



## Case Report

# Resection of granulomatous tissue resolves silicone induced hypercalcemia



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## ABSTRACT

Because of the increasing trend of body contour enhancements with injections, implants, and fillers, clinicians should be on high alert for the possibility of silicone-induced hypercalcemia as one of the differential diagnoses in a patient with history of silicone use. Hypercalcemia as a result of silicone injections has been reported, and there is concern that there will be more cases given the popularity of cosmetic silicone. Cases involved a mother and daughter (70 & 55 years) who presented in 2013 with hypercalcemia after cosmetic silicone injections in 2007. Evaluation showed 1,25-dihydroxyvitamin D-mediated hypercalcemia and progressive renal dysfunction; lymph node biopsy showed granulomatous silicone lymphadenitis. MRI of the pelvis revealed abnormal signal enhancement within the subcutaneous gluteal adipose tissue and enlarged inguinal lymph nodes. For persistent hypercalcemia and hypercalciuria, surgical resection of silicone material and granulomas is a successful approach to normalize the serum calcium level.

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## 1. Introduction

Hypercalcemia as a result of silicone injections has been reported, and there is concern that there will be more cases as the popularity of cosmetic silicone grows. We report two cases (mother and daughter) of silicone-induced hypercalcemia that resolved after surgical removal of granulomatous tissue.

## 2. Case 1

A 50-year-old Latina woman was referred to University of Texas MD Anderson Cancer Center for evaluation of hypercalcemia. This patient had received 3 injections of 'silicone'-like material in each gluteal region for cosmetic purposes in 2007 from an unlicensed individual. Between 2010–2013 she developed inguinal lymphadenopathy, induration over the injection area, fatigue, polyuria, intermittent confusion, weight gain, tingling and numbness and hair loss. In 2013 she was found to have a corrected serum calcium of 16.7 mg/dL (8.4–10.2 mg/dL), 1,25-dihydroxyvitamin D of 71 pg/mL (18–78 pg/mL),

intact parathyroid hormone level of 5 pg/mL (9–80 pg/mL), an undetectable parathyroid hormone-related protein and angiotensin converting enzyme (ACE) level of 96 U/L (8–53 U/L). She was hospitalized, hydrated, treated with corticosteroids (prednisolone 20 mg) and referred for evaluation.

The patient developed nephrolithiasis in 2007 and had ureteral stent placement in 2012. She had frequent urinary tract infections, migraine headaches, depression, anxiety, arthritis, and hypothyroidism. Physical examination revealed an anxious female; abdominal examination was remarkable for abdominoplasty and firm palpable bilateral inguinal lymph nodes. There was hyperpigmentation and induration over the buttocks consistent with post-inflammatory hyperpigmentation and fibrosis due to silicone injection. Numerous firm nodules were palpated in the gluteal area bilaterally. Laboratory testing revealed serum calcium of 10.24 mg/dL (Table 1) and serum creatinine of 1.7 mg/dL (eGFR 44 mL/min/1.73 m<sup>2</sup>) (0.6–1.00 mg/dL; 80–120 mL/min/1.73 m<sup>2</sup>). Pelvic MRI revealed abnormal signal enhancement within the subcutaneous adipose tissue over the gluteal region and enlarged lymph nodes. The largest node in the right inguinal region was 1.5 × 1.8 × 2.2 cm; biopsy of a right inguinal lymph node showed granulomatous silicone lymphadenitis. Histologic sections of the lymph node showed diffuse involvement by non-necrotizing granulomatous inflammation with numerous variably sized vacuoles and foreign-body giant cells. In addition to the vacuoles, scattered round, pigmented, foreign material-containing

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**Table 1**  
Laboratory results for case 1 and case 2 with corresponding reference levels.

Test	Case 1		Case 2		References
	Pre-presentation Oct 2013	Post-presentation Oct 2014	Pre-presentation Oct 2013	Post-presentation Oct 2014	
Serum calcium (mg/dL)	17.3	10.2	11.5	9.6	8.4–10.2
Parathyroid hormone (pg/mL)	5	16	<3.0	22	9–80
25-OH vitamin D (ng/mL)	28	39	24	20	30–100
1,25-OH vitamin D (pg/mL)	71	69	89	65	18–78
Serum phosphate (mg/dL)	3.5	3.6	3.5	3.8	2.5–4.5
CTX beta Crosslaps (pg/mL)	244	574	274	865	40–840
Serum creatinine (mg/dL)	1.4	0.66	1.3	0.99	0.6–1.00
Angiotensin converting enzyme (U/L)	96	37	65	26	8–53
Glomerular filtration rate (mL/min)	40	95	40	55	80–120
Luteinizing hormone (mIU/mL)	62.2				1.0–11.4 Postmenopausal 7.7–58.5
Estradiol, S (pg/mL)	<12.0				Postmenopausal <55

central vacuoles were also present. On the initial evaluation at MD Anderson, the patient had Cushingoid features and requested cessation of corticosteroids; she was subsequently treated with pentoxifylline (400 mg two times a day). Pentoxifylline is a competitive nonselective phosphodiesterase inhibitor that raises intracellular ATP, activates protein kinase A, and inhibits TNF  $\alpha$  and leukotriene synthesis, thereby reducing inflammation. The patient tolerated pentoxifylline.

Over the next 2 months, she showed signs of persistent hypercalcemia. The patient resumed corticosteroids and pentoxifylline was increased (400 mg four times a day). Serum calcium level remained in the high normal range (Fig. 1) without improvement of renal function. Suboptimal response to medical therapy resulted in a decision for surgical intervention. She underwent sharp excisional debridement of the granulomatous tissue in her buttocks and 90% of the granulomatous tissue was successfully resected. Serum calcium, 1,25-dihydroxyvitamin D, intact PTH and renal function normalized (Table 1).

### 3. Case 2

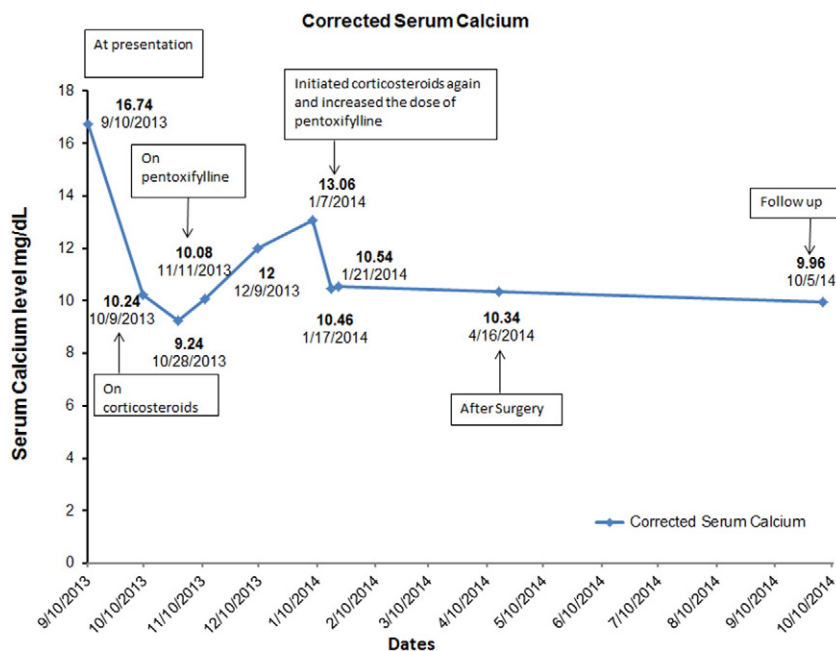
The mother received one 'silicone' injection in each gluteal region in 2007, from the same unlicensed individual. Co-morbidities included nephrolithiasis (2010), diabetes mellitus, Hashimoto's thyroiditis, and

GERD. In 2012, the patient presented with fatigue, abdominal bloating, diarrhea, urinary tract infections, cold intolerance, polydipsia, and polyuria. Serum calcium was 13 mg% (8.4–10.2 mg/dL). She received similar treatment with corticosteroids and was subsequently referred to MD Anderson Cancer Center for further management.

She appeared as a well-nourished Latina patient. Induration and hyperpigmentation were noted in the gluteal region with inguinal lymph node enlargement. Serum calcium was 9.74 mg/dL, ACE level of 60 U/L (8–53 U/L) and 1,25-dihydroxyvitamin D level was 106 pg/mL (18–78 pg/mL); intact parathyroid hormone was 23 pg/mL (9–80 pg/mL). Consider factors such as age and potential effect on renal function as well as comorbidity of diabetes mellitus, case 2 was not considered for aggressive medical management that was initially attempted for case 1. After her daughter's successful surgical resection of granulomatous material, the patient underwent sharp excisional debridement of the granulomatous tissue. Delayed healing of surgical incision was evident.

### 4. Discussion

We report that surgical excision of granulomatous tissue leads to resolution of silicone induced hypercalcemia. A large number of



**Fig. 1.** Serum calcium level and interventions at various time points for Case 1.

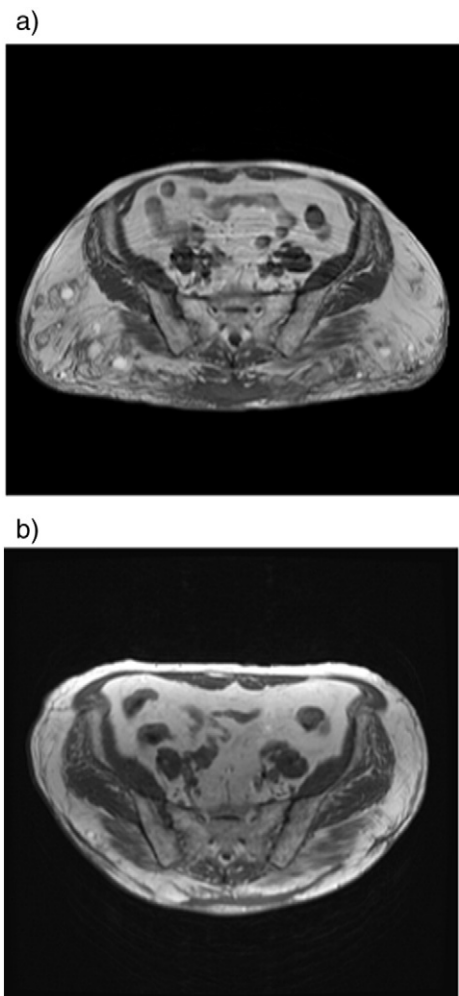
substances, such as paraffin, petrolatum, vegetable oils, liquid petrolatum, hydrous wool fat, sesame oil, and beeswax have been used for cosmetic purposes. However, when introduced into the body, these produce foreign-body granulomas (e.g., oleoma, paraffinoma, or lipogranuloma) (Winer et al., 1964). Injectable silicone has been used extensively over the last 40 years for soft tissue augmentation (Schwartzfarb et al., 2008). Silicones are long-chained polymers of dimethylsiloxane and may be liquid, resin, or solid depending on the length of their polymeric chain (Winer et al., 1964). The most common of these silicone polymers, medical fluid 360, is a clear, colorless fluid characterized by properties such as chemical inertness, high hydrophobicity, low volatility, resistance to decomposition by heat, and low surface tension (Braley, 1973). Although considered biologically inert, this material has been implicated in a variety of adverse reactions, including granulomas, disfiguring nodules, and lymphedema, with latent periods ranging from weeks to decades (Schwartzfarb et al., 2008; Bigata et al., 2001; Chasan, 2007; Rapaport et al., 1996). For these reasons, it is generally recommended that silicone injections be performed only by trained physicians using medical-grade silicone (Bigata et al., 2001).

There have been 6 reports of hypercalcemia secondary to silicone injections for cosmetic purposes (Agrawal et al., 2013; Kozeny et al., 1984; Loke and Leow, 2005; Schanz et al., 2012; Camuzard et al., 2013; Visnyei et al., 2014). Silicone spallation from the roller-pump insert in dialysis blood lines that led to accumulation of silicone and granuloma formation was seen in 2 dialysis patients (Altmann et al., 1987). Persistent hypercalcemia in these 2 cases eventually resolved after replacement with silicone-free blood lines (Altmann et al., 1987). Hypercalcemia with increased levels of plasma calcitriol (1-25-dihydroxyvitamin D3) is commonly seen in granulomatous diseases such as sarcoidosis, tuberculosis, leprosy, and fungal infections (Lafferty, 1991). The pathogenesis of granuloma formation in response to silicone particles is unclear. It is believed to occur under the regulatory influence of cytokines produced by local mononuclear phagocytes, T cells, dendritic cells, fibroblasts, and other local cells. The activation of these cells is triggered by adulterants added to silicone to enhance fibroplasia or denature host proteins adsorbed to the silicone. Fibrinogen that adsorbs to silicone surfaces undergoes a conformational change that causes it to display two previously hidden epitopes. These epitopes can induce an inflammatory response leading to the influx of neutrophils and macrophages (Desai et al., 2006).

The conversion of calcidiol to calcitriol occurs via a 1- $\alpha$  hydroxylase in the kidney proximal tubule and is stimulated by PTH. In granulomatous diseases, activated mononuclear cells (particularly macrophages) produce calcitriol from calcidiol independent of PTH signaling, stimulating increased gastrointestinal calcium absorption and hypercalcemia and hypercalciuria (Sharma, 2000). Parathyroid hormone is normally suppressed as seen in our two patients. Hypercalcemia in silicone granulomas has also been attributed to accelerated prostaglandin production. The macrophages in the granulomas are loaded with silicone particles, which stimulate arachidonic acid metabolism that results in prostaglandin synthesis (Bommer et al., 1984). Typical of 1,25 dihydroxyvitamin D<sub>3</sub>-mediated hypercalcemia, we noted the correction of hypercalcemia and normalization of serum calcitriol levels caused by short-term administration of glucocorticoids. We therefore concluded that the source of hypercalcemia and elevated calcitriol levels in our patient was extra-renal as none of the recognized stimulators of renal vitamin D<sub>3</sub> conversion (PTH, sex steroids, elevated calcidiol, or hypophosphatemia) (DeLuca, 1978) were present in this patient with renal insufficiency. Another interesting feature of these two cases is the apparent dose–response relationship between the number of injections the patients had and the severity of the hypercalcemia. It is unclear whether this is coincidental or has pathophysiologic significance. Untreated or chronic hypercalcemia can have a deleterious effect on renal function, lead to acute kidney injury, nephrolithiasis — as was seen in these cases (Auron et al., 2009; Schulze, 1982). Resolution of

hypercalcemia in case 1 resulted in recovery of renal function. Laboratory results have also shown the bone resorption marker serum CTX increase markedly in both cases following surgical resection. Bone resorption marker serum CTX is physiologically elevated during childhood, growth, and fracture and trauma healing. Many diseases, such as hyperparathyroidism, hypercalcemia of malignancy, and bone metastases, can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover is also found in age-related and postmenopausal osteopenia and osteoporosis (Christgau et al., 2000; Garnero et al., 2001). These could possibly explain the elevated bone resorption marker serum CTX in our cases.

A granulomatous reaction in case 1 was identified with a regional lymph node biopsy, which is similar to the findings of earlier case reports (Agrawal et al., 2013; Kozeny et al., 1984; Schanz et al., 2012; Camuzard et al., 2013; Desai et al., 2006). Most of these cases were treated with corticosteroids and etanercept, but in none of these cases is there long-term follow-up data. Etanercept reduces cytokine levels by selectively binding to TNF- $\alpha$  and preventing it from associating with its cell surface receptor. The dilemma we faced in these patients was profound hypercalcemia and significant side-effects of corticosteroids — a problematic combination. While there was concern about the potential for surgical complications from this procedure, it was the combination of the hypercalcemia and severe local soft tissue manifestations with no prospect for elimination of the silicone



**Fig. 2.** a: T1-weighted 1.5 Tesla MR Examination of the pelvis at time of diagnosis shows extensive deposition of silicone in gluteal subcutaneous tissue bilaterally. b: Similar MR examination of the pelvis about 6 months following resection of the infiltrated silicone shows minimal residual deposit.

material that led to a decision for surgical intervention. To the best of our knowledge, these cases describe the first examples of the use of this approach to treat a serious medical problem. MR examinations of the pelvis shows minimized residual deposit comparing 6 months following resection and at time of diagnosis (Fig. 2a and b). Both patients have been followed for more than one year and have not had recurrence of their hypercalcemia. We recognize, however, that the debridement was not complete and there is potential for recurrence, as the serum calcium values have declined to the upper normal limit.

## 5. Conclusion

Because of the increasing trend of body contour enhancements with injections, implants, and fillers using silicone, clinicians should be on high alert of the possibility of silicone-induced hypercalcemia as one of the differential diagnoses in a patient with history of silicone use. For persistent hypercalcemia and hypercalciuria, surgical resection of silicone material and granulomas is a successful approach to normalize the serum calcium level.

## Conflicts of interest

None.

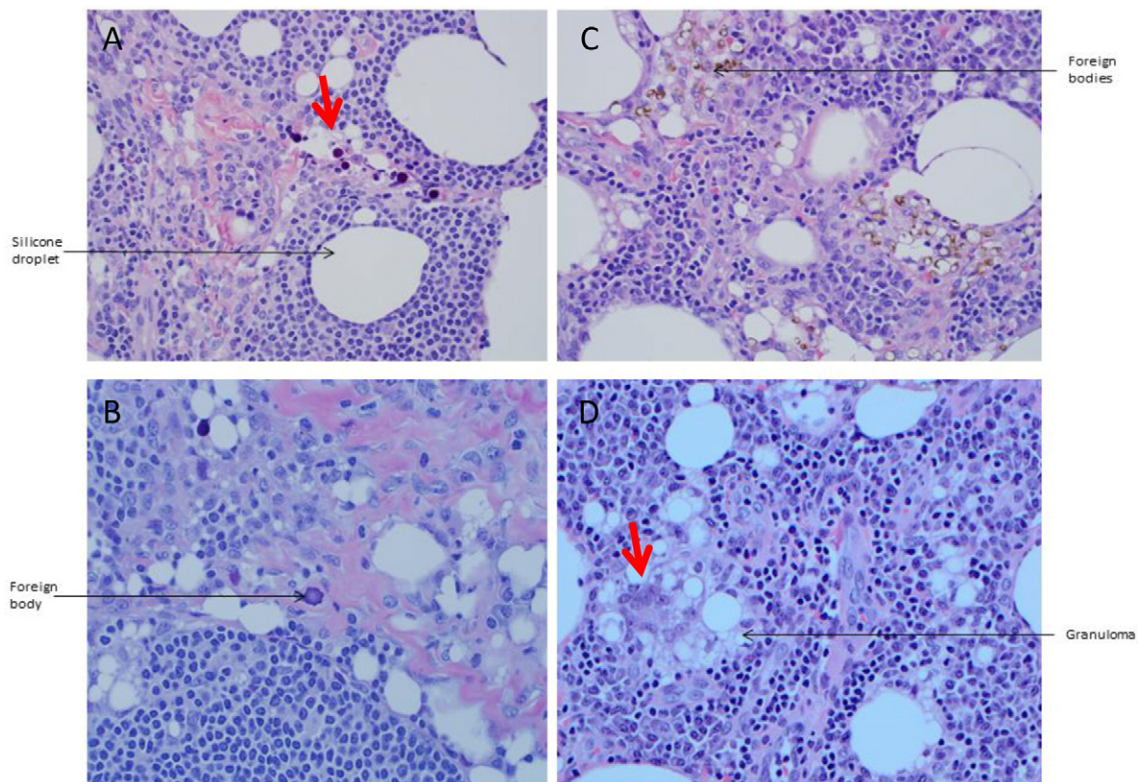
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## Appendix A

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**Fig. 1.** Granuloma formation. A: Numerous vacuoles in the lymph node, imparting a Swiss cheese appearance, along with several Psammoma bodies in the adjacent area (red arrow). B: Higher power view of the Psammoma bodies. C: Brown colored foreign bodies. D: Non-casating granuloma with a giant cell (red arrow) in the center, surrounded by numerous mature plasma cells and small lymphocytes. Hematoxylin and eosin stain, 200 $\times$  (A), 400 $\times$  B, C, D.

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