INTERNAL MEDICINE

□ CASE REPORT □

A Rare Presentation of Subclinical Cushing's Syndrome as a Pubic Fracture

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Abstract

Osteoporosis and bone fractures are commonly seen in patients with Cushing's syndrome (CS). Fractures usually occur in the vertebrae and ribs whereas pubic fractures are less common. Similar to obvious hypercortisolemia, subclinical hypercortisolemia can increase the risk of fractures. However, in subclinical cases, bone fractures are very rarely seen as the presenting symptom. We herein report the case of a 62-year-old postmenopausal woman who was presented with a pubic fracture. During the evaluation of the fracture, thoracoabdominal magnetic resonance imaging of the patient demonstrated an adrenal mass. Although the patient did not show any signs of overt hypercortisolism, an endocrinologic evaluation revealed hypercortisolism due to an adrenal tumor. Adrenalectomy was performed, which resulted in a cure of the disease. During the orthopedic follow-up, the patient's pubic area pain gradually improved, and the pubic fracture healed without any accompanying new bone fractures. One year after the surgery, a remarkable improvement was detected in the patient's bone density in spite of the lack of administration of any medications for osteoporosis. Subclinical CS can present as a pubic fracture, and awareness of this relationship can help physicians to diagnose the disease.

Key words: Cushing's syndrome, pubic fracture, bone fracture, adrenocortical adenoma

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Introduction

Endogenous hypercortisolism can adversely affect bone, resulting in fractures in up to 30-67% of patients (1). The vertebrae and ribs are the most commonly involved sites whereas pubic fractures are infrequent (2, 3). Several studies have shown that even subclinical cortisol hypersecretion can lead to bone loss and fractures, as happens in the presence of overt glucocorticoid (GC) excess (4-6).

Although bone fractures are frequently seen in patients with Cushing's syndrome (CS), they are rarely observed as the first presenting symptom of the disease, especially in subclinical cases (2). We herein report the case of a postmenopausal woman in whom an adrenal mass was detected during the evaluation of the etiology of a pubic fracture and who was diagnosed with subclinical CS. One year after her recovery from CS, the patient's osteoporosis improved. To the best of our knowledge, this is the first documented case of subclinical CS presenting as a pubic fracture.

Case Report

A 62-year-old woman presented to our hospital with a two-week history of pain in her left hip and left pubic region. She did not report any trauma. She had been diagnosed with hypertension two years previously and was under medication (amlodipine, 10 mg/day). She was not a smoker and had a normal weight [body mass index (BMI), 23 kg/m^2] without any cushingoid features (such as purple striae, easy bruising, proximal muscle weakness or plethora) on a physical examination. The 24-hour ambulatory systolic and diastolic blood pressure values were high (145/98 mmHg). Routine laboratory results were unremarkable, ex-

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Table 1. Preoperative and Postoperative Clinical and Laboratory Findings of the Present Patient

Measurement	Preoperative	Postoperative
Fasting blood glucose (70-100 mg/dL)	90	85
Blood urea nitrogen (5-20 mg/dL)	24	22
Creatinine (0.6-1.3 mg/dL)	0.87	0.73
Total Calcium (8.5-10.6 mg/dL)	9.33	9.47
Phosphorus (2.5-4.6 mg/dL)	3.8	3.7
Sodium /potassium (136-144/ 3.5-5.1 mmol/L)	134 /3.6	139/3.9
Alcaline phosphatase (32-126 IU/L)	150	130
Alanine aminotransferase (10-40 IU/mL)	21	16
Glyco hemoglobin A1c (%)	5.1	4.7
Total cholesterol (0-200 mg/dL)	200	155
Trigliseride (<150 mg/dL)	148	87
LDL-cholesterol (0-100 mg/dL)	100	95
HDL-cholesterol (35-85 mg/dL)	36	43
Hemoglobin (14-17.5 g/dL)	12	11.3
White blood cells (4.4-11.3×10³ µ/L)	8.4	5.8
Neutrophil cell	70.1%	61.3%
Lymphocyte cell	15%	22%
Eosinophil cell	0.4%	0.1%
Platelet (150-450×10³ µ/L)	400	302
25 OH vitamin D (11.1 - 42.9 ng/mL)	30	28
Parathormone (1.3-9.3 pmol/L)	4	3.8
Follicle stimulating hormone (10.87-58.64 mIU/mL)	40	45
Luteinizing hormone (10.87 - 58.64 mIU/mL)	45	40
Estradiol (<20 – 40 pg/mL)	<20	<20
Prolactin (2.74 - 19.64 ng/mL)	18.27	16.2
Thyroid stimulating hormone (0.34-4.25 µIU/mL)	1.0	2.1
24 hour systolic/diastolic blood pressure (mmHg)	145/98	120/82

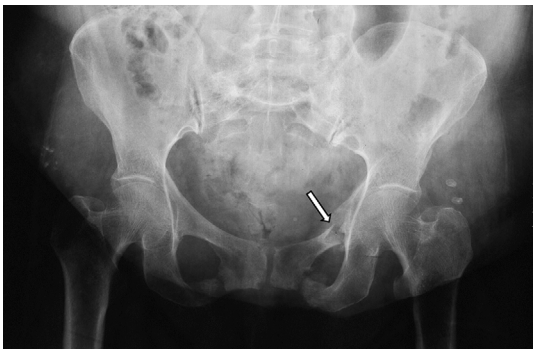

Figure 1. Plain radiography shows a fracture in the inferior pubic ramus.

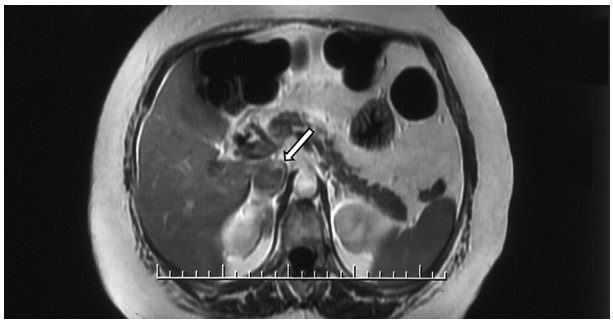

Figure 2. Adrenal magnetic resonance imaging revealed a mass in the right adrenal gland.

cept for an increased serum level of alkaline phosphatase (Table 1). Plain radiographs showed a fracture in the inferior pubic ramus (Fig. 1). A bone mineral density (BMD) analysis revealed osteoporosis (lumbar total T score: -4.2, total femoral T score: -3.5, femoral neck T score: -3.4). Under suspicion of a pathological fracture, a bone scan was performed using technetium 99 m. Fractures in the left acetabulum and both ischial pubic bones with probable metastatic findings in the sacroiliac joints were observed during the procedure. Diagnoses of breast cancer and gynecological malignancy were ruled out on breast and gynecological ultrasound and mammography. On a further oncologic survey using thoracoabdominal magnetic resonance imaging, we incidentally detected a right adrenal mass with dimensions of 25×36 mm (Fig. 2). Although the patient had no findings related to CS on the physical examination, a diagnosis of CS was questioned and the related tests were performed due to the presence of an adrenal mass. The patient's urinary cortisol levels were found to be high. The plasma adrenocorticotropic hormone (ACTH) and cortisol concentrations did not exhibit a circadian rhythm, and the cortisol level was not suppressed (>1.8 µg/dL) during overnight 1-mg and standard 2-mg dexamethasone suppression tests (Table 2). As a result of these findings, the patient was diagnosed with subclinical

Table 2. Preoperative and Postoperative Endocrinological Data of the Adrenal Tumor

Measurement	Preoperative	Postoperative
Morning plasma cortisol (6.7-22.6 mg/dL)	16.8	0.7
Midnight plasma cortisol (<5 mg/dL)	15.6	
Urinary free cortisol (20-90 µg /day)	371	85
Morning plasma Adrenocorticotrophic hormone (7.2-63.6 pg/mL)	1.14	12.2
Midnight plasma Adrenocorticotrophic hormone (pg/mL)	3.1	
[a] Plasma cortisol after overnight 1 mg Dexamethasone Test (<1.8 µg/dL)	20	1.0
[b] Plasma cortisol after standard 2 mg Dexamethasone Test (<1.8 µg/dL)	25.3	
[c] 8 mg Dexamethasone Test:		
Plasma cortisol (µg/dL)	24	
Urinary free cortisol (µg/day)	309	
Plasma renin activity (0.98-4.18 ng/mL/hour)	2.6	
Plasma aldosterone concentration (40-330 pg/mL)	220	
Urinary metanephrine (52-341 µg/day)	74	
Urinary normetanephrine (88-444 µg/day)	105	
Urinary vanillylmandelic acid (1-9 mg/day)	1.4	

[a]1 mg Dexamethasone was given orally at 11:00 PM and the concentration of serum cortisol was measured the next day at 8:00 AM. The cut off was considered 1.8 µg/dL.

[b]0.5 mg Dexamethasone was given orally every 6 h for a total of eight doses. Serum cortisol was measured 6 h after the last dose. The cut off was considered 1.8 µg/dL

[c]1 mg Dexamethasone was given orally every 6 h for a total of eight doses. Serum cortisol was measured 6 h after the last dose and 24 hour urine was collected for measurement of the urine free cortisol level from 8 AM on the second day to 8 AM on the third day of dexamethasone administration. Suppression of less than 50% compared to baseline in the serum and urinary cortisol was considered significant in favor of adrenal origin.

CS. The plasma and urinary cortisol levels were suppressed by less than 50% following the administration of 8 mg of dexamethasone, and the plasma morning ACTH concentration was <5 pg/mL. The levels of urinary metabolites of catecholamines and the ratio of the ambulatory morning plasma aldosterone concentration to plasma renin activity (<20) were within the normal ranges (Table 2). Therefore, the final diagnosis was ACTH independent subclinical CS. Eventually, the patient underwent laparoscopic right adrenalectomy, and the pathological examination demonstrated adrenocortical adenoma. Postoperatively, repeated basal cortisol levels were very low and suppressed following dexamethasone suppression tests. GC replacement therapy was initiated after the surgery and gradually stopped six months later. The patient's blood pressure was normal under therapy with amlodipin (10 mg once a day). No orthopedic interventions were performed to treat the fracture. The patient's pubic area pain gradually improved, and remarkable pubic fracture healing was detected three months after adrenalectomy. During the one-year follow-up in the orthopedic outpatient clinic, the patient did not experience any new bone fractures. Although no drugs were used to treat her osteoporosis, she showed a significant improvement in bone density one year after the operation (lumbar total T score: -2.2, total femoral T score:-2.2, femoral neck T score: -2.0).

Discussion

Autonomous GC production without specific signs or symptoms of overt hypercortisolism is termed subclinical CS. This condition is usually caused by the presence of a cortisol-secreting adrenal adenoma (7). The diagnosis of subclinical CS generally relies on the presence of two of the following biochemical alterations of the hypothalamic-pituitary-adrenal axis: an unsuppressed plasma cortisol level after a dexamethasone suppression test, an elevated 24-hour urinary free cortisol level, the loss of normal circadian cortisol secretion with an elevated plasma cortisol level at midnight and a low morning serum ACTH level in cases of subclinical CS due to adrenal adenomas (7, 8). The present patient did not show any findings of CS on the physical examination; however, her hormonal results were consistent with a diagnosis of CS caused by an adrenal tumor.

Subclinical CS is associated with several complications, including hypertension, central obesity, impaired glucose tolerance, diabetes and hyperlipidemia (9). Moreover, subclinical endogenous hypercortisolemia can lead to osteoporosis and fractures, as seen in our patient. The similar prevalence of vertebral fractures and low BMD values observed in subjects with overt and subclinical CS have been explained by a longer exposure to cortisol excess, although mild, in pa-

tients with the subclinical disorder (5).

The multifactorial pathogenesis of bone loss in CS depends on the direct and indirect effects of GCs on bone tissue. GCs induce apoptosis of osteoblastic cells and osteocytes, with a consequent decrease in bone formation (10). Therefore, patients with CS have decreased skeletal alkaline phosphatase and osteocalcin levels, indicating an decreased osteoblastic activity. We believe that the elevated alkaline phosphatase level observed in our case was due to the bone fracture. On the other hand, GC excess stimulates osteoblasts to increase the production of RANKL (the receptor activator of NF-kappa B-RANK ligand, which enhances osteoclastogenesis) and reduces the production of osteoprotegerin, which inhibits osteoclastic differentiation. These actions stimulate increased bone resorption (11).

Besides their direct effects on bone, GCs affect bone indirectly via calcium homeostasis. Although GCs reduce calcium absorption from the gastrointestinal tract and renal tubules, the parathyroid hormone levels are not elevated in most patients with GC-induced osteoporosis, indicating that hyperparathyroidism does not play a central role in bone loss in CS patients (8). The parathormone levels observed in our case were also in the normal range. GC excess decreases the osteoblastic production of insulin-like growth factor-I (IGF-I), thus leading to a decrease in bone formation (12). However, the serum IGF-1 levels are reported to be normal in such cases.

Although GCs inhibit estrogen and testosterone production by suppressing gonadotropin release, which plays an additional role in the pathogenesis of GC-induced osteoporosis, large multicenter studies have shown that the increased prevalence of bone fractures in patients with SC is not associated with the gonadal status or duration of menopause (4, 6, 13, 14). Curing CS restores normally coupled bone metabolism and remarkably improves BMD (8). Similarly, in the present case, one year after adrenalectomy a significant improvement in bone density was detected, despite the fact that she was not given any medications or exercise therapies to treat osteoporosis. Moreover, no new bone fractures were detected and her pubic fracture healed remarkably during the orthopedic follow-up (she was followed up for the fracture by an orthopedic team in another city in which she lived; thus, her control plain graphs were not obtained). Based on these findings, we strongly believe that the pubic fracture observed in this case was due to subclinical hypercortisolism regardless of the status of menopause.

Fractures are rarely observed as the first presenting symptom of subclinical CS. Only three patients with subclinical CS presenting with bone fractures have been identified in the literature (2). Two of these patients had multiple vertebral fractures, one of them had calcaneus and femoral neck fractures (2). Therefore, to the best of our knowledge, this case is the first case of subclinical CS that presented with a pubic fracture.

We herein reported the case of a patient with subclinical CS who presented with an uncommon presenting symptom, a bone fracture. This case demonstrates the need to be alert to the possible presence of CS when encountering bone fractures with an unusual localization, even if the patient is in the postmenopausal period.

The authors state that they have no Conflict of Interest (COI).

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