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An unusual case of hypercortisolism with multiple weight-bearing bone fractures

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Summary

Glucocorticoid excess, either from exogenous exposure or through endogenous overproduction, is a common cause of secondary osteoporosis. We report a 52-year-old woman presenting with multiple stress fractures of the lower extremities, despite various osteoporosis therapeutic regimens. Investigations led to the diagnosis of hypercortisolism of pituitary origin. Pituitary surgery was unsuccessful, justifying a treatment of ketoconazole. In the absence of densitometric osteoporosis, assessment of bone microstructure using high resolution peripheral quantitative computed tomography revealed alterations of both the cortical and trabecular compartments. This case illustrates that hypercortisolism may cause bone fragility in the absence of marked changes in areal bone mineral density.

KEY WORDS: fractures; secondary osteoporosis; Cushing's syndrome; glucocorticoids; bone mineral density.

Introduction

Secondary osteoporosis is defined as low bone mass and microarchitectural alterations leading to fragility fractures due to an underlying disease or medication (1). Glucocorticoid-induced bone loss is a common cause, given the relatively frequent use of glucocorticoid therapy in 0.5% to 2.5% of adults (2). However, endogenous hypercortisolism affects also bone and approximately 30-67% of patients with Cushing's syndrome develop fractures, mainly of the vertebrae (3). Here, we report the case of a postmenopausal woman with multiple peripheral stress fractures without clinical symptoms and continuing to fracture despite multiple osteoporosis treatments, thus suggesting a secondary cause of bone fragility. Additional investigations revealed Cushing's disease.

Case report

A 52-year-old woman, engaged in regular physical exercise, was referred to our service in August 2008 because of repeated metatarsal fractures without significant trauma. Body mass index (BMI) was 19.6 kg/m² for a weight of 52 kg and a height of 163 cm. Previous laboratory data excluded overt secondary causes of fractures, such as multiple myeloma, hyperthyroidism, primary hyperparathyroidism, or celiac disease.
In 2002, she reported fractures of the right olecranon, the first left metatarsal with delayed consolidation in 2005, the third right metatarsal in 2007, and the fourth right metatarsal in 2008. Risk factors for bone fragility were a surgically-induced menopause in 2007 (total hysterectomy) treated by estrogen replacement, smoking history (stopped in 1994), and a positive family history (osteoporosis without fractures in the patient's mother). Since 2002, her daily calcium intake consisted of two dairy products and a calcium supplement (1000 mg/d) with vitamin D (800 UI/d).
In 2005, areal bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) (Hologic, Waltham, MA, USA) indicated osteopenia (Figure 1). A second DXA examination in March 2007 detected a BMD decrease at all measured sites. Osteoporosis treatment included estrogen replacement therapy and a 3-month course of oral ibandronate from August to November 2007 before switching to subcutaneous daily teriparatide in November 2007. Ten months after teriparatide introduction, DXA measurement showed a gain of 5% in lumbar spine and 8% in proximal femur. Plasma calcium and phosphate values were within normal ranges, whereas bone turnover markers were in the lower part of reference intervals, despite the osteoanabolic effect of teriparatide (Table 1). A morning cortisol value slightly over the upper limit of the normal range (580 nmol/L) was not considered sufficient to further assess hypercortisolism in a patient lacking clinical signs, such as obesity, 'moon face', myopathy, excess of abdominal fat, or purple striae. Further continuation of teriparatide for a total period of 18 months was recommended.
In January 2009, she developed a second left metatarsal aseptic necrosis detected by magnetic resonance imaging (MRI), followed by a fracture of the fourth left metatarsal in February and the right external femoral condyle in April. A new DXA examination showed an increase in lumbar spine BMD and a moderate gain in the hip. Laboratory data in March 2009 showed no particularities, except for bone turnover markers in the lower part of the normal range (Table 1). A second morning cortisol value was in the normal range. After completing the

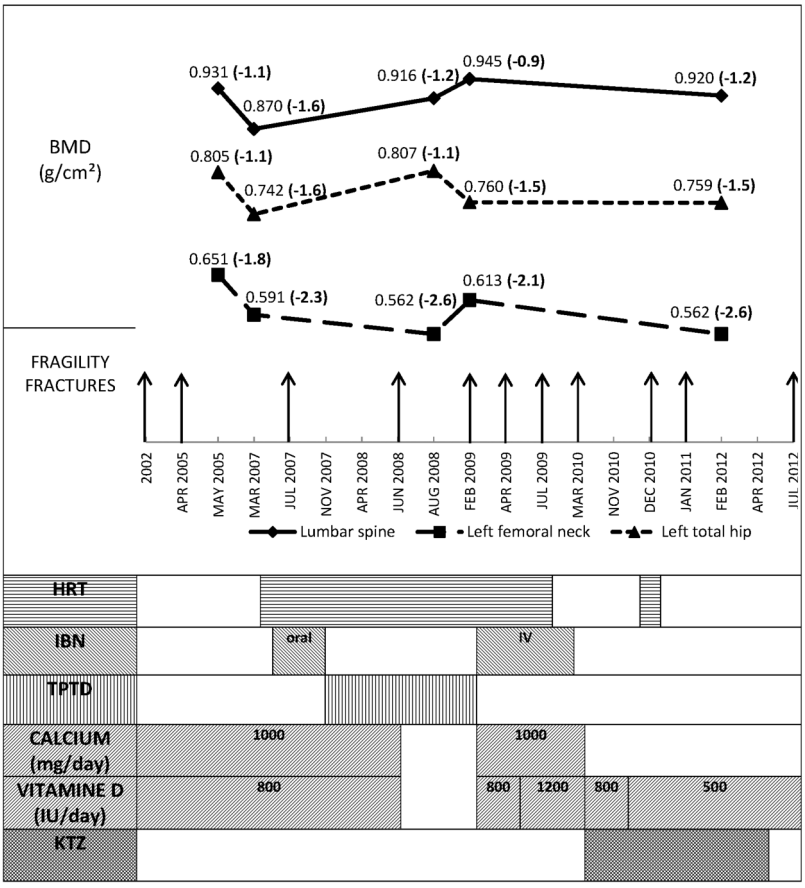

Figure 1 - Bone mineral density, fracture occurrence and therapeutic regimens.
Black arrows correspond to the fragility fractures sustained in the following sites in chronological order: right olecranon, first left metatarsal, third right metatarsal, fourth right metatarsal, fourth left metatarsal, right knee (femur lateral condyle), right calcaneus (anterior), right calcaneus (posterior), right knee (femur medial condyle), left knee (femur medial and lateral condyle), left knee (femur medial and lateral condyle), left knee (tibia internal plateau).
The numbers in parenthesis are T-scores.
Abbreviations: HRT = hormonal replacement therapy, IBN = ibandronate, TPTD = teriparatide, KTZ = ketoconazole, IV = intravenous, IU = international Units, mg = milligram.

course of teriparatide, intravenous ibandronate was initiated in addition to hormone replacement therapy in February 2009. In June 2009, she sustained a new fracture of the right calcaneus. Due to poor tolerance, the patient stopped estrogen replacement in July 2009.
The discrepancy between the unfavorable clinical evolution, laboratory data, and BMD values led to additional investigations. Despite normal basal cortisol levels, urinary free cortisol (UFC) excretion (4) was twice the upper normal limit and raised the suspicion of hypercortisolism. In August 2009, this was confirmed by the non-suppression of the serum cortisol level in a low-dose dexamethasone test (Table 1). A first measurement of serum ACTH was normal, whereas a second one showed a clear increase. However, MRI examination of the pituitary sella in November 2009 failed to identify an adenoma.
In February 2010, a catheterization of the petrosal venous sinus coupled with a corticotropin-releasing hormone (CRH) stimulation test indicated a left-side pituitary origin of ACTH. A transsphenoidal surgery with left lateral hypophysectomy was finally performed in April 2010. The postoperative course was marked by a persistence of hypercortisolism with UFC more than three times the upper normal limit. A conservative approach with ketoconazole treatment was initiated and allowed to well control serum and UFC levels. Three consecutive MRIs failed to detect a pituitary adenoma but the patient declined the option of bilateral surrenalectomy.
Meanwhile, two more stress fractures were detected by MRI: one in the femur right medial condyle in December 2010, and one in the femur left medial and lateral condyle in January 2011. However, since ketoconazole-induced eucortisolism was achieved, our patient had a fracture-free interval of 18 months.
In February 2012, a DXA examination showed osteoporosis values in both femoral necks without vertebral fracture in vertebral fracture assessment (VFA). Despite worsening of some DXA values, there was a progressive normalization of bone resorption markers (Table 1). In the absence of any bone-acting treatment, bone remodeling markers were in the premenopausal range and the favorable clinical course was attributed to the sustained resolution of hypercortisolism by ketoconazole, associated with normal UFC values. No further bone treatment was prescribed.
In April 2012, ketoconazole was stopped to reevaluate the opportunity of bilateral surrenalectomy. In May 2012, distal radius and tibia bone microstructure was evaluated by high-resolution peripheral quantitative computed tomography (HR-pQCT, XtremCT, Scanco Medical, Bruttisellen, Switzerland) to further assess bone fragility. At distal tibia, both cortical and trabecular compartments were altered, while the distal radius showed a more prominent trabecular involvement (Table 2).
In July 2012, another fracture of the left knee (tibia medial plateau) was detected by MRI. Laboratory data showed an increase of the urine cortisone/cortisol ratio and dexamethasone failed to suppress morning cortisol, thereby confirming the recurrence of hypercortisolism.

Discussion

Osteoporosis is a disease affecting primarily postmenopausal women as a consequence of sex hormone deficiency. Howev-

Table 1 - Laboratory values.

DATES			AUG 2007	AUG 2008	AUG 2009	OCT 2009	APR 2010[4]	MAY 2010	OCT 2010	APR 2011	FEB 2012	AUG 2012
Analysis	**Units**	**Reference Range**										
Alb.-corrected Ca	mmol/l	2.2-2.6	2.23	2.44					2.38			2.34
Phosphate	mmol/l	0.8-1.5	1.13	1.16					1.46			
25-OH-Vitamin D	nmol/l	50-120[1]	135						91		77	97
PTH	pmol/l	1.6-8.2	**9.9**						3.9			7.35
Bone ALP	µg/l	4.7-27		16.5								11.9
CTX (Crosslaps)	ng/l	0.19-0.53		0.2					**0.75**		0.43	0.51
P1NP	µg/l	15.1-58.6							**82**		42	32
Cortisol[2]	nmol/l	100-540		**580**			381	453			210	
Cortisol DXM[3]	nmol/l	< 140			**373**							**271**
Urinary free cortisol	nmol/24	40-240			**449**		**684**	**832**	109	163	46	142
Cortisone/Cortisol		1.5-4.0										**27.6**
ACTH at 8 am	pmol/l	1.6-13.9			9.9							
ACTH at 8 am	ng/l	10-60				**79**						
Hypercortisolism diagnosis					↑							
ACTH dependency						↑						
Left lateral hypophysectomy							↑					
Ketoconazole treatment									→			

Abbreviations: Ca = calcium, PTH = parathyroid hormone, ALP = alkaline phosphatase, CTX = C-terminal telopeptide, P1NP = procollagen Type 1 N-terminal propeptide, UFC = urinary free cortisoluria of 24 h, ACTH = adrenocorticotropin hormone, DXM = dexamethasone.
[1] Therapeutic target of 25-OH-vitamin D level
[2] Morning cortisol at 7.-8 am
[3] Morning cortisol after low-dose dexamethasone test (1 mg dexamethasone at midnight)
[4] First results after resection of adenoma in April 2010.
The numbers in bold are values outside the reference range.

er, various disorders or medication can cause bone loss, referred to as secondary osteoporosis (1). Among these, glucocorticoid excess, either endogenous or exogenous, plays an important role. The diagnosis of secondary osteoporosis can be challenging, particularly in the case of occult manifestation of the underlying disease or when the fractures appear in the postmenopausal context. Our patient is an example of the misleading presentation of secondary osteoporosis. She lacked the typical morphologic features of hypercortisolism with only the retrospective identification of some aspecific symptoms, such as fatigue, slight muscular weakness, and skin fragility with a tendency to ecchymosis.

It is well established that patients on oral glucocorticoids fracture at a higher BMD value than those with postmenopausal osteoporosis, suggesting alterations of other determinants of bone strength, such as bone microstructure (5). Similar findings have been documented in patients with Cushing's syndrome (6). A possible explanation could be that glucocorticoid excess may cause alterations in bone material properties, in microarchitecture, and in bone remodeling. These determinants of bone strength are not captured by areal BMD measurement (7). In general, glucocorticoid excess affects trabecular more than cortical bone. Thus, trabecular thinning and perforation may contribute to bone fragility (8). Cortical porosity and endosteal resorption may also be observed with long-term treatment (9).

HR-pQCT assesses distal radius and tibia trabecular and cortical microstructure (10). In a recent study, Li et al. (11) used this technique to examine the relationship between vertebral fractures and peripheral bone microstructure in patients with systemic lupus erythematosus on chronic corticosteroid therapy. They found lower total, cortical, and trabecular BMD, together with reduced trabecular thickness in patients with vertebral fractures. As far as endogenous hypercortisolism is concerned, one study assessed bone microstructure in 10 Japanese patients (four premenopausal and six postmenopausal women) with Cushing's syndrome using pQCT (12). Total and cortical BMD, as well as bone area, periosteal circumference, and polar strength strain index were lower only in premenopausal women with Cushing's syndrome. However, both the small

Table 2 - Distal Tibia and Radius Bone Microstructure Using High-Resolution Peripheral Computed Tomography (HR-pQCT).

Parameters	Left tibia	T-score*	Left radius	T-score*
Densities (mg HA/cm³)				
D100	201.9	- 2.49	188.6	- 2.44
DTrab	111.0	- 2.15	61.5	- 1.13
DComp	814.0	- 3.71	833.3	- 3.07
Microstructure				
BV/TV (%)	9.3	- 2.11	5.1	- 3.00
Tb.N (mm^{-1})	1.32	- 1.97	0.98	- 3.96
Tb.Th (mm)	0.070	- 0.94	0.052	- 1.6
Tb.Sp (mm)	0.686	+ 2.66	0.967	+7.93
Tb.1/N. SD (mm)	0.323	+ 2.72	0.710	+13.6
Ct.Th (mm)	0.70	- 2.24	0.52	- 0.93
Geometry				
CSA (mm^2)	613.5	- 1.50	251	- 0.24

*T-scores were calculated using mean values and standard deviations derived from a cohort of healthy young adult women (n=124; mean age 20.4 ± 0.6 years) (16). Examination was performed in May 2012.

Abbreviations: D100 = average bone density, Dtrab = trabecular bone density, Dcomp = cortical volumetric density, BV/TV = trabecular bone volume to tissue volume, Tb.N = number of trabeculae, Tb.Th = trabecular thickness, Tb.Sp = trabecular separation. Ct.Th = cortical thickness, Tb.1/N.SD = StDev of 1/Tb.N, inhomogeneity of network, CSA = cross-sectional area.

sample size and the more severe hypercortisolism in the premenopausal compared to the postmenopausal group (UFC, 318 ± 139 mg/day *vs* 193 ± 76 mg/day) do not allow to draw definitive conclusions.

DXA examination of our patient initially revealed osteopenia that evolved into osteoporosis (femoral neck T-score, -2.6), although these findings are unlikely to explain the high frequency of fractures. Distal tibia HR-pQCT results allowed to demonstrate lower bone densities both in cortical and trabecular compartments. All trabecular bone values, with the exception of trabecular thickness, were altered in a consistent manner. Thus, the peripheral skeleton low microstructural values could have contributed to the high fracture occurrence in our patient.

The lack of therapeutic response to various antiosteoporotic agents is surprising. Even teriparatide did not appear to influence the bone turnover marker P1NP. Our patient did not respond to ibandronate either and only treatment aimed at reducing hypercortisolism, such as ketoconazole, had an effect on biochemical markers. However, the bone impact of ketoconazole in patients after unsuccessful pituitary surgery is controversial with one study showing a persistently low BMD, despite achievement of eucortisolism (13).

Another interesting feature in our patient is the bone weight-bearing distribution of fractures. Indeed, the initial presentation included metatarsal fractures, which are sites consisting mostly of cortical bone, before the later involvement of other sites with trabecular bone, such as the calcaneus and tibia plateau. In February 2012, VFA showed no vertebral fracture. By contrast, a recent report of the European Registry on Cushing's syndrome (14) revealed that the overall frequency of DXA alterations was comparable in the spine and hip (64% *vs* 62%, respectively). Furthermore, there was a preferential occurrence of vertebral and rib fractures (41% and 39%, respectively) compared to peripheral bone (8%, wrist and metatarsal; 5%, hip fractures). In a review of 30 published cases up to 2000 (15), there was only one calcaneus fracture, but accompanying a hip fracture. Only 3 cases were without any vertebral or rib fractures. Similar to our patient, these data indicate that the predominant weight-bearing bone localization is very rare in Cushing's syndrome.

In conclusion, hypercortisolism is a rare, but possible cause of secondary osteoporosis and may present with fractures as the primary manifestation of the disease. Predominantly peripheral fractures are possible, as in our case, without spine involvement. Fractures occurring without marked BMD decreases should lead the clinician to investigate microstructural alterations.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Acknowledgments

Authors' roles: GP participated in data collection and analysis, and drafted the manuscript. BU participated in data collection and analysis, and drafted the manuscript. MG performed endocrine assessments. SZ performed densitometric examinations. RR performed the data analysis and manuscript revision.

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