



Research Letter

Calcifications due to estrogen injections



Dear Editors:

Estrogen is a well-known therapy used for the prevention and treatment of menopause and osteoporosis. Estrogen is available as an injection, oral pill, and in topical forms, which are absorbed through the skin and can have systemic effects. The side effects of estrogen are widespread, including breast pain, abdominal pain, vomiting, hypertension, myocardial infarction, stroke, and endometrial cancer. Calcification specifically due to estrogen injections has not been reported. However, calcification in soft tissues has been reported after corticosteroid injections. The accumulation of insoluble steroid acts as a foreign body and induces a chronic granulomatous inflammatory process, with subsequent dystrophic calcification (Conti and Shinder, 1991). Intravenous infusions of sodium thiosulfate (STS) have shown efficacy in the treatment of calcification (Kroshinsky and Fairley, 2018).

An 84-year-old female patient presented to the dermatology clinic with masses on the buttocks. The lesions were not painful when sitting but caused difficulty walking. She had a history of gluteal intramuscular estrogen injections but no history of other medications with a risk of calcification or granuloma formation. The physical examination revealed irregular hard subcutaneous nodules on the bilateral upper buttocks.

Imaging of the pelvis was obtained by computed tomography (CT) without intravenous contrast to determine the extent of depth/muscular involvement (Fig. 1). The CT scan revealed benign bilateral flank/gluteal calcified granulomas, likely secondary to injections. The differential based on the presentation and CT imaging included dystrophic and metastatic calcification. Results of metastatic calcium workup, which included a complete metabolic panel, serum vitamin D, serum phosphorous, urinary calcium, and parathyroid hormone level, were negative.

The patient denied further evaluation for autoimmune disease and inflammatory causes of granulomatous disease. Excision by general surgery was recommended for treatment due to the extent of the calcifications. Intralesional STS was considered but deferred because of the large amount and frequency necessary for resolution of the patient's calcifications. The patient deferred further treatment.

Estrogen injections may cause subcutaneous nodular granulomas in soft tissue but, to our knowledge, have not yet been reported to cause calcifications. The clinical and physical presentation of the patient, along with the imaging, support granuloma formation with subsequent dystrophic calcification as an adverse effect of estrogen injections. Dystrophic calcifications have been reported from local corticosteroid injections, including dexamethasone and triamcinolone hexacetonide (Conti and Shinder, 1991; Friemann et al., 1997; Raghavendran et al., 2008). A patient with epicondylitis humeri radialis was treated with two injections of dexamethasone and then formed calcifying granulomatous peritendinitis. However, this calcification may have been a result of the soja bean oil used as a carrier for dexamethasone in the patient (Friemann et al., 1997). Triamcinolone hexacetonide has a solubility in water of 0.0004% w/v at 25°C, which causes subcutaneous calcifications more likely to form after injections (Raghavendran et al., 2008). Cosmetic dermal silicone injections also may cause the formation of granulomas (Bigatà et al., 2001). The purity of the silicone used was unknown, and the pathogenesis for this adverse effect is also unknown (Bigatà et al., 2001).

Calcium deposition can occur from dystrophic or metastatic calcification and can be determined by further work up and evaluation after a history and physical examination have been performed. Serum calcium, phosphate, parathyroid hormone, and vitamin D₃ levels should be ordered to evaluate for abnormalities and a possible metastatic cause (Kroshinsky and Fairley, 2018). If abnormalities are present, correction is necessary to decrease the likelihood of future calcification. Dystrophic calcification has occurred in autoimmune connective tissue diseases, and further evaluation for etiologies (e.g., dermatomyositis or systemic sclerosis) can be performed if suspected based on the clinical presentation (Kroshinsky and Fairley, 2018).

A genetic analysis for a hereditary disorder may also be considered if suspected (Kroshinsky and Fairley, 2018). Depending on the extent of the calcifications and the interference with function for dystrophic calcium deposition, treatment with surgical excision or intralesional STS can be considered. This case demonstrates that dystrophic calcification should be considered as a cause of subcutaneous nodules localized to areas of prior estrogen injections.



Fig. 1. Peripherally calcified structures in the left gluteal/flank subcutaneous tissues consistent with granulomas or heterotopic ossification. The structure on the left measures a maximum of $5.2 \times 7.8 \times 7.7$ cm, and the largest structure on the right measures $6.7 \times 4.0 \times 4.1$ cm. Scattered smaller ring calcifications in the gluteal/flank subcutaneous fat are consistent with granulomas likely secondary to injections.

Declaration of Competing Interest

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Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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