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CASE REPORT

Acute kidney injury and hypercalcemia associated with veterinary supplements applications in adult man

Injúria renal aguda e hipercalcemia associadas a aplicações de suplementos veterinários em homem adulto

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Abstract

The compound "ADE" is an injectable oil for veterinary use which contains large amounts of vitamins A, D and E. The parenteral application in humans leads to a granuloma reaction which triggers hypercalcemia. A 42-year-old man was admitted with lower limb pain, nephrolithiasis and nephrocalcinosis. Laboratory tests revealed creatinine 4.59 mg/dl, calcium 13.3 mg/dl and parathormone 13.8 pg/ml. He underwent an ureterolithotripsy, stent placement, intravenous crystalloid fluids, and corticosteroid. He improved symptoms, kidney function and normalized serum calcium. The "ADE"-induced hypercalcemia diagnosis can be challenging. The early diagnosis may avoid negative outcomes.

Keywords: acute kidney injury; chronic kidney disease; hypercalcemia; nephrolithiasis; veterinary drugs.

Resumo

O composto "ADE'' é um óleo veterinário injetável que contém grandes quantidades de vitaminas A, D e E. A aplicação parenteral causa reação granulomatosa e hipercalcemia. Um homem de 42 anos foi admitido com dor no membro inferior, nódulos musculares endurecidos, nefrolitíase e nefrocalcinose. O laboratório revelou creatinina 4,59 mg/dl, cálcio 13,3 mg/dl e paratormônio 13,8 pg/ml. Foi tratado com ureterolitotripsia, cateter duplo-J, cristaloide intravenoso e corticoterapia. Ele apresentou melhora dos sintomas, função renal e normalizou cálcio. O diagnóstico da hipercalcemia pelo "ADE'' pode ser desafiador. O diagnóstico precoce pode evitar desfechos negativos.

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Palavras-Chave: injúria renal aguda; doença renal crônica; hipercalcemia, nefrolitíase; medicações veterinárias.

INTRODUCTION

Hypercalcemia is mainly caused by primary hyperparathyroidism and malignancy. However, exogenous causes should be remembered as important etiology of hypercalcemia[1]. Vitamin D intoxication figures out as one of the main issues, given the easy availability and widespread use of this supplementation, frequently without medical evaluation[2]. Moreover, a particular and unusual form of vitamin D intoxication may be the human use of parenteral veterinary supplements, such as the compound "ADE'', for aesthetic purposes. This practice has been done, especially by non–competitive bodybuilders, due to its potential to induce local muscle swelling and "pseudohypertrophy"[3].

The compound ADE is a parenteral multivitamin with restricted use recommendations for veterinary practice, especially in cattle, horses, and pigs. Manufacturers indicate it for the prophylaxis or treatment of hypovitaminosis A, D, and E and for the management of infectious diseases. Each 100 ml of the product contains, on average, 20,000,000 IU of Vitamin A, 5,000,000 IU of Vitamin D3, and 6,800 IU of Vitamin E. Recommended doses may vary but can reach up to 5 ml every 120 days for animals in fattening periods[3].

We present a patient who presented hypercalcemia, nephrolithiasis, nephrocalcinosis, and kidney injury followed by multiple large amounts of vitamins A, D, and E muscle application. An informed consent form was signed for the publication of the case.

CASE REPORT

A 42-year-old man has come to the emergency department due to lower left limb pain following a motorcycle accident. He reported chronic lower back pain over the past eight (8) years, and he had never sought any medical treatment. He

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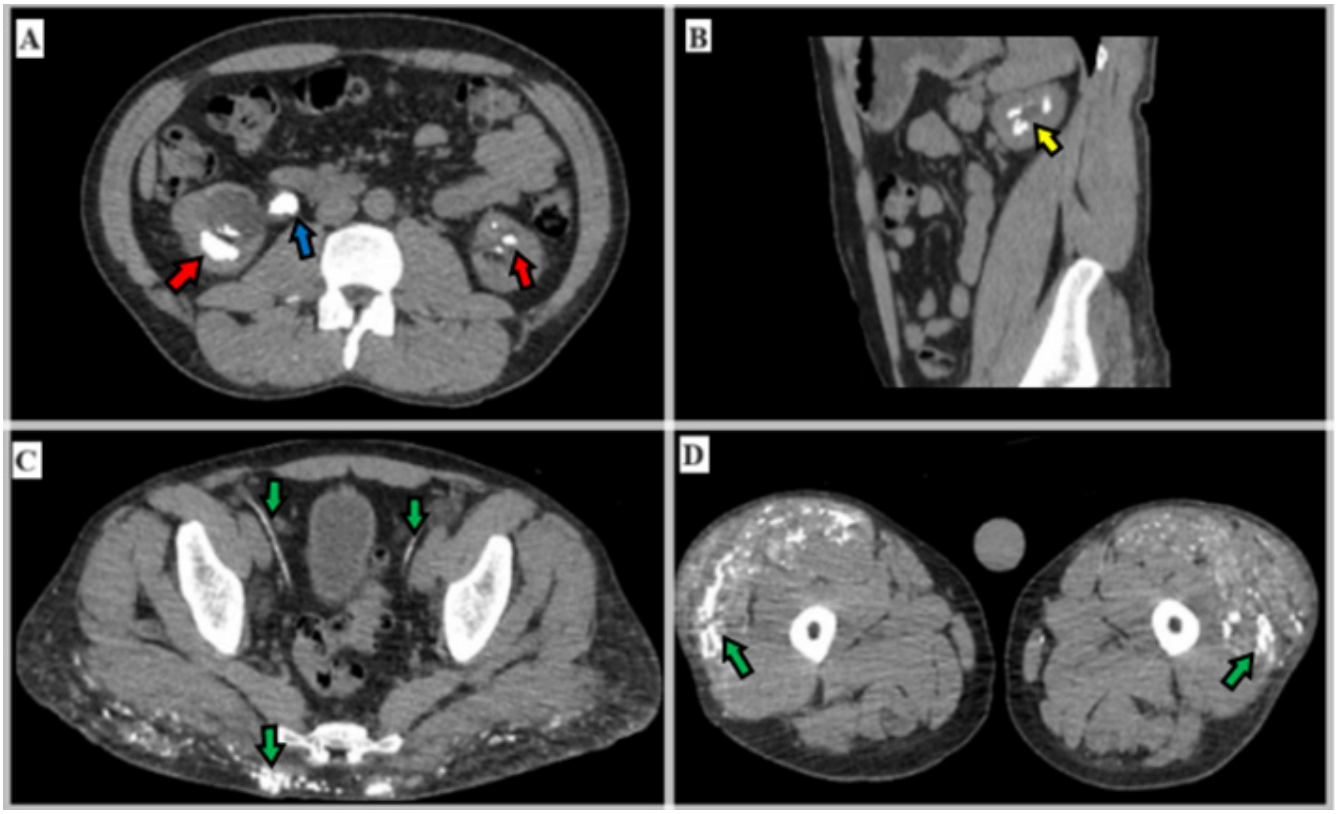
denied recent anti-inflammatories use or other medications, except for sporadic common analgesics. On admission, the physical examination revealed blood pressure 136 x 95 mmHg, heartbeat 88 bpm, and extensive abrasions and pain in the left lower limb, without edema. Multiple hardened nodules measuring approximately 5 cm in several muscles over the chest and upper and lower limbs were noted. The heart, pulmonary, and abdominal exams were normal. He reported several applications of veterinary supplements with high doses of vitamins A, D, and E (10 ml in each muscle) over three (3) years for aesthetic purposes. It occurred about ten (10) years ago, and there have been no further applications since then. He denied any anabolic steroid use. Laboratory tests revealed hemoglobin 12.5 g/dL, platelet count 342,000/mm³, creatinine 4.59 mg/dl, urea 147 mg/dL, sodium 132 mEq/L, potassium 4.8 mEq/L, and calcium 13.3 mg/dl. The 25-OH-vitamin D level was 18.4 ng/ml (normal range 20-60 ng/ml), and parathormone was 13.8 pg/ml (normal range 12-88 pg/ml). A knee joint x-ray showed a tibial plateau fracture, and surgical internal fixation with plate and screws was needed. The abdominal tomography revealed bilateral nephrolithiasis and nephrocalcinosis, right obstructive ureterolithiasis, and extensive vas deferens and myoadipose compartments calcifications (figure 1).

Figure 1. Abdominal tomography showing: [A] bilateral nephrolithiasis (red arrows) and right-sided obstructive ureterolithiasis (blue arrow); [B] nephrocalcinosis (yellow arrow); [C, D] extensive calcifications in vas deferens, myoadipose compartments of gluteus and lower limbs (green arrows).



The patient underwent a right ureterolithotripsy and bilateral stent placement for urinary drainage. He was treated with vigorous crystalloid solution administration and prednisone 1 mg/kg for four (4) weeks, followed by weaning over 15 days. The patient had clinical and laboratory test improvement and was discharged with serum calcium 8.5 mg/dl and creatinine 3.3 mg/dl. There was no need for hemodialysis. Kidney function and calcium levels remained stable at 30 days after discharge.

DISCUSSION

The compound “ADE'' is an injectable oil for veterinary use that contains large amounts of vitamins A, D, and E. Meanwhile, it has also been used by bodybuilding athletes as the fat-soluble vitamin solvent generates a foreign body reaction and local "pseudohypertrophy"[3,4]. The parenteral application of this veterinary supplement leads to a granuloma reaction that increases the extra-renal vitamin D conversion in calcitriol, the vitamin D active form, by the macrophages[3]. The same mechanism is described after mineral oil injection, with paraffinoma formation[1,5]. The onset time of hypercalcemia after injection of cosmetic substances is approximately eight (8) years[6]. Furthermore, each 100 ml of the product has 5,000,000 IU of vitamin D3, which may lead to vitamin D intoxication, with subsequent conversion to calcitriol, overstimulating intestinal absorption of calcium[7]. Such mechanisms are mainly responsible for the development of hypercalcemia[3,7].

Vitamin A intoxication is also one of the known causes of hypercalcemia, possibly through changes in bone metabolism[8]. Since the compound “ADE” contains very high amounts of vitamin A (20,000,000 IU on average) and has been applied throughout several years by the reported patient, a vitamin A intoxication may have contributed to the hypercalcemia genesis. General symptoms of hypercalcemia tend to be similar in different etiologies. The main determinants of the intensity of symptoms are the magnitude and the speed of onset of hypercalcemia[9]. The clinical manifestations may include several systems, such as cardiovascular, neurological, gastrointestinal, and renal. Hypercalcemia can lead to a wide spectrum of kidney involvement, including acute kidney injury and/or chronic kidney disease, depending on the reversibility of the damage[3,7,10]. The mechanisms involved in AKI-hypercalcemia are the direct hemodynamic effect of reversible vasoconstriction[11,12], dehydration resulting from polyuria mediated by acquired nephrogenic diabetes insipidus11, and, in those patients with sustained hypercalciuria and nephrolithiasis, acute obstructive uropathy resulting from migration of calcium-containing stones into the collecting system. Hypercalciuria resulting from hypercalcemia, through the deposition of calcium in the medullary interstitial region and formation of Randall's plaques, acts as a risk factor for tubulointerstitial fibrosis, nephrolithiasis, and nephrocalcinosis. The present patient evolved with hypercalcemia, nephrolithiasis, and nephrocalcinosis, which are related to a higher risk of chronic kidney disease[13,14.]

The treatment of hypercalcemia generally depends on the magnitude of serum calcium levels and the underlying cause. In mild cases, with calcemia < 12 mg/dl, treatment of the etiological factor is sufficient[10]. In moderate to severe cases, vigorous infusion of crystalloid solution is indicated, aiming to restore intravascular volume and increase calciuria[10]. Physicians should take care of the risk of hypervolemia, especially in patients with heart diseases and compromised kidney function. Loop diuretics can be associated if fluid overload evidence is found[10]. After normal blood volume is restored, bone resorption inhibitors can be initiated. The main pharmacological agents used are denosumab and bisphosphonates, which are effective in reducing calcemia after 2-4 days, and their effect may last for a few weeks. Denosumab is the first choice in patients with severely worsened kidney function, as it does not require renal clearance for its elimination[10]. In severe cases, as patients with life-threatening neurological symptoms, the rapid correction of calcium levels is needed, and calcitonin may play a role. Its effect is achieved within a few hours, and administration can be repeated every 6 hours for up to 48 hours, after which tachyphylaxis develops[10]. In granulomatous diseases, foreign body reactions, and hematological malignancies, glucocorticoids can be considered, as they inhibit the production of calcitriol by mononuclear and neoplastic cells. Its long-term use is not recommended given the multi-systemic toxicity[10,15]. In cases of vitamin D-mediated hypercalcemia, antifungals such as ketoconazole, by inhibiting 1-alpha-hydroxylase, have also been shown to be effective as a long-term strategy for controlling hypercalcemia. Since those antifungals block cytochrome P450 enzymatic activity, drug interactions should be monitored[15]. Surgical treatment with granuloma removal after injection of oily compounds has been reported a few times, with varied results, and generally not feasible due to the extent of these lesions, generally being diffuse[6]. In patients with impaired kidney function and severe hypercalcemia that is refractory or with contraindications to other medication, dialysis may be performed[10]. The reported patient was treated with intravenous saline hydration and prednisone due to presumptive granuloma-induced hypercalcemia. As the presented patient applied the veterinary supplement more than ten (10) years before hospital admission, we hypothesize that vitamin D previously stored in different muscles was completely metabolized, so hypervitaminosis D was not identified at that moment. It was not possible to measure calcitriol levels as the test was not available in our hospital. Hypercalcemia can also be a result of the granulomatous reaction to a foreign body, which may explain the positive response to corticosteroid treatment.

Although there is popular knowledge of ''cosmetic doping'', especially in the gym environment, this practice has been sometimes reported in scientific literature as a clear etiological factor for the complications described above. This report highlights the complications related to the misuse of veterinary supplements by humans. Detailed data collection and physical examination can help physicians evaluate the right etiology of hypercalcemia, allowing for early diagnosis and treatment in order to avoid negative long-term outcomes.

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