Case Report

Free Silicone-Induced Granulomatosis and Hypercalcemia in a Transgender Female

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Abstract

Introduction
Vitamin D derangements are a rare but important cause of hypercalcemia. Granulomatous disease is a primary cause of vitamin D derangements and is frequently associated with sarcoidosis, tuberculosis, and in the present case, foreign body granulomatosis. Liquid or injectable silicone is used as a filler for cosmetic body contouring. Transgender patients may seek silicone injections as part of gender affirmation surgeries. Granuloma formation is a rare but well-described complication of injectable silicone.

Case Description
A 40-year-old, assigned male at birth (AMAB) transgender female patient, with a history of HIV and chronic kidney disease (CKD) stage 3b, was admitted to the emergency department for evaluation of hypercalcemia. One year prior, the hypercalcemia was attributed to CKD secondary to HIV or HIV medications. The patient presented after two weeks of polyuria and polydipsia. Her vital signs were stable, and the physical exam, EKG, and chest x-ray were unremarkable. Labs were notable for calcium (14.1 mg/dL, assay normal range 8.5-10.5 mg/dL) and acute-on-chronic kidney disease. Follow-up labs were consistent with a vitamin D aberration causing hypercalcemia, raising suspicion for granulomatous disease. CT chest/abdomen/pelvis without contrast demonstrated diffuse skin thickening of the bilateral breasts and buttocks with associated ill-defined soft tissue density and scattered punctate calcifications. No hilar adenopathy or lung abnormalities were observed, decreasing the suspicion of sarcoidosis or an infectious etiology. The patient disclosed having received free silicone injections to which the hypercalcemia was attributed. After single doses of calcitonin (100U SC/IM) and zoledronic acid (4 mg IV), her hypercalcemia resolved. Kidney function gradually returned to baseline with IV fluids.

Conclusion
This case illustrates the importance of readily recognizing the imaging characteristics of free silicone granulomatosis, which showed subcutaneous fat infiltrated with soft tissue nodules and calcifications. The distribution of findings in the bilateral breast and buttocks and history of free silicone injections were most useful in arriving at a diagnosis and treatment plan.

Keywords
transgender persons; hypercalcemia; foreign-body granuloma; body contouring; dermal fillers/administration & dosage; dermal fillers/adverse effects; cosmetic techniques; subcutaneous injections

Introduction
Hypercalcemia is a commonly encountered disorder that can result from multiple etiologies and cause significant morbidity and mortality if not properly evaluated and treated.[1,2] Clinical manifestations of hypercalcemia can vary and are usually present with a calcium level of greater than 12 mg/dL. Hypercalcemia can be mild (10.5 to 11.9 mg/dL), moderate (12 to 13.9 mg/dL), or a hypercalcemic crisis (14.0 to 16.0 mg/dL). The most common symptoms of hypercalcemia include abdominal pain, nausea/

vomiting, bone pain, fatigue, constipation, lethargy, and/or altered mental status. Hypercalcemia can also present with nephrolithiasis, pancreatitis, and/or cardiac arrhythmias.[1] Vitamin D derangements are a less common but important cause of hypercalcemia. Granulomatous disease is the main perpetrator in vitamin D derangements and is a hallmark of sarcoidosis, tuberculosis, or, as we will describe in the case below, foreign body granulomatosis.[1,2]

Vitamin D (1,25 dihydroxyvitamin D) is a steroid hormone responsible for increasing the absorption of calcium and phosphate, primarily from the gut.[2,3] Inactive vitamin D is normally converted to its active form by 1-alpha-hydroxylase found in renal tubular cells, but the enzyme is also found in macrophages. Renal cells have a well-established negative feedback mechanism to lower 1-alpha-hydroxylase (CYP27B1) production when 1,25 dihydroxyvitamin D is high. Vitamin D regulatory mechanisms are limited in macrophages, leading to abnormally elevated vitamin D levels in granulomatous disease caused by foreign bodies, sarcoidosis, or tuberculosis.[2,3]

Liquid or injectable silicone is a non-biodegradable, inert material used as an injectable filler for cosmetic body contouring. Granuloma formation is a rare but well-described complication of injectable silicone.[4,5] Injectable silicone is not FDA-approved for aesthetic procedures of the face or body. Practitioners administering silicone, in the United States (US) or abroad, may be unlicensed or unqualified to do so.[5]

The majority of patients seeking cosmetic procedures such as body contouring are female. Male-to-female transgender patients are a small subset who may seek such procedures as part of gender affirmation. Gender-affirming therapies have been shown to improve quality of life and self-esteem. In addition, gender affirming surgeries generally have a high satisfaction rate.[6]

We present a case in which a patient, assigned male at birth (AMAB), transgender female, was admitted for worsening, severe hypercalcemia. The hypercalcemia was eventually attributed to granulomatosis from free silicone injections of the breasts and buttocks performed several years prior.

Case Description

A 40-year-old, assigned male at birth (AMAB), transgender female patient, with a history of human immunodeficiency virus (HIV) and chronic kidney disease (CKD) stage 3, was admitted for evaluation of hypercalcemia. Her home medications included antiretroviral therapy with rilpivirine and dolutegravir and vitamin D supplementation. One year prior to the current ED admission, she had been evaluated as an outpatient for hypercalcemia. This prior workup revealed an inappropriately normal parathyroid hormone (PTH), normal PTH-related protein, and a low vitamin D level. Her hypercalcemia at that time was attributed to CKD secondary to HIV or HIV medications. Two weeks prior to emergency department (ED) presentation, she was found to have elevated calcium levels and discontinued her vitamin D supplementation.

The patient presented to the ED on the recommendation of her nephrologist due to a 2-week history of polyuria and polydipsia. The outpatient lab work revealed worsening acute-on-chronic kidney injury and persistent elevation of calcium up to 13.6 mg/dL. Upon presentation to the ED, her vital signs were stable. Physical exam, EKG, and chest X-ray were unremarkable. Labs were notable for elevated calcium (14.1 mg/dL, assay normal range 8.5-10.5 mg/dL) and acute-on-chronic kidney disease with a blood urea nitrogen (BUN) of 48 mg/dL and creatinine of 2.75 mg/dL (our patient's baseline was 1.6 mg/dL). Follow-up laboratory studies revealed a low 25-hydroxyvitamin D level (18 ng/mL, assay normal range 30-80 ng/mL), appropriately low PTH (7 pg/mL, assay normal range 7.5-53.5 pg/mL), a non-detectable PTHrP, elevated 1,25-dihydroxyvitamin D level (130 pg/mL, assay normal range 21-65 pg/mL), and elevated ionized calcium (7.94 mg/dL, normal assay range 4.50-5.30 mg/dL). These laboratory findings were consistent with a vitamin D aberration causing hypercalcemia, raising suspicion for granulomatous disease such as sarcoidosis. An angiotensin-converting enzyme (ACE) level was obtained, which was within normal limits. Both urine protein electrophoresis (UPEP) and serum protein electrophoresis (SPEP) were negative making multiple myeloma less likely. Further imaging with CT chest/abdomen/pelvis without contrast was obtained. The CT demonstrated diffuse skin thickening of the bilateral

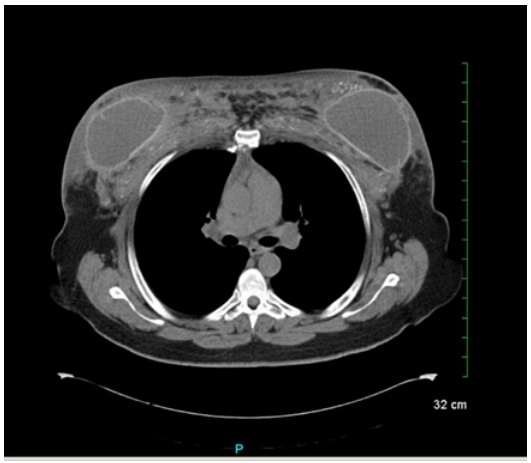

Figure 1. An axial CT image at the level of the breasts demonstrating abnormal, diffuse soft tissue density replacing fatty tissue about the implants with associated scattered calcifications. The pectoralis muscles were also involved (posterior to the implants).

breasts and buttocks with associated ill-defined soft tissue density and scattered punctate calcifications within the subcutaneous fat, pectoralis, and gluteus muscles (**Figures 1** and **2**). Additionally, bilateral breast implants were noted. No hilar adenopathy or lung abnormalities were observed, decreasing the suspicion for sarcoidosis or an infectious etiology such as tuberculosis. However, there was bilateral inguinal and axillary adenopathy with the largest individual node measuring up to 2 cm (**Figure 3**).

An ultrasound-guided axillary lymph node biopsy was performed and showed non-specific reactive lymphadenitis without evidence of granulomatous disease. Imaging findings prompted further discussions with the patient about prior surgeries or procedures. The patient divulged a history of receiving bilateral breast and buttock free silicone injections in Mexico several years prior. This new information helped guide the discussions among pulmonology and radiology services with the consensus that the lymphadenopathy and soft tissue findings were consistent with granulomatosis due to free silicone injection and was the likely cause of the hypercalcemia.

Overall, the patient's hospital course was uneventful. She was initially given single doses of calcitonin (100U SC/IM) and zoledronic acid (4 mg IV) with IV fluids throughout her hospital stay. The hypercalcemia resolved and her kidney function returned to baseline. She did not require any additional medications upon discharge and received a plan for close follow-up with nephrology on an outpatient basis.

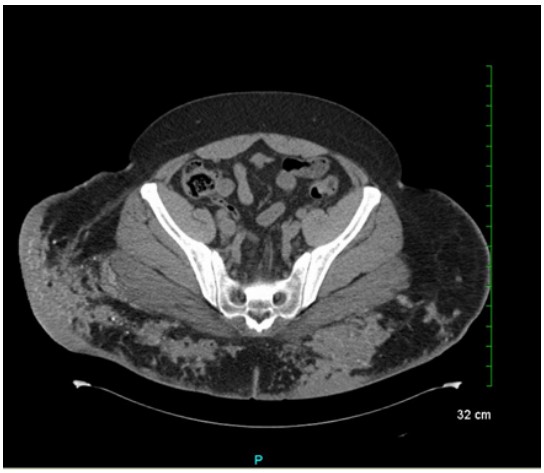

Figure 2. An axial CT image at the level of the gluteus also demonstrating abnormal soft tissue density replacing fatty tissue over the gluteus muscles with scattered associated calcifications.

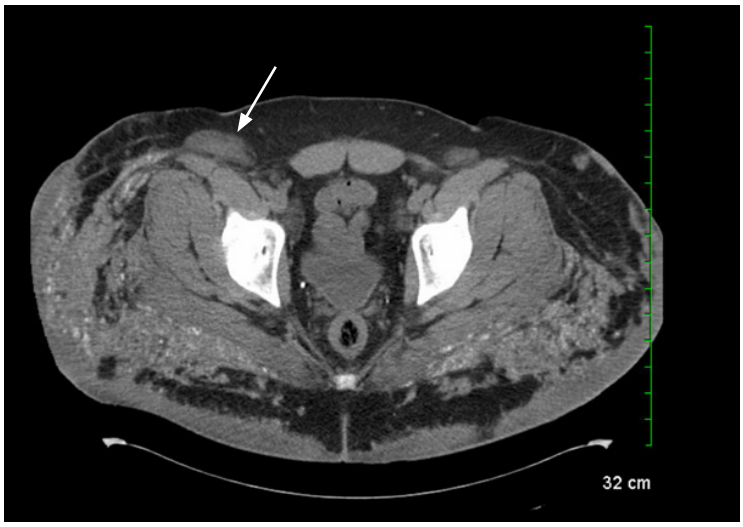

Figure 3. An axial CT image at the level of the pelvis demonstrating enlarged bilateral inguinal lymph nodes. The lymph node that was biopsied is denoted by the white arrow.

Discussion

Symptomatic hypercalcemia can be the first manifestation of a serious disease, including malignancy, and it is imperative that it be worked up. Primary hyperparathyroidism and malignancy are revealed as the etiology for hypercalcemia in approximately 90% of patients.[1,7] Malignant etiologies include carcinomas, leukemias, multiple myeloma, and lymphomas. As was shown in our case, vitamin D derangement caused by granulomatous disease is a less common but important cause of hypercalcemia. Elevated blood calcium levels result from abnormally high levels of active vitamin D. The enzyme 1-alpha-hydroxylase (CYP27B1) converts 25-hydroxyvitamin D (inactive form) to 1,25-dihydroxyvitamin D (active form). It is expressed in many tissues, but renal expression plays an important role in vitamin D and calcium homeostasis. Renal production of 1-alpha-hydroxylase enzyme (CYP27B1) has a well-established negative feedback mechanism, which limits production in the presence of 1,25-dihydroxyvitamin D(product). Macrophages are a main cell type involved in the granuloma reaction: their overexpression of 1-alpha-hydroxylase (CYP27B1) is the main cause of hypercalcemia in granulomatous disease. Macrophage production of 1-alpha-hydroxylase (CYP27B1) does not have the same negative feedback mechanism as renal production and there is continued 1-alpha-hydroxylase (CYP27B1) expression even when 1,25-dihydroxyvitamin D is abundant. This leads to abnormally increased levels of 1,25-dihydroxyvitamin D, which in turn, increases blood calcium levels, primarily by increasing the absorption of calcium in the gut.[3,7,8] Work-up algorithms typically include evaluation of the vitamin D abnormalities seen in granulomatous disease such as sarcoidosis and tuberculosis.[1] However, it is important to also include foreign body granulomatous disease in the differential, particularly in transgender individuals who underwent large-scale body contouring procedures.

Our case illustrates the importance of readily recognizing the imaging characteristics of free silicone granulomatosis. As we observed, the CT will show infiltration of subcutaneous fat with soft tissue nodules and associated calcifications. Ultrasound findings vary but are usually associated with hypoechoic, shadowing masses that may or may not have an echogenic anterior margin but can sometimes mimic simple cysts. MRI often shows nodules that are hypointense on T1-weighted images, and intermediate intensity on T2-weighted images less than water.[9,10] Although not routinely performed, silicone-sensitive MR sequences have been described in breast MR to aid in detecting silicone implant rupture. These MR sequences null fat and suppress water signal intensity, causing silicone to appear bright against the dark breast tissue.[11] PET/CT appearance of free-silicone granulomatosis has also been described as low-level hypermetabolic activity associated with the above CT findings. However, PET/CT is non-specific and can sometimes

present a diagnostic dilemma in a patient with cancer or when an infection is suspected. Other nuclear medicine exams such as gallium-67 or MDP-Tc-99 bone scan can also show non-specific soft tissue uptake.[12] In the present case, the most helpful clues for the radiologist were the distribution of findings in the bilateral breast and buttocks as well as clinical history of prior free silicone injections.

Free silicone injections were banned by the FDA in 1992 and there is ongoing work to assess their safety. The ban was lifted in 2006 for ophthalmic use only. Free silicone is not FDA-approved as a dermal cosmetic filler, even on a small scale.[5] Serious associated complications such as cellulitis, necrosis, pneumonitis, systemic sclerosis, and embolization have been described. Granuloma formation is another known complication of free silicone injection. The risk of granuloma formation increases with the use of free silicone in large volumes, intramuscular injection, and the use of non-medical grade silicone, all 3 of which likely occurred in our patient.[3] Despite the lack of FDA approval, body contouring with free silicone still occurs both in the US and abroad. There are many published examples of free silicone injection granulomatosis and hypercalcemia, the majority of them occurring in female patients.[13,14] There are a few case reports of similar complications in transgender females.[15] Our case was unique in that the history of prior free silicone injection was initially withheld, leading to delayed diagnosis and potentially unnecessary diagnostic workup including biopsy.

Conclusion

The transgender community is a small but growing population. Historically, transgender patients have experienced unequal treatment resulting in a greater burden of health disparities and outcomes.[16] Transgender patients may lack access and resources to gender-affirming care from licensed and qualified medical professionals. They may also be reluctant to divulge details about prior surgeries or treatments that might directly affect their health. Their reluctance may be due to prior negative clinical experiences from implicit or explicit bias, judgment, and/or discrimination from the healthcare system. Clinicians must take a thorough history from patients who are transgender as it relates to prior gender-affirming treatments. It is important to create a safe and non-judgmental environment for these patients to freely discuss their medical history and ongoing needs.

Acknowledgment

Michael G. Flynn, PhD, Medical Writer, provided writing and copyediting assistance on the final version of the manuscript.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Drs Goldsmith, Helmly, Kinger, and Pando are employees of Memorial Health University Medical Center, a hospital affiliated with the journal's publisher.

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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