Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 3 Article 14

2024

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Recommended Citation

Martinez-Cruz, Maria; Madsen-Barbosa, Thayse Lozovoy; Antoni, Fidini; and Haas, Christopher (2024) "Endocrine Shades of Silicone Fillers: A Case of Calcitriol-Mediated Hypercalcemia," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 14: Iss. 3, Article 14.
DOI: 10.55729/2000-9666.1349
Available at: https://scholarlycommons.gbmc.org/jchimp/vol14/iss3/14

CASE REPORT

Endocrine Shades of Silicone Fillers: A Case of Calcitriol-mediated Hypercalcemia

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Abstract

Background: **The inflammatory reaction of foreign body granulomas (FBG) may be so vast that it leads to severe systemic effects.**

Case report: **A 42-year-old woman was referred to the ED with severe recurrent symptomatic hypercalcemia associated with worsening kidney function. She had presented multiple times with similar complaints. Severe hypercalcemia (13.8 mg/dL) was noted, with appropriately low PTH, elevated PTHrP, low 25-hydroxyvitamin D, and normal 1,25-dihydroxyvitamin D levels. She admitted having significant subcutaneous silicone filler injections in the hips six years prior. Admission workup revealed a normal 25-hydroxyvitamin D, but a marked elevation of 1,25-dihydroxyvitamin D (138 pg/mL). Whole-body PET-CT demonstrated moderate 2-18F-fluoro-2-deoxy-D-glucose (FDG) uptake within the subcutaneous adipose tissue of the lateral aspects of the gluteal regions. She was diagnosed with silicone filler injection-induced hypercalcemia, secondary to granulomatous inflammation. Her calcium level normalized a month after the initiation of prednisone.**

Discussion: **FBG may occur years after filler injection. In rare cases, a significant granulomatous immune response leads to uncontrolled production of calcitriol. Pro-inflammatory cytokines can also upregulate PTHrP expression in macrophages, further contributing to hypercalcemia. Treatment focuses on general hypercalcemia management and FBG remission, most effectively achieved with anti-inflammatory corticosteroid doses. Nevertheless, further studies are needed to evaluate its long-term treatment efficacy.**

Conclusion: **Granulomatous inflammation from silicone filler injection can cause hypercalcemia by uncontrolled production of calcitriol and increased PTHrP production by macrophages and giant cells.**

Keywords: Hypercalcemia, Silicone-induced granuloma, Calcitriol, PTHrP

1. Introduction

The use of soft tissue fillers for body contouring dates to the beginning of 20th century.[1] One of the first substances used was injectable silicone-derived products. Its off-label use grew exponentially in the 1950s following toxicology reports highlighting its physiologically inert properties, suggesting a relatively favorable safety profile.[2,3] In 1965, a prototype of purified synthetic polymers in the form of injectable silicone was evaluated in FDA-approved phase one studies revealing no apparent major adverse events in a short-term follow-up.[3,4] Nevertheless, inconsistencies in standardization and lack of long-term follow-up, in addition to increasing data revealing serious adverse effects, eventually led to the recommendation against the use of silicone fillers by the FDA in the 1970s.[1,3]

Amongst the diverse complications, granuloma formation is one of the most devastating, oftentimes leading to disfigurement.[5] In rare cases, the granulomatous immune response is so vast that it leads to severe systemic disease. We report a case of silicone-induced hypercalcemia secondary to increased granuloma-mediated production of calcitriol.

Received 5 September 2023; revised 11 February 2024; accepted 21 March 2024.
Available online 7 May 2024

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https://doi.org/10.55729/2000-9666.1349

2. Case description

A 42-year-old woman was referred to the emergency department by her endocrinologist for hypercalcemia and worsening glomerular filtration rate (GFR) noted on routine blood work. She endorsed a two-week history of generalized weakness, myalgias, polyuria, polydipsia, and intermittent constipation. Her comorbidities include chronic kidney disease (CKD) stage 3, micro-nephrolithiasis, gastroesophageal reflux disease, chronic cervical and lumbar neuropathic pain, and depression. Surgical history was remarkable for extensive cosmetic intervention – saline-filled breast implants, rhinoplasty, aesthetic vaginoplasty, silicone filler injections, and solid silicone buttock implants.

A year and a half before the current presentation, she was admitted for similar complaints. Laboratory diagnostics at that time demonstrated severe hypercalcemia (13.8 mg/dL; reference range (Ref) 8.7–10.4 mg/dL) and acute on chronic renal insufficiency (3.97 mg/dL, baseline 0.69 mg/dL three years prior, Ref 0.5–0.8 mg/dL). Additional workup showed normal TSH (1.749 UI/L, Ref 0.450–4.5 UI/L), an appropriately low parathyroid hormone (PTH) (15.8 pg/mL, Ref 18.4–80.1 pg/mL), a mildly elevated PTH related peptide (PTHrP) (7.7 pmol/L, Ref 0.0–3.4 pmol/L), a low 25-hydroxyvitamin D (14.1 ng/mL, Ref 30–100 ng/mL), and a normal 1,25-dihydroxyvitamin D (67.3 pg/mL, Ref 24.8–81.5 pg/mL). A CT of chest, abdomen, and pelvis was unrevealing except for small kidneys compatible with CKD. Her hypercalcemia was attributed to Milk-Alkali syndrome, from excessive milk consumption and calcium-containing antacids which were subsequently discontinued. She received fluid resuscitation and zoledronic acid 4 mg IV one time, with subsequent normalization of calcium levels. Six months after this original presentation, she was readmitted for hypercalcemia at 12.8 mg/dL. Additional workup was unremarkable, including urine and serum protein electrophoresis, kappa/lambda ratio, and complement levels. She received fluids and subcutaneous Calcitonin 300 IU twice daily for four days. She was discharged on intranasal salmon calcitonin, which she had used intermittently.

On the current presentation, she reported having silicone filler injections in the lips, cheeks, and hips applied by a non-healthcare provider six years ago. One year later, she had induration and intermittently tender erythematous hips and lateral upper thighs. She had no family history of endocrinopathies, premature fractures, or malignancies.

The patient was hemodynamically stable. Physical examination revealed indurated erythematous nodules localized to the hips (Fig. 1). She again demonstrated hypercalcemia (12.1 mg/dL) and elevated serum creatinine (4.71 mg/dL). Additional workup demonstrated an appropriately suppressed PTH (9.6 pg/mL), normal TSH (2.240 uUI/L), mildly elevated vitamin A (84.2 mcg/dL, Ref 20–62 mcg/dL), normal 25-hydroxyvitamin D (30.5 ng/mL), low PTHrP (<2 pmol/L), mildly elevated serum angiotensin-converting enzyme (91 U/L), a negative QuantiFERON-TB gold, and marked elevation of 1,25-dihydroxyvitamin D (138 pg/mL). A whole-body PET-CT demonstrated moderate FDG uptake within the subcutaneous adipose tissue of the lateral aspect of bilateral gluteal regions from above the iliac crests to the upper thighs (Fig. 2). She received fluid resuscitation and initiated on prednisone 20 mg PO daily with normalization of calcium levels (9.7 mg/dL) within a month. She is maintained on prednisone 10 mg daily.

3. Discussion

"Silicone" is the common terminology referring to a family of synthetic compounds containing the chemical element silicon;[6] polydimethylsiloxane is the chemical nomenclature of liquid forms.[7] Despite the lack of biocompatibility studies of silicone injections, it was utilized for soft tissue augmentation,[3] with the initial polydimethylsiloxane prototype evaluated in FDA-approved studies revealing promising results. Nevertheless, it was subsequently banned in 1967 after reports of catastrophic side effects, including migration, deformity, and death.[3,8]

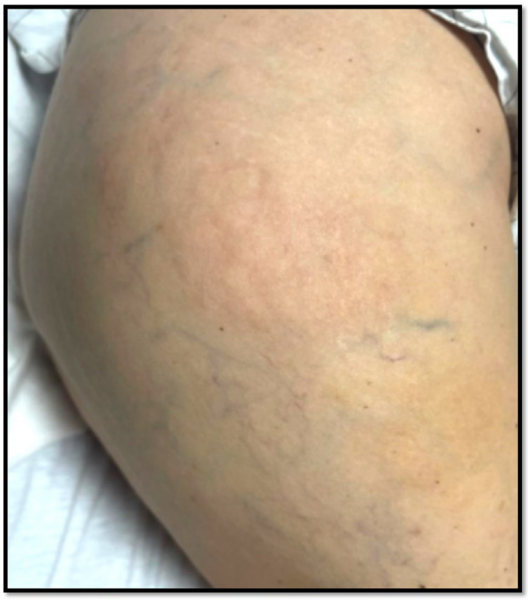

Fig. 1. Skin findings noted in right hip on physical exam.

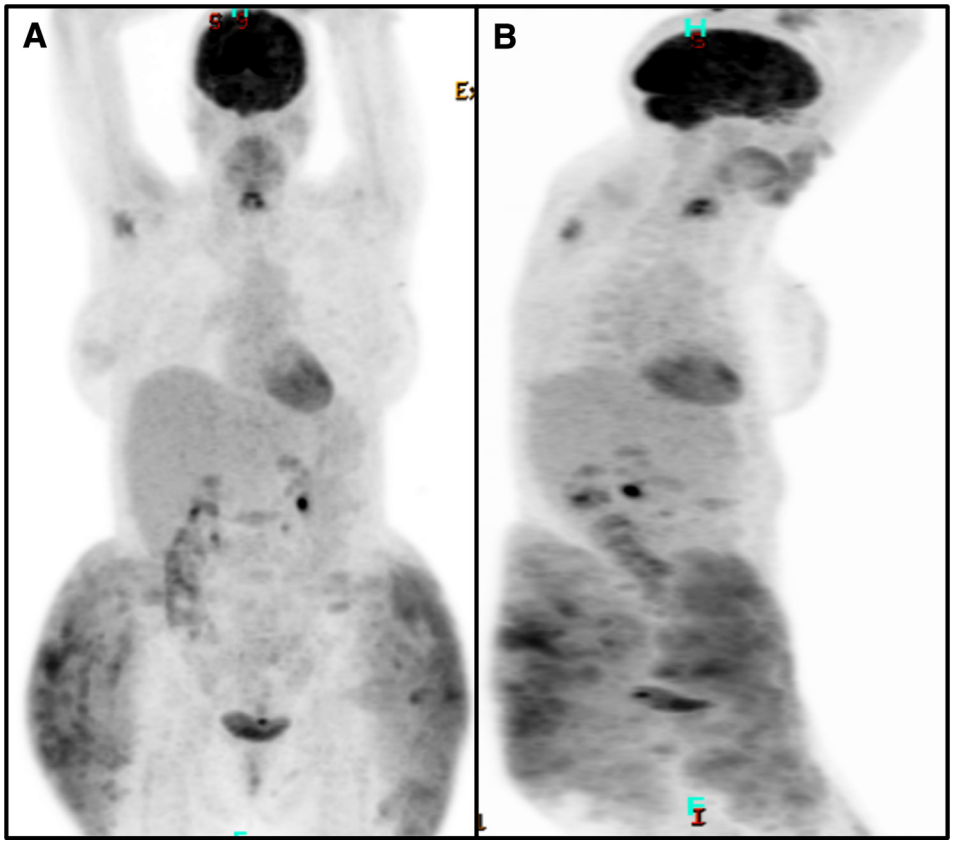

Fig. 2. Total body fluorodeoxyglucose positron emission tomography (PET)/CT scan. Panel A: Anteroposterior view. Panel B: Right lateral view. Noted diffuse moderate FDG uptake in the subcutaneous adipose tissue of bilateral gluteal regions greatest laterally extending inferiorly to the level of the hips and upper thighs, measuring on the order 31 cm in superior to inferior extent bilaterally. The left-side area has a SUV max of 4.9, and the right-side area has SUV max of 5.4.

Foreign body granuloma (FBG) is an exaggerated non-allergic chronic inflammatory reaction that can occur with nearly all dermal fillers; silicone is no exception.[9] The occurrence of FBG depends on the molecular characteristics of the filler, presence of adulterants/purity, technique, volume injected, and local vascularity.[8] Fillers with longer half-lives, like injectable silicone, have a higher probability of causing FBG,[10] as ineffective phagocytosis is the principal pathophysiologic process in granuloma formation.

Silicone-induced FBG may manifest as an edematous granuloma, also known as lipogranuloma, characterized by an extracellular microcyst - a mixture of massively vacuolated mononuclear macrophages and giant cells.[11] The resultant inflammatory microenvironment leads to increased capillary permeability, manifesting as edema, erythema, and/or purple discoloration in injected areas, as noted in our patient (Fig. 1).[10] This microenvironment is theorized to predispose to a hypersensitivity reaction that may manifest many years after its injection and can recur;[12] one documented FBG reaction developed 28 years later.[13] Our patient experienced recurrent nodules within two years. Hypercalcemia can occur anywhere within a few months up to 28 years afterwards.[16] Moreover, the FDA noted the potential danger of unapproved use in gluteal or breast augmentation, given the extensive vascularity of these areas.[17] Use of higher quantities may also predispose to higher rates of FBG responses.

In rare cases, the overwhelmingly inflammatory granulomatous immune response leads to overactivity of 1-alpha-hydroxylase in activated macrophages and giant cells.[14] In contrast to renal 1-alpha-hydroxylase, which is regulated by a negative feedback mechanism, macrophage 1-alpha-hydroxylase isoforms are not subject to this.[15] This leads to unregulated production of 1,25-dihydroxyvitamin D and subsequent severe PTH-independent hypercalcemia. Despite the eventual confirmation of elevated serum calcitriol levels, our patient had initially low 25-hydroxyvitamin D. Although uncommon, this feature has been previously reported.[18] In this setting, the relative ratio of

25-hydroxyvitamin D to 1,25-dihydroxyvitamin D can be calculated, as less substrate is available for 1-alpha-hydroxylase.[16]

Our patient had initial mildly elevated PTHrP despite the absence of malignancy. This is seen in other granulomatous diseases, including sarcoidosis,[19] mycobacterial infection,[20,21] and siliconoma.[22] It has been suggested that proinflammatory cytokines like interleukin 6 and Tumor Necrosis Factor alfa upregulate PTHrP expression in macrophages.[23,24] However, a subsequent admission revealed low PTHrP. There are reports of silicone-related FBG cases of both elevated[31,32] and low PTHrP levels.[30,33,34] Our case demonstrates a unique increase and subsequent decline in PTHrP as well as a normal and subsequent increase in calcitriol which is not well addressed in current literature.

In addition, mildly elevated ACE levels were also found in our patient, a common feature of granulomatous-like reactions, including sarcoidosis, and sarcoid-like reactions, such as silicone-induced FBG.[25] The progressive decline in our patient's GFR may be multifactorial. Nephrolithiasis, interstitial fibrosis, and nephrocalcinosis are well-described consequences of severe long-standing hypercalcemia and hypercalciuria,[26] however, indirect effects of systemic cytokine release on nephrons and the tubulointerstitial compartment are seen in granulomas.[23,27,28]

While the gold-standard of silicone-related FBG diagnosis remains tissue biopsy, dynamic imaging studies such as 2-18F-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET) can identify tissues with active granulomatous reactions by increased FDG uptake[29] as observed in our patient (Fig. 2). Treatment is focused on general hypercalcemia management and FBG remission. Given the underlying pathophysiology, corticosteroids are the mainstay of therapy by inhibiting the macrophage-derived 1-alpha-hydroxylase, reducing proinflammatory cytokine release by binding to cytokine promoter region in macrophages, and further decreasing PTHrP expression. Corticosteroids also reduce gastrointestinal calcium absorption and inhibit osteoclast function.[23] In those unable to tolerate corticosteroids, alternatives include minocycline, cyclosporine, and allopurinol, all of which demonstrate variable efficacy.[18] Edwards et al. achieved successful control of hypercalcemia with surgical resection of silicone material in the gluteal region.[30] Nevertheless, surgery has been ineffective in other cases.[22] Surgery can be complex if the affected area is extensive and may cause further deformities, but may be considered if hypercalcemia persists. Our patient exhibited normalization of serum calcium and 1,25-dihydroxyvitamin D after glucocorticoids.

4. Conclusion

Liquid silicone is commonly used for aesthetic augmentation despite the myriad of potential complications. FBG is a complex, hypersensitivity-like reaction that develops secondary to macrophage overactivation, an inflammatory microenvironment with capillary permeability, and subsequent granuloma formation leading to downstream elevations in calcitriol and ACE with resultant hypercalcemia, renal disease, and deformation. This complication is unpredictable, occurring months to years after application. Although rare, FBG-related hypercalcemia should be considered in the differential diagnosis of hypercalcemia, especially in those with a history of body contour enhancements with fillers or implants of any nature. Long-term management is challenging, but corticosteroids seem to be the most effective therapy.

Disclaimers

This case has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

Sources of support

The authors did not receive any dedicated financial support for this paper and have no conflicts of interest to disclose.

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