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Caso Clínico

Spontaneous Vertebral Fractures in a Young Patient with ACTH-Independent Hypercortisolism

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A B S T R A C T

Osteoporosis at a young age should prompt clinicians to search for secondary causes, namely endogenous Cushing's syndrome. This very rare disease leads to high levels of glucocorticoids and prone patients to fractures, mainly in the vertebrae. Herein we present a young patient with osteoporosis and spontaneous vertebral fractures due to ACTH-independent Cushing's syndrome. A 46 year-old male with a 2-year history of osteoporosis presented with extremely painful thoracic hyperkyphosis and florid features of Cushing's syndrome, confirmed biochemically and by imaging as ACTH-independent hypercortisolism. Dual-energy X-ray absorptiometry revealed total Z-scores in the lumbar spine and femoral of -1.9 SD and -2.3 SD, respectively. Spinal magnetic resonance imaging revealed multiple vertebral fractures with focal thoracic medullar edema. Surgical excision of an adrenal adenoma and medical therapy with biphosphonates led to remission of all Cushing's associated comorbidities and to a remarkable improvement in dual-energy X-ray absorptiometry, mainly in the lumbar spine (total Z-score 0.4 SD). Endogenous Cushing's syndrome should always be thought in the context of severe osteoporosis at a young age. The delivery of the best therapy for osteoporosis in this context depends on its recognition.

Fracturas Vertebrais Espontâneas num Doente Jovem com Síndrome de Cushing ACTH-Independente

Palavras-chave:
Fraturas Espontâneas
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R E S U M O

A osteoporose em idade jovem deve alertar os clínicos para a investigação de causas secundárias, nomeadamente a síndrome de Cushing endógena. Esta doença rara causa níveis elevados de glucocorticóides e susceptibiliza os doentes a fracturas ósseas, maioritariamente nas vértebras. Apresentamos um caso clínico de um doente jovem com osteoporose e fracturas vertebrais espontâneas no contexto de síndrome de Cushing ACTH-independente. Homem de 46 anos, com história com 2 anos de evolução de osteoporose, com hipercifose torácica dolorosa e sinais clínicos marcados de síndrome de Cushing. Esta foi confirmada por bioquímica e imagiologia como síndrome de Cushing ACTH-independente. A densitometria óssea revelou Z-*scores* totais na coluna lombar e no fémur de -1,9 DP e de -2,3 DP, respectivamente. A ressonância magnética da coluna vertebral revelou múltiplas fracturas vertebrais e edema medular torácico focal. A excisão cirúrgica de um adenoma da suprarrenal e a terapêutica médica com bifosfonatos levaram à remissão de todas as comorbilidades associadas à síndrome de Cushing e a uma melhoria marcada da densitometria óssea, maioritariamente na coluna vertebral lombar (Z-*score* total de 0,4 DP). A síndrome de Cushing endógena deve ser sempre ponderada em contexto de osteoporose grave em idade jovem. A aplicação da melhor estratégia terapêutica para a osteoporose neste contexto depende do seu reconhecimento clínico.

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Introduction

Endogenous Cushing's syndrome (ECS) affects 2:1 000 000 habitants per year.[1] It is usually caused by an abnormal ACTH secretion from a pituitary lesion, and less frequently by an independent adrenal overproduction of cortisol.[2] This entity leads to excessive glucocorticoid exposure and to a wide set of clinical features. Some of the most discriminatory features are facial plethora, reddish purple striae, easy bruising, proximal myopathy and osteoporosis at a young age.[1] Fifty percent of patients with ECS develop osteoporosis, and the vast majority are prone to fractures, mainly in the vertebrae.[3]

Case Report

A 46-year-old Caucasian male was referred to our department with a 10 year-history of hypertension, to perform a screen for endocrine causes of hypertension. He also had a 10 year-history of uncontrolled back pain and muscle weakness. Past medical history was relevant for osteoporosis diagnosed 2 years before the referral and chronic obstructive pulmonary disease. He was on inhaled fluticasone for 1 year, lisinopril 10 mg/day, amlodipine 10 mg/day and calcium plus vitamin D supplements.

Physical examination was remarkable for a blood pressure of 190/119 mmHg, facial plethora, central obesity, extremely painful thoracic hyperkyphosis, proximal muscle weakness in the upper and lower limbs, bruising and thin skin. Biochemical evaluation revealed pre-diabetes *mellitus* (glucose 6.5 mmol/L / 118 mg/dL; reference: 3.5-6.1 mmol/L / 70-110 mg/dL), hypertriglyceridemia (4.9 mmol/L / 404 mg/dL; reference: <1.7 / 150 mg/dL), high free 24-hour urinary cortisol in two instances (604.2 and 501.7 mmol/d / 218 and 181 ug/dL; reference: 27.7-166.4 mmol/d / 10-60.3 ug/dL) and high morning serum cortisol after an overnight dexamethasone suppression test (607.2 mmol/L / 22 ug/dL; reference: <5 mmol/L / 1.8 ug/dL). Adrenocorticotropic hormone (ACTH; <1.1 pmol/L / <5 pg/mL; reference: <11 pmol/L / <50 pg/mL) was suppressed, consistent with ACTH-independent hypercortisolism. Abdominal computerized tomography revealed a well-defined, hypodense, 3 cm lesion in his left adrenal gland suggestive of an adenoma. Dual-energy X-ray absorptiometry (DEXA) showed Z-scores in the lumbar spine and total hip 20% and 36% below the expected score for his age, respectively (Table 1). Spine X-ray revealed lordosis and scoliosis with a decrease in height in dorsal (D7, D8, D11, D12) and lumbar vertebrae (L1). Spinal magnetic resonance imaging revealed multiple vertebral fractures with medullar edema at the level of the 6th thoracic vertebrae (Fig. 1). Due to a normal neurological examination, the patient was elected for conservative management and started on alendronate 70 mg plus cholecalciferol 5800 UI/week and elemental calcium 500 mg/day. A left adrenalectomy was performed and pathology revealed an adrenocortical adenoma. The patient started on hydrocortisone (10 mg at wakening, 5 mg at lunch and 5 mg at 17h00), which was maintained for 5 years due to low serum cortisol levels (higher peak: 187.7 mmol/L / 6.8 ug/dL) at annual short Synacthen test (inhaled fluticasone was stopped 15 months after surgery). After 5 years of remission, the patient maintains minimal back pain elicited by exercise. He has normal hemodynamic, glucose and lipid profiles, remaining only on biphosphonate therapy, calcium and vitamin D supplements. A significant improvement in DEXA Z-scores was also seen, mainly in the bone mineral density (BMD) of the lumbar spine (Table 1).

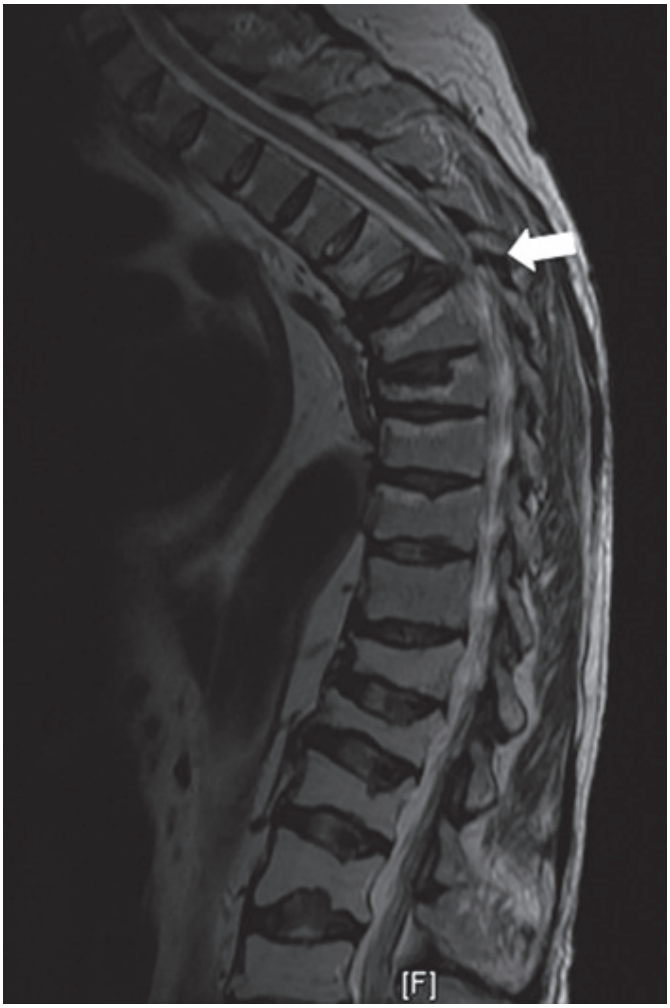

Figure 1. Spinal magnetic resonance imaging: sagital T2 gadolinium enhancement showing multiple vertebral fractures and medullar edema at the level of the 6th thoracic vertebrae (white arrow).

Discussion

Factors contributing to secondary osteoporosis are present in 30% of post-menopausal women and in 50% - 80% of men.[4] Thus, it is always worth to consider its presence, particularly in unusual clinical scenarios.[1,4] ECS should always be suspected when osteoporosis is diagnosed at a young age, especially when the most discriminatory features of this syndrome coexist.[1] In

Table 1. Dual-energy X-ray absorptiometry (DEXA) in the preoperative and postoperative periods: Z-scores in the central lumbar spine and femoral neck.

Region	Z-Score (SD‡)	
	Preoperative period	Postoperative period†
L1	-0.2	0.1
L2	-2.2	-0.3
L3	-2.1	0.5
L4	-2.9	1.0
Total (L1-L4)	-1.9	0.4
Neck	-1.9	-1.6
Trochanter	Not measured	-1.8
Total	-2.3	-2.0

‡ SD: standard deviation
† Five years post-surgery

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one study, subclinical ECS was found in 10.8% of cases with severe osteoporosis where screening for hypercortisolism was performed.[5]

Glucocorticoid-induced osteoporosis (GIO) is characterized by a rapid increase in bone resorption (3 to 9 months), followed by a progressive long-term suppression of bone formation. GIO occurs by both direct and indirect mechanisms. The main direct effects of glucocorticoids occur on osteoblasts. They suppress the proliferation and differentiation of osteoblast precursors (inhibition of Wnt/β-catenin pathway; commitment of osteoblast progenitor cells to adipocytes - via peroxisome proliferator activator-receptor γ 2 and CCAAT enhancer binding protein signaling); increase apoptosis of osteoblasts and osteocytes – cells that sense and repair bone microdamage – (activation of caspase 3; inhibition of local production of IGF1); and inhibit the synthesis of type I collagen by osteoblasts (and the matrix available for new bone formation). Glucocorticoids increase the differentiation of osteoclasts (enhanced expression of RANK-L and M-CSF and decreased production of osteoprotegerin, an antagonist of RANK-L); and inhibit osteoclast apoptosis – leading to an increase in their life span –. Indirect effects are caused by decreased intestinal calcium absorption and increased renal calcium excretion through inhibition of vitamin D action; feedback inhibition of gonadotropins and decreased estrogen and testosterone levels.[6] GIO affects mainly the vertebral bodies, due to a higher impact of glucocorticoids on trabecular bone, which predominates in the vertebrae.[7] Importantly, the validity of measurements of BMD, as a predictor of fractures, has not been established in GIO.[4] Hypercortisolism seems to impair bone microarchitecture more than density, and this might justify the increase in fractures at higher BMD values than expected[7] (has also shown in our patient). In one study, 40% of eugonadal men with subclinical hypercortisolism had a fracture at normal or slightly reduced BMD.[8] Methods that evaluate bone architecture instead of BMD, such as the trabecular bone score (TBS), may be more appropriate in the context of GIO. However, these techniques are not as widely available as DEXA, and this tool remains the standard method for evaluation of bone status in usual clinical practice.[7] Thus, it is nowadays recommended that the BMD threshold to treat in the context of GIO should be at scores in the osteopenic range.[4] The influence of inhaled fluticasone on the 5 years postoperative BMD of our patient (available preoperative BMD was determined 1 year previous to fluticasone treatment) is difficult to ascertain, as this treatment was suspended 15 months after surgery. Additionally, inhaled glucocorticoids have been inconsistently associated with detrimental effects on BMD in adults.[4,9,10] Although patients with COPD have lower BMD and higher risk of fractures when compared with controls, inhaled glucocorticoids do not appear to have additional detrimental effects on these parameters.[9]

Identifying the cause of secondary osteoporosis is paramount to select the correct treatment, either medical, surgical or both,[4] as illustrated in our case. Successful surgical therapy of ECS leads to a significant improvement in BMD 3 to 6 months after intervention, mainly in the lumbar spine.[11,12] A considerable proportion (40%) of patients remain with BMD at the osteopenic range[12] but the majority of published data reported a limited follow-up time,[11,12] which may hinder the evaluation of the true impact of ECS reversal in BMD. Considering the glucocorticoid effects on calcium and vitamin D metabolism described above, administration of supplemental calcium (1000 mg/day) and vitamin D (1000-2000 UI/day) to restore vitamin D levels above 40 ng/mL are recommended.[4] Alendronate, risedronate and zoledronic acid are indicated to prevent and treat GIO.[4] They increase BMD in GIO, and alendronate and risedronate have shown to reduce the incidence of vertebral GIO-related fractures up to 48 weeks of treatment.[13-15] Teriparatide is also indicated in the treatment of GIO. Although it is more effective than alendronate to increase BMD, its superiority in preventing GIO-related fractures remains to be proven in specifically designed study endpoints.[4]

From its subclinical forms to the full-blown syndrome, ECS should always be considered in the context of severe osteoporosis. The delivery of the best therapy for GIO depends on this recognition.

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