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Case report

CLINICAL IMPROVEMENT AFTER REMOVAL OF HYPERCALCEMIA-CAUSING GRANULOMAS

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Abstract

In this report, we present the case of a woman with clinical characteristics of hypercalcemia due to ectopic production of 1,25(OH)2D. She reported a history of aesthetic surgery with gluteal fillers. The formation of granulomas after these interventions were previously described. In this case, surgical removal of the foreign formations was attempted with clinical stability during 3 years.

Key word: hypercalcemia, vitamin D, granulomas

Resumen

Mejoría clínica posterior a la eliminación de granulomas causantes de hipercalcemia

Presentamos el caso de una mujer con características clínicas de hipercalcemia secundaria a la producción ectópica de 1,25(OH)2D. La paciente informó una historia de rellenos glúteos con fines estéticos. La formación de granulomas posterior a este tipo de intervenciones fue previamente descrita por otros autores. En este caso se intentó la extirpación quirúrgica de las formaciones extrañas con estabilidad clínica durante 3 años.

Palabras clave: hipercalcemia, vitamina D, granulomas

Prevalence of hypercalcemia varies depending on the clinical setting in which it is diagnosed, and more than 90% of the cases arise as a consequence of malignancy or hyperparathyroidism[1,2]. It can be classified into PTH-mediated or PTH-independen , depending the mechanism of its production[3-5]. An infrequent cause of hypercalcemia is extra renal production of active vitamin D or 1,25(OH)2D (calcitriol)[3,6]. Regulating enzyme in the vitamin D activation is 1α-hydroxylase (CYP27B1) and is located at several body tissues[7]. Granulomatous diseases such as sarcoidosis, tuberculosis, leprosy and aesthetic injections with silicone or polymethylmethacrylate can generate hypercalcemia mediated by the production of 1,25(OH)2D[3,8]. Inflammatory cells that make up the granuloma, such as macrophages, are capable of expressing 1α-hydroxylase and cause a characteristic clinical picture of overproduction of vitamin D, determined mainly by increased intestinal absorption of calcium (Ca^{++})[8,9]. Laboratory tests of these individuals affected by granulomatous diseases may show hypercalcemia, inhibited or decreased PTH, hyperphosphatemia, hypercalciuria. Increased or inadequately normal 1,25(OH)2D levels, and elevated angiotensin-converting enzyme activity are usually observed[3,10]. Negri et al described a series of cases in women who presented clinical manifestations of 1,25(OH)2D-mediated hypercalcemia

secondary to the formation of granulomas due to injection of polymethylmethacrilate for aesthetic purposes[11]. A complication in this series of cases was impaired renal function[11]. Glucocorticoids and ketoconazole constitute treatment options, inhibiting the 1α-hydroxylase activity[11,14]. However, prolonged use could cause unwanted events and side effects. Surgery to remove filling material is a topic of debate. For this reason, we present the case of a woman with multiple clinical manifestations of hypercalcemia mediated by 1,25(OH)2D who underwent surgery.

Case report

A 48-year-old woman was admitted to our institution in October 2017 for metabolic evaluation. During the previous year she had 6 episodes of acute renal pain, for which she was admitted to the emergency room repeatedly. An initial laboratory obtained at another institution showed calcium (10.3 mg/dL) levels slightly above the range (range 8.5-10 mg/dL) and inhibited PTH (13pg/mL) levels (range 15-65 pg/mL). Additionally, during that year, endoscopic interventions were performed for treatment of kidney stones. She reported a history of buttock aesthetic surgery in 2011. Shortly after surgery she began with gradual swelling and hardening of the buttock region. In 2015, lipoaspiration of the material and a biopsy were performed. Histological findings included fibroadipose tissue and striated muscle with the presence of histiocytes and isolated multinucleated giant cells of the foreign body type that encompass numerous vacuoles with translucent material. Foreign body-type gigantocellular granuloma was found.

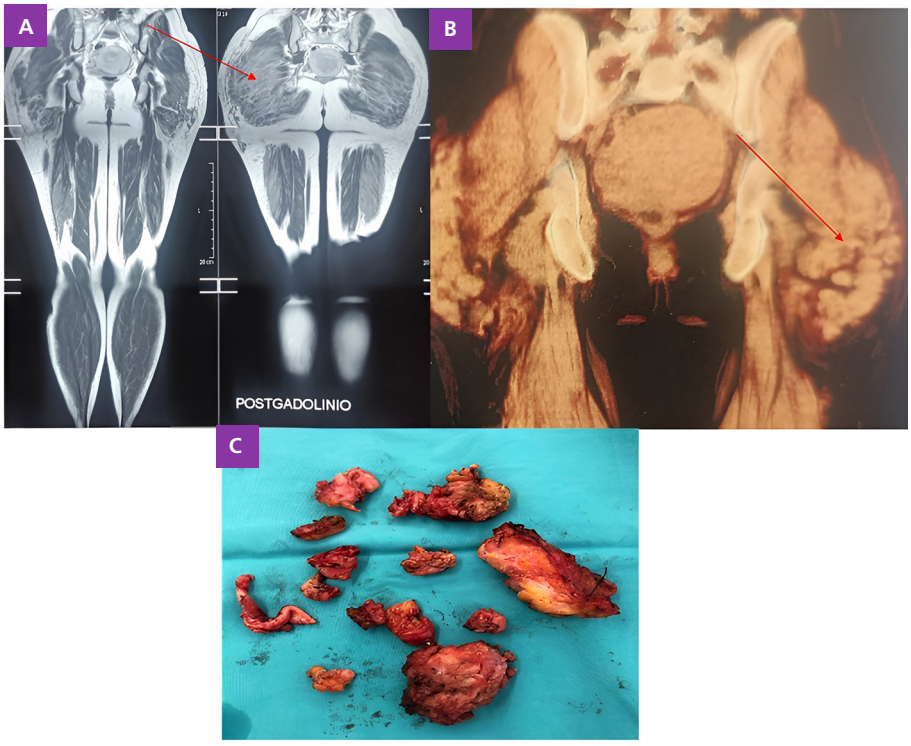
Table 1 shows the initial laboratory and its evaluation throughout this time. Work up included magnetic resonance imaging of the hip and lower limbs and computerized tomography (Fig. 1A). Due to suspicion of ectopic production of 1,25(OH)2D, a single dose of denosumab was indicated in December 2017. Patient suffered a wrist fracture in January 2018, for which she had to undergo surgery, in addition to multiple other surgeries for relapsing kidney stones in the same year. She received 8 injections of triamcinolone 30 mg in the gluteal region during 2018 and 2019. At that time, improvements were observed in the levels of calcium, B-Cross Laps,1.25(OH)2D and 24-h urinary calcium (Table 1), but she had 5 episodes of renal pain again with new surgical interventions. For this reason, a foreign body resection surgery was performed in 2020 (Fig. 1 C).

Incision was performed in the gluteal fold with scalpel (23 blade). Pathological tissue had irregular shape and very embedded to the surrounding tissue. Consequently, each mass was dissected and the big pieces were removed in small fractions with electro scalpel. The patient

Tabla 1 | Laboratory on admission and changes during follow-up

Laboratory and reference range	2017	2018 (December)	2020 (post-cx)	2022	2023
Serum calcium (8.8-10.5 mg/dL)	10.2	9.2	9.4	9.9	9.6
Ionic calcium (4.5-5.20 mg/dL)	4.76	4.8	4.6	4.9	4.6
Serum phosphate (2.5-4.5 mg/dL)	4.0	3.3	3.5	3.5	3.4
Parathyroid hormone (10-65 pg/mL)	11.1	19.9	20.6	15.9	16.2
B-CrossLaps (74-550 pg/mL)	605	341	333	417	592
Osteocalcin (11-43 ng/mL)	20.1	12.2	11.8	13.2	13.6
Bone alkaline phosphatase (<21 ug/L)	4.2	3.6	4.2	6.3	6
Vitamin D (20-30 ng/mL)	47.3	34.4	47.9	59	54.6
1,25 dihydroxyvitamin D3 (18-60 pg/mL)	30	19	-	-	54.8
Angiotensin converting enzyme (<52 U/L)	109	-	-	-	-
Creatinine (0.6-1.10 mg/dL)	0.69	0.68	0.71	0.68	0.51
24-h urinary calcium (≤ 220 mg/24 h)	902	400	274	218	270
24-h urinary creatinine (740-1570 mg/24 h)	1356	1365	1187.8	1032	1109.1
Creatinine clearance (ml/min)	127	133.4	116.2	105.5	109.1
24-h urinary sodium (40-150 mEq/L)	146	148	118.8	90.4	85
24-h urinary oxalato (0-45 mg/24 h)	54	65	52	60.3	44.1
24-h urinary citrate (>350 mg/24 h)	1273	1679	1076	942	809.2
24-h urinary magnesium (60-150 mg/24 h)	138	115	133.6	94.2	132.4

Figura 1 | A: Magnetic resonance imaging. Hyperintense signal on T2 sequence in both buttocks involving the middle and lower gluteal muscles associated with inflammatory processes B: Computerized tomographic of buttocks and thighs. Alterations in muscular planes with pseudonodular pattern. C: Resection of pathological tissue. Granulomas are shown after surgery



was followed during three years showing clinical and biochemical stability.

Informed consent was requested and given by the patient for this presentation.

Discussion

The case of a woman diagnosed with symptomatic hypercalcemia secondary to extra renal production of 1,25(OH)2D is presented. In granulomatous diseases, inflammatory mediators such as interferon are capable of stimulating the production of the enzyme 1 alpha hydroxylase. 1α-hydroxylase enzyme is responsible for activating vitamin D. In recent years, and with the increase number of procedures of filling the buttocks or other parts of the body, numerous cases of vitamin D-producing granulomas have been described[11]. Negri et al presented a case series of 4 women with polymethylmethacrylate injections, who after 6 months developed hypercalcemia. The clinical manifestations in those women were variable. All patients in this series presented deterioration of renal function [11]. Among the factors involved in the physiopathogenesis of hypercalcemia, intestinal calcium absorption and increased bone resorption are mainly described[3,4]. For this reason, oral glucocorticoids or glucocorticoids injected into granuloma sites and bisphosphonates could be used for their treatment[12,13]. Additionally, ketoconazole could be used in this situation, by inhibiting alpha 1 hydroxylase in individuals with sarcoidosis[14]. In our patient, clinical manifestations such as kidney stones and wrist fracture were observed. For this reason, treatment with denosumab and triamcinolone was prescribed. The patient continued to be symptomatic, so it was decided removing surgically the foreign material. This same intervention was previously performed in patients with granulomas secondary to silicone implant for aesthetic purposes[15]. As reported by Edwards et al, we observed stability in serum and urinary calcium over time and continue with periodic observations. With this case we open the debate on surgery as an additional therapeutic method in these cases.

Conflict of interest: None to declare

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