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Article type: Clinical image

Received: April 16, 2019.

Accepted: May 15, 2019.

Published online: May 21, 2019.

ISSN: 1897-9483
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Short title: Hypercalcemia associated with sodium thiosulfate

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Conflict of interest: none declared.
An 18-year-old female was admitted to our hospital complaining of hardening in her breasts over the previous two weeks and dyspnea for one week. Chest computed tomography (CT) and mammography revealed diffuse calcification patches bilaterally in lungs and breasts (Fig.1A-B). Her medical history was remarkable for severe pneumonia seven months prior and the patient had lost 12.5kg during that month of illness with a body mass index (BMI) of 13.2 kg/m$^2$. In addition, the patient experienced painful dermal ulcers four months prior for unknown reasons (Fig.1C).

Serum calcium, phosphorus, parathyroid hormone, creatinine, 25-hydroxy vitamin D, tumor markers, immunoglobulins, type I collagen C-terminal telopeptide (CTX) and bone alkaline phosphatase (BALP) tests were within normal ranges on admission. In order to identify the cause of calcifications, a lung biopsy was performed which revealed diffuse calcifications in the alveolar septa and arteriolar walls when stained with hematoxylin (Fig.1D). The patient was subsequently diagnosed with calciphylaxis of non-uremic origin and received intravenous sodium thiosulfate (STS) therapy at a dose of six grams per day. There were no side effects observed. After two months of STS treatment, the lung and breast calcifications were improved (Fig.1E-F). However, serum calcium levels increased dramatically to 4.09 mmol/l (reference range 2.10-2.70 mmol/l), and parathyroid hormone was suppressed to 0.90 pmol/l (reference range 1.60-6.90 pmol/l). STS was then discontinued immediately. CTX levels increased to 9.28 ng/ml (reference range 0.29-0.57 ng/ml) and BALP increased to 57.2 ug/l (reference range 11.4-24.6 ug/l). Therefore, the patient was given one dose of 4 mg intravenous zoledronate. Serum calcium and CTX concentrations decreased
to normal range on the following day. No recurrence has been observed over two years of follow up.

Calciphylaxis is a rare and life-threatening syndrome. It is characterized by small vascular calcifications which cause painful ischemic dermal ulcers or visceral calcifications [1]. In the present case, a history of pneumonia and rapid weight loss might have contributed to calciphylaxis [1-2]. The effects of STS in the treatment of calciphylaxis are mediated by forming highly soluble calcium thiosulfate, as well as vasodilatory and antioxidant properties [3]. To the best of our knowledge, hypercalcemia has never been described in STS treatment. Remarkably, a previous animal study demonstrated that STS could potentially jeopardize bone integrity [4]. Therefore, we hypothesized that bone damage resulted in hyperactivity of osteoblasts and osteoclasts in this case, which induced hypercalcemia. The elevation of CTX and BALP after STS therapy confirmed this speculation.

In addition, it should be mentioned that most calciphylaxis causes only vascular calcifications. Severe diffuse calcifications involving multiple organs, like in this patient, are quite rare. Thus, we speculated that large amounts of soluble calcium thiosulfate, which had a much higher production than could be excreted by kidneys, might also be an initiator of hypercalcemia. Therefore, a lower dosage of STS should be recommended for non-dialysis calciphylaxis patients with large-area calcifications, or dialysis should be administered intermittently during STS treatment. Finally, this case study underscores the importance of monitoring serum calcium levels during STS treatment while more evidence on the optimal STS dosage for calciphylaxis patients is still needed.
Acknowledgements: This work was funded by Key Projects of Sichuan Province (grant number: 2017FZ0077, recipient: L.R). We would like to thank Juan Huang (J.H), MD from the Department of Endocrinology and Metabolism, Sichuan University West China Hospital for her kind help on the diagnosis and differential diagnosis of the present patient.

References


A. Chest computed tomography shows diffuse calcification patches in bilateral lungs.
B. Mammography reveals diffuse calcifications in bilateral breasts. Calcified vessels are noted with white arrow.
C. A large and deep dermal ulcer with the size about 4×4 cm is present on the left thigh of the patient (picture was taken by the patient herself after the ulcer was treated with gentian violet).
D. Histologic examination of lung tissues (hematoxylin/eosin stain, original magnification $\times 100$) revealed diffuse calcifications of the vascular walls and alveolar septa (black arrows).
E & F. Calcifications of the lungs (E) and breasts (F) improved after sodium thiosulfate treatment.