


# Case Series: Hypercalcemia From Granulomatous Silicosis Developing After COVID-19 Infection

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## Abstract

Hypercalcemia is one of the most commonly encountered laboratory abnormalities in clinical medicine. Various causes have been well established. However, it is likely that the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may be a newly found cause of this frequent finding, especially amongst those with a history of cosmetic surgery, specifically by means of silicone injection. In this case series, we describe 2 patients presenting with symptomatic hypercalcemia likely from their prior silicone injections. Interestingly, each patient only developed symptoms of hypercalcemia following infection with SARS-CoV-2.

## Keywords

endocrinology, radiology/imaging, other

## Introduction

Cosmetic surgery has become an ever more popular trend over the last few years. According to the American Society of Plastic Surgeons,<sup>1</sup> there were nearly a quarter million more cosmetic procedures performed in 2018 than in 2017. Although patients have various reasons for desiring such elective alterations in their appearance, these procedures are not without potential complications. Hypercalcemia linked to silicone injections has been well recognized in the literature; however, the percentage of those presenting with symptomatic hypercalcemia is extraordinarily low.<sup>2</sup>

## Case I

A 44-year-old transgender male-to-female patient from Central America with a past medical history of alcoholic cirrhosis, long-term pancreatitis, long-term gastritis, depression, and a history of COVID-19 complicated by a subacute pulmonary embolism approximately 3 months prior to presentation presented to the emergency department with 2 days of progressive abdominal pain rated 9/10 accompanied by 2 episodes of nonbloody nonbilious vomiting. The patient was in her usual state of health until the abdominal pain began. She denied any fevers, chills, chest pain, shortness of breath, headaches, dizziness, bright red blood per rectum, hematemesis, melena, or diarrhea. She reported a history of constipation for an indeterminate period of time. Her last alcoholic

drink was 1 week prior to admission. Physical exam was unremarkable aside from a long-term umbilical hernia and mild diffuse abdominal tenderness. The patient later endorsed a history of smoking, as well as a history of silicone injections in the breasts and gluteal regions when she was in her early 30s. Medications included apixaban, furosemide, spironolactone, lactulose, folic acid, famotidine, escitalopram, gabapentin, and pantoprazole.

In the emergency department, imaging showed a small amount of pericholecystic fluid with wall thickening in the area of the fundus of the gallbladder, suggestive of cholelithiasis. A computed tomography (CT) scan of the abdomen and pelvis revealed findings consistent with “long-term pancreatitis in the exacerbation phase.” She was hypercalcemic

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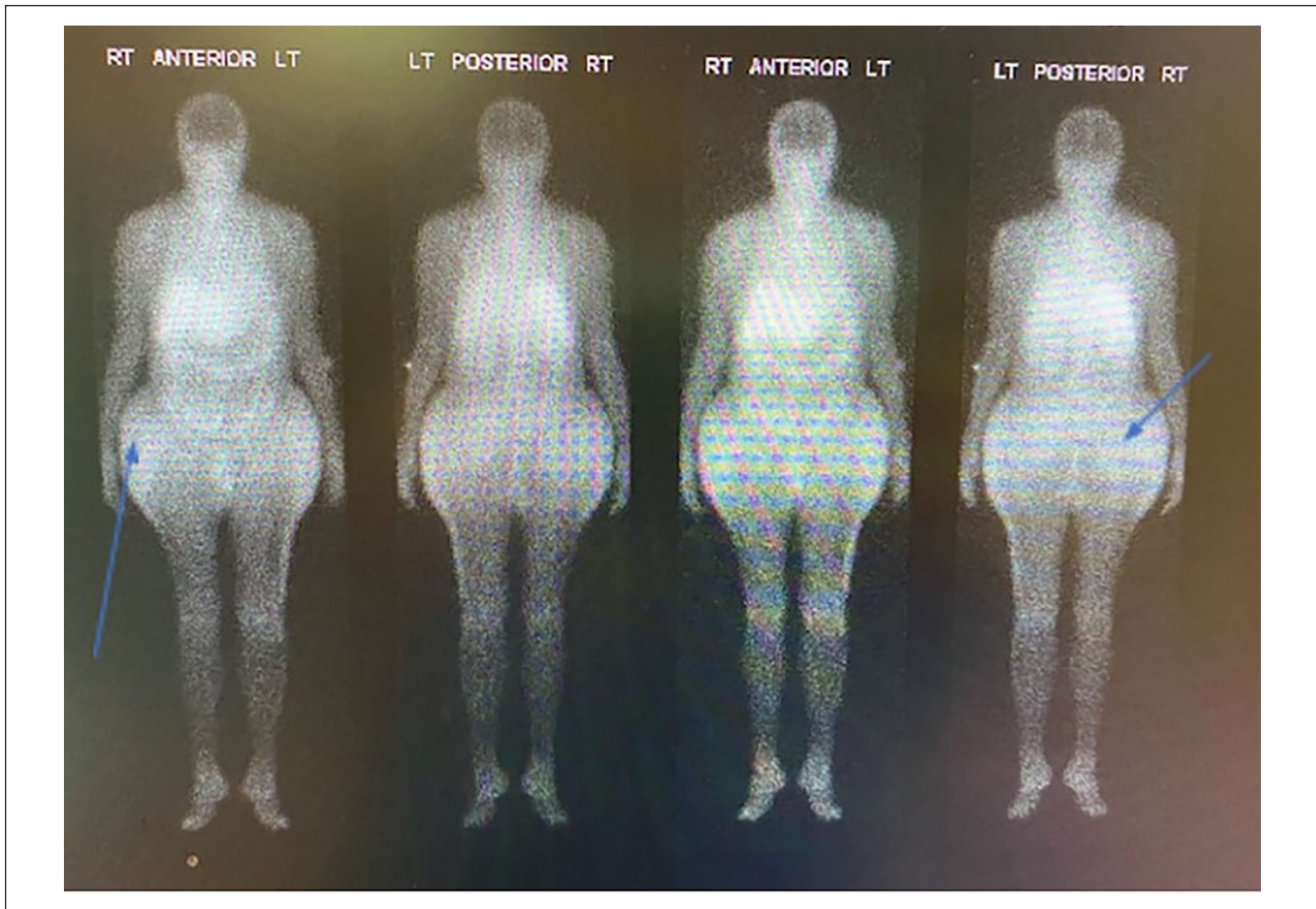
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**Figure 1.** Gallium scan revealing increased areas of uptake due to granulomatous disease. LT→Left, RT→Right.

to 13.5 mg/dL (reference range: 8.6-10.2 mg/dL), with an ionized calcium of 6.78 mg/dL (reference range: 4.5-4.9 mg/dL), creatinine 1.62 mg/dL (reference range: 0.7-1.30 mg/dL), and lipase 667 units/L (reference range: 10-140 units/L). Alcohol level was negative. The patient was admitted with a diagnosis of acute on long-term pancreatitis with pain exacerbated by cholelithiasis, and new-onset hypercalcemia.

The patient was hydrated with normal saline, and calcium decreased to 11.6 mg/dL. Magnesium was persistently low at 1.2 mEq/L (reference range: 1.6-2.6 mEq/L) and was aggressively repleted. HIV and human T-cell lymphotropic virus type (HTLV) were negative. The patient was treated with morphine for pain. While admitted, further workup of the hypercalcemia revealed a low 25-hydroxyvitamin D of 9.0 ng/mL (reference range: 32-100 ng/mL), normal 1-25 dihydroxyvitamin D of 35.7 pg/mL (reference range: 19.9-79.3), low parathyroid hormone (PTH) 3.8 pg/mL (reference range: 15-65 pg/mL), and parathyroid-related hormone (PTRH) <2.0 (normal). Angiotensin-converting enzyme (ACE) was elevated to 276 U/L (reference range: 12-82 U/L).

As the serum calcium remained elevated despite ongoing saline, the endocrinology consultant suggested the possibility

of silicone granulomatosis causing hypercalcemia after the patient revealed prior silicone injections for cosmetic reasons. The initial CT of the abdomen and pelvis was again reviewed; this time, marked infiltration and calcifications in the anterior chest wall, buttocks, and thighs were highlighted, prompting further investigation with a gallium study. A gallium scan demonstrated abnormally increased uptake within the bilateral hips, where the patient had known silicone injections (Figure 1). Once the patient's abdominal pain subsided, she was discharged with outpatient follow-up with a plan to monitor her calcium levels.

One week later, she was found to have calcium elevated to 13.9 mg/dL and started on prednisone 60 mg for 7 days, followed by prednisone 10 mg for 14 days. After the steroid taper, calcium was found to be 8.6 mg/dL. The patient was referred to plastic surgery for possible removal of the injected silicone material, as this could potentially provide absolute reversal of the patient's symptomatic hypercalcemia. However, surgery was of limited value due to the infiltrative nature of silicone. Ultimately, 3 to 5 months later, the calcium remained within normal range without further treatment.

**Table 1.** Laboratory Levels.

| Component                                   | Ref range and units   | Values (Case 1) | Values (Case 2)  |
|---|-----------------------|-----------------|------------------|
| Angiotensin I-converting enzyme             | 14-82 UL              | 276             | 139: 201         |
| Parathyroid hormone                         | 15-65 pg/mL           | 3.8, 6.2        | 14, 9            |
| 1-25 Dihydroxyvitamin D                     | 19.9-79.3 pg/mL       | 29.1, 357       | 116, 83          |
| History of COVID infection                  | No                    | Yes             | Yes              |
| Calcium 3-4 months prior to COVID infection | <b>8.6-10.2 mg/dL</b> | <b>8.4, 8.5</b> | <b>9.2, 10.3</b> |
| Calcium prior to steroids                   | 8.6-10.2 mg/dL        | 13.9, 13.8      | 15.7, 15.9       |
| Calcium after ending steroids               | 8.6-10.2 mg/dL        | 8.6             | 10.9             |
| Calcium weeks later                         | 8.6-10.2 mg/dL        | 9.4             | 106              |

Bold Indicates to covid infection.

## Case 2

A 51-year-old woman from South America with a past medical history of anemia, hypertension, kidney stones, and COVID-19, 4 months prior (a positive antigen test without symptoms) was evaluated in the emergency department after being found to have calcium of 15.7 mg/dL in clinic. The patient endorsed fatigue, night sweats, lightheadedness, nausea, right flank pain with radiation to the right lower quadrant, urinary frequency, diffuse bone pain, constipation for the past 1 month, and weight loss of about 15 lb over the past 6 months. The patient denied any chest pain, shortness of breath, abdominal pain, or dysuria. Physical exam was benign except for severe tenderness to palpation over the buttocks and hips.

Laboratories on admission were significant for calcium 15.9 mg/dL (reference range: 8.6-10.2 mg/dL), creatinine 1.33 mg/dL (reference range: 0.5-1.20 mg/dL), 1-25 dihydroxyvitamin D 116.0 pg/mL (reference range: 19.9-79.3), and 25 hydroxyvitamin D 21.0 ng/mL (reference range: >30 ng/mL). Parathyroid hormone was low (15.3 pg/mL, reference range: 15.0-65.0), and alkaline phosphatase was within normal limits. Of note, ACE was found to be elevated to 139 U/L (reference range: 14-82 U/L).

The patient was hydrated and treated with calcitonin, decreasing her calcium to 11.3 mg/dL and her creatinine to 0.98 mg/dL. On further interviewing of this patient (admission Day 4), it was discovered that she had silicone injections in her buttocks approximately 23 years ago by a local doctor. Her calcium continued to be >11 mg/dL despite in vitro fertilization (IVF) and calcitonin. Computed tomography scan of the abdomen and pelvis showed no evidence of malignancy; however, it was significant for extensive bilateral granulomatous calcifications of the patient's buttocks. The patient was started on steroid treatment with prednisone 60 mg daily. Ultimately, she was discharged after 5 days (once her calcium decreased to 10.6 mg/dL) and was given a 2-week course of prednisone; on return to clinic 3 weeks later (1 week after completion of her steroid taper), her calcium remained at 10.9 mg/dL. Four months later, this patient's calcium was found to be only mildly elevated to 10.6 mg/dL (Table 1).

## Discussion

Although silicone-induced hypercalcemia has been described in the literature, it is often not immediately considered as a cause.<sup>3</sup> In the cases above, silicone administration was not reported by either patient during their initial encounters. Intriguingly, their symptomatic hypercalcemia occurred shortly after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These cases are the first described possible link between SARS-CoV-2 infection and symptomatic hypercalcemia years after administration of silicone for cosmesis. In Case 1, the patient's chief complaint of abdominal pain was treated as acute on long-term pancreatitis given her prior history. Only upon further interviewing, the patient was focus placed on silicone as a cause. Ultimately, the workup of her hypercalcemia revealed a possible link between viral infection and prior silicone injection.

In Case 2, initial differential diagnoses for hypercalcemia included hyperparathyroidism, malignancy, vitamin D intoxication, milk-alkali syndrome, granulomatous disease, and hyperthyroidism.<sup>4</sup> Of note, the patient had not been taking any medications such as lithium or hydrochlorothiazide, which would affect calcium levels. Her low PTH excluded hyperparathyroidism, and low PTHrH made malignancies, such as squamous cell carcinoma, gastric cancer, multiple myeloma, and urothelial cancer less likely.<sup>4,5</sup> There was no evidence for vitamin D intoxication or milk-alkali syndrome.<sup>5,6</sup> The normal 1-25 dihydroxyvitamin D in the setting of low PTH and PTHrH suggested autonomous production of activated vitamin D.

Primary hyperparathyroidism and malignancy account for >90% of cases of hypercalcemia.<sup>6</sup> Other causes include lung disease (sarcoidosis and tuberculosis), hypervitaminosis A, immobilization, and Paget's disease; hypercalcemia secondary to granulomatous disease specifically due to silicone is extraordinarily low on that list.<sup>3</sup> Most commonly, hypercalcemia occurs when a hormone such as PTH or PTHrP (malignancy) activates cells that resorb bone and increase the amount of calcium reabsorbed in the kidney and stimulate production of 1-25 dihydroxyvitamin D, which then stimulates absorption of calcium in the intestine.<sup>7</sup> In

granulomatous disease, activated mononuclear cells, particularly macrophages, in the lungs and lymph nodes produce 1-25 dihydroxyvitamin D (activated vitamin D), which prompts calcium absorption in the gut, independent of PTH.<sup>8</sup> It is also not uncommon to find PTHrP in biopsies of granulomatous tissue, thus worsening the already elevated blood calcium levels.<sup>8</sup> ACE is commonly found to be elevated in granulomatous diseases, providing a more direct path to diagnosis in these cases.<sup>9</sup>

While signs and symptoms of hypercalcemia tend to be relatively nonspecific, they may include psychiatric and cognitive dysfunction, fatigue, polyuria, polydipsia, constipation, abdominal pain, anorexia, and muscle weakness.<sup>7</sup> Treatment of hypercalcemia, regardless of the cause, includes hydration and addressing the underlying pathology. Depending on the elevation of the calcium and the associated symptoms, calcitonin, bisphosphonates, or denosumab may be used to lower the calcium.<sup>10,11</sup> The current mainstay treatment for granulomatous cause of hypercalcemia (along with diagnoses causing excess vitamin D production) consists of a 1 to 2-week prednisone taper; diminishing calcium intake to 400 mg/day or less may also be beneficial.<sup>5</sup> Previously, 5-fluorouracil, isotretinoin, tacrolimus, and etanercept were commonly used; however, steroids have been found to be more effective.<sup>12</sup> Reports have described silicone granulomas responding well to minocycline and doxycycline due to their immunomodulatory properties.<sup>13</sup> Methotrexate may also be used to treat inflammation caused by silicosis via increased release of adenosine and immunosuppression through apoptosis and clonal deletion of T-cells.<sup>13</sup> Long-term outcomes documented in these patients range from complete remission with steroids, to overt renal failure due to long-term elevated calcium levels.<sup>13</sup>

Although much is to be learned about COVID-19, it is understood that granulomatous tissue is filled with macrophages, and COVID-19 causes a substantial increase in the number of activated macrophages in the body.<sup>14</sup> This may be why both patients presented with an exacerbation of hypercalcemia a few months after COVID-19 infection, and levels remained low weeks after the completion of the steroid treatment. Notably, there are now case reports documenting lymph node biopsies of those recently diagnosed with COVID-19 pneumonia demonstrating noncaseating granulomas; the occurrence of granulomatous disease after SARS-CoV-2 infection reveals many links in the pathogenesis of sarcoidosis and COVID-19.<sup>15</sup> Therefore, it may be beneficial to further investigate the link between the novel virus and subsequent newly discovered or worsening granulomatous disease, presenting as symptomatic hypercalcemia.

## Conclusion

Hypercalcemia is frequently encountered in clinical medicine. Although hyperparathyroidism and malignancy account

for most of cases of hypercalcemia, it is important to consider alternative causes based on various clinical scenarios, such as a history of cosmetic surgery, specifically concerning silicone.<sup>1</sup> We now recognize that it is also important to ask about a history of SARS-CoV-2 infection, as millions of people have been infected worldwide. We are just beginning to understand the protean manifestations of this virus. If SARS-CoV-2 does increase activated macrophages in granulomatous tissue, in the future, we may see more episodes of acute hypercalcemia in patients infected by the virus who also have a large burden of silicone-induced tissue granulomas.

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## Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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## References

1. American Society of Plastic Surgeons. New plastic surgery statistics reveal trends toward body enhancement. <https://www.plasticsurgery.org/news/press-releases/new-plastic-surgery-statistics-reveal-trends-toward-body-enhancement>. Published March 11, 2019. Accessed September 27, 2021.
2. Kozeny GA, Barbato AL, Bansal VK, Vertuno LL, Hano JE. Hypercalcemia associated with silicone-induced granulomas. *N Engl J Med*. 1984;311:1103-1105. <https://pubmed.ncbi.nlm.nih.gov/6548295/>. Accessed September 27, 2021.
3. Jacobs TP, Bilezikian JP. Clinical review: rare causes of hypercalcemia. *J Clin Endocrinol Metab*. 2005;90:6316-6322. <https://pubmed.ncbi.nlm.nih.gov/16131579/>. Accessed September 27, 2021.
4. Lafferty FW. Differential diagnosis of hypercalcemia. *J Bone Miner Res*. 1991;6:S51-S59. <https://pubmed.ncbi.nlm.nih.gov/1763670/>. Accessed September 27, 2021.
5. Tebben R, Singh PJ, Kumar RJ. Vitamin D-mediated hypercalcemia: mechanisms, diagnosis, and treatment. *Endocr Rev*. 2016;37:521-547. <https://pubmed.ncbi.nlm.nih.gov/27588937/>. Accessed September 27, 2021.

6. Skugor M. Disease management: hypercalcemia. [www.clevelandclinimed.com/medicalpubs/diseasemanagement/endocrinology/hypercalcemia/default.htm](http://www.clevelandclinimed.com/medicalpubs/diseasemanagement/endocrinology/hypercalcemia/default.htm). Published June 5, 2019. Accessed September 27, 2021.
7. Mayo Clinic. Hypercalcemia: symptoms and causes. <https://www.mayoclinic.org/diseases-conditions/hypercalcemia/symptoms-causes/syc-20355523>. Published 2018. Accessed September 27, 2021.
8. Tachamo N, Donato A, Timilsina B, et al. Hypercalcemia associated with cosmetic injections: a systematic review. *Eur J Endocrinol*. 2018;178:425-430. <https://pubmed.ncbi.nlm.nih.gov/29453201/>. Accessed September 27, 2021.
9. Studdy PR, Lapworth R, Bird R. Angiotensin-converting enzyme and its clinical significance: a review. *J Clin Pathol*. 1983;36:938-947. [www.ncbi.nlm.nih.gov/pmc/articles/PMC498427/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC498427/). Accessed September 27, 2021.
10. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;19:558-567. <https://pubmed.ncbi.nlm.nih.gov/11208851/>. Accessed September 27, 2021.
11. Pimentel L, Barnadas M, Vidal D, Sancho F, Fontarnau R, Alomar A. Simultaneous presentation of silicone and silica granuloma: a case report. *Dermatology (Basel, Switzerland)*. 2002;205:162-165. <https://pubmed.ncbi.nlm.nih.gov/12218233/>. Accessed September 27, 2021.
12. Chen TA, Mercado CL, Topping KL, Erickson BP, Cockerham KP, Kossler AL. Disseminated silicone granulomatosis in the face and orbit. *Am J Ophthalmol Case Rep*. 2018;10:32-34. <https://www.sciencedirect.com/science/article/pii/S2451993617302074>. Accessed September 27, 2021.
13. Yedla AN, Perez E, Lagari V, Ayala A. Silicone granulomatous inflammation resulting in hypercalcemia: a review of the literature. *AACE Clinical Case Reports*. 2018;5:e119-e123. <https://pubmed.ncbi.nlm.nih.gov/31967015/>. Accessed September 27, 2021.
14. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol*. 2020;20:355-362.
15. Mertz P, Jeannel J, Guffroy A, et al. Granulomatous manifestations associated with COVID19 infection: is there a link between these two diseases? *Autoimmun Rev*. 2021;20:102824. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8056977/>. Accessed September 27, 2021.