized calcium, Cr: Creatinine, PO4: Phosphorus, 24-h uCa: 24-hour urine calcium, 25 D: 25 Hydroxyvitamin D

sive clinical compromise. Some of these calcifications required palliative surgical management, which included resection of the calcified masses in the gluteal areas to reduce the pain and improve the functionality of the patient. The treatment of calcitriol-mediated hypercalcemia is difficult. Zoledronic acid was administered first, prior to the confirmation of calcitriol-mediated hypercalcemia, and did not result in improvement. In our hospital, the measurement of calcitriol is referred to a specialized laboratory, and the results are typically returned in two weeks. Antiresorptive medications such as zoledronic acid inhibit proliferation and induce apoptotic cell death in osteoclasts (20); however, when hypercalcemia is secondary to an increased 1-alpha-hydroxylase activity, an antiresorptive medication is not a useful treatment, as demonstrated in our case. Corticosteroids are recommended as a first-line therapy for patients with granulomatous reactions if there are no contraindications (18). Prednisone 30 mg/day was administered but did not improve the calcium levels. Oral glucocorticoids inhibit the activity of the mononuclear cells and modulate the cytokines involved in granulomatous inflammation (19). Low-dose glucocorticoids (e.g., 20-30 mg/day of prednisone) are recommended; however, higher doses have been used (e.g., 40–60 mg/day of prednisone) (20). An improvement in calcium levels by the second day may be seen, but a full response is usually observed after 7 to 10 days of treatment, depending on the prednisone dose. However, in this case, oral glucocorticoids did not improve the hypercalcemia. Other medications such as chloroquine and hydroxychloroquine inhibit the conversion of 25-OH-D to calcitriol, reducing urinary and serum calcium levels (21); however, chloroquine use must be limited to 6 months to avoid eye toxicity (18). Chloroquine administration to our patient did not improve the calcium level. Sevelamer (22) was used because it may reduce the calcium phosphorus product. Sevelamer is a cross-linked polymer free of metal or calcium that contains multiple amines separated by one carbon from the polymer backbone. In the gut partial ionization binds sevelamer to phosphorus, reducing phosphorus absorption and decreasing serum calcium levels and ectopic calcifications, however its complete action mechanism needs to be deeply understood (23). Sevelamer reduces the bioavailability and effects of oral calcitriol and consequently may promote disease control (24). Ketoconazole inhibits macrophage 1 alpha-hydroxylation of 25-OH-D₃(25) and should be considered if there is no response to glucocorticoids or if side effects occur (26); however, ketoconazole was not used in this case. Some case reports have suggested using other therapies such as calcitonin (12, 27), a calcium-restricted diet (6), surgical resection (7, 13, 15), denosumab (12) and local injections of triamcinolone (12). Surgical resection is not recommended due to the extensive long-standing calcific deposits, and due to the extensive nature of the procedure. In this patient, surgical management was only done for palliative reasons to improve functionality and to obtain pathological confirmation. This case informs the medical community on how, in rare cases, a foreign-body reaction can cause a granulomatous reaction leading to severe hypercalcemia, widespread calcifications and even life-threatening consequences. In patients with calcitriol mediated hypercalcemia of unclear etiology, a complete and deep interview of the past medical history is extremely important. Questioning about the patient's cosmet-

ic intervention history is mandatory, no matter how far in the past the procedures were conducted. Hypercalcemia can take considerable time to become clinically evident and can appear months or even years after cosmetic procedures are performed. A retrospective investigation should be conducted in patients with hypercalcemia complications, such as chronic kidney disease, calcinosis cutis and nephrocalcinosis.

To our knowledge, there are only 14 case reports in the medical literature on this topic (Table 1). One study included four cases in females, and another included ten individual cases. The most common injected products were polymethylmethacrylate (PMMA) and liquid injectable silicone, and all of them were used for cosmetic purposes, including interventions in the buttocks, cheeks, lower extremities (thighs, legs) and deltoids. Young females were the most common population undergoing these cosmetic interventions. Weight loss, fatigue, and pain at the injection site were common complaints among most of the reviewed cases. The patient discussed in this study presented most of the signs and symptoms described.

Finally, the need to be recognized by others as “good looking” and to physically fit into a social representation of beauty has created a bigger demand for cosmetic interventions. Governmental regulations in all countries and warnings for patients and cosmetic practitioners should be mandatory.

Conclusion

A foreign-body reaction may trigger a granulomatous reaction that causes secondary hypercalcemia and multiple organ compromise. The growing population of patients with a history of unknown STF injection for cosmetic purposes demonstrates the importance of maintaining a high index of suspicion for calcitriol-mediated hypercalcemia as a differential diagnosis in these patients. It is important to alert the public health system of the consequences of such indiscriminate treatments. Unsupervised cosmetic procedures can have severe endocrine and multiple-organ complications such as those reported here. This case demonstrates the importance of considering calcitriol-mediated hypercalcemia as a differential diagnosis in cases of PTH-independent hypercalcemia.

Contributors

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Competing interests

All the Authors declare that they have no competing interests.

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