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A Young Adult Woman with Severe Osteoporosis due to Cushing's Disease: A Case Report and Literatures Review

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Abstract

In patients with Cushing's syndrome, the most common cause is iatrogenically excessive use of glucocorticoids. The second most common form is Cushing's disease. Glucocorticoids have a direct effect on bone, causing inhibition of bone formation and enhancing bone resorption. Glucocorticoid-induced osteoporosis (GIOP) is one of the most important side effects of glucocorticoid use, as it could result in an increased risk of fractures. However, severe osteoporosis due to endogenous hypercortisolism was relatively uncommon in the clinical setting, especially for a young adult woman. Therefore, we present a case of a 35-year-old premenopausal woman with Cushing's disease who presented with a low trauma fracture. We hope that our experience of this case will remind doctors to be aware of this unusual complication of Cushing's disease. (J Intern Med Taiwan 2016; 27: 267-273)

Key Words: Cushing's disease, Low trauma fracture, Osteoporosis, Premenopausal woman

Introduction

Glucocorticoid-induced osteoporosis (GIOP) is one of the most important side effects of glucocorticoid use, as it could result in an increased risk of fractures[1].

Glucocorticoids have a direct effect on bone, causing inhibition of bone formation and enhancing bone resorption[1]. Most patients with GIOP are attributed to exogenous glucocorticoid use; however, severe osteoporosis due to Cushing's disease, a disease with endogenous glucocorticoid excess, was relatively uncommon in the clinical setting, especially for a young adult woman. One previous literature reported that in patients with Cushing's disease, women have less evident fractures than men (9% vs 29%, $p< 0.05$)[2]. Therefore, we present a case of a 35-year-old premenopausal woman with Cushing's disease who presented with a low trauma fracture.

Case presentation

A 35-year-old woman was admitted to our orthopedic department because of left pubic bone fracture after falling from a standing height on a rainy day. She was a well-nourished, non-pregnant and premenopausal woman who never delivered

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a child. She ever got multiple rib fractures after motorcycle accident one year before admission. She had regular menstrual cycles and denied smoking, alcohol consumption, taking any medication and drug containing ingredients of steroid or Chinese herb. According to her family history, her grandmother had oral cancer and two aunts had breast cancer. Physical exam showed central fat distribution with overweight based on criteria in Taiwan (body mass index: 26.5 kg/m^2) and bilateral proximal weakness of four limbs (muscle power: 4). She was referred to our oncologist's and endocrinologist's service to rule out pathological fractures.

During follow-up period at our out-patient department, initial lab data revealed serum calcium (Ca): 9.3 mg/dL, inorganic phosphorus (P):3.5 mg/dL, albumin: 4.71 g/dL, alkaline phosphatase (Alk-P): 76 U/L, intact parathyroid hormone (I-PTH): 24.8 pg/mL, serum creatinine: 0.62 mg/dL, hemoglobin: 13.9 g/dL, thyroid-stimulating hormone (TSH): 0.485 μU/mL, free T4: 1.00 ng/dL, normal serum pattern of PEP (protein electrophoresis)/IFE (immunofixation electrophoresis) and negative finding of urine PEP/IFE, cancer antigen 15-3 (CA15-3): 12.0 U/mL, carbohydrate antigen 19-9 (CA19-9): 21.02 U/mL, carcinoembryonic antigen (CEA): 0.90 ng/mL, serum 25-hydroxyvitamin D (25[OH]D): 8.61 ng/mL; all serum data aforementioned were within normal range except for the serum 25[OH]D (Table 1).

Initial image study with chest, thoracolumbar spine and pelvis X-ray showed old fractures at bilateral ribs, old compression fracture at T11 and new fracture of left superior/inferior pubic ramus (Figure 1). Due to family history of breast cancer, mammography for her bilateral breasts was arranged and showed negative finding. Computed tomography from neck to pubic symphysis in 5 mm slice thickness confirmed the fractures corresponding to X-ray findings, generalized decreased bone mineral density and no evidence of visceral malignancy.

Table 1. Laboratory study

	Serum levels	References ranges
Calcium	9.3	7.9~9.9 (mg/dL)
Phosphorus	3.5	2.4~4.7 (mg/dL)
Albumin	4.71	3.5~5.5 (g/dL)
I-PTH	24.8	14~72 (pg/mL)
Alk-P	76	28~94 (U/L)
TSH	0.485	0.35~5.50 (μU/mL)
FT4	1.00	0.76~1.64 (ng/dL)
Hemoglobin	13.9	12~16 (g/dL)
Creatinine	0.62	0.44~1.03 (mg/ dL)
FSH	6.8	2.5~10.2 (μU/mL)
LH	5.5	1.9~12.5 (μU/mL)
Estradiol	49.4	12.5~166 (pg/mL)
Prolactin	12.0	2.8~29.2 (ng/mL)
25[OH]D	8.61	≧30 (ng/mL)
Total protein	7.2	6.3~8.0 (gm/dL)
Albumin	4.1 (56.8%)	3.5~5.5 (gm/dL)
α1-globulin	0.3 (4.5%)	0.1~0.4 (gm/dL)
α2-globulin	0.7 (9.3%)	0.3~1.0 (gm/dL)
β-globulin	0.9 (12.7%)	0.3~1.4 (gm/dL)
γ-globulin	1.2 (16.7%)	0.5~1.8 (gm/dL)
Albumin/globulin	1.31	1.2~1.5

Alk-P, alkaline phosphatase; FSH, follicle-stimulating hormone; FT4, free thyroxine; I-PTH, intact parathyroid hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone; 25[OH]D, 25-hydroxyvitamin D.

Bone scan demonstrated old and new fractures aforementioned and no visible uptake of malignancy. Dual-energy x-ray absorptiometry (DXA) showed low bone mineral density (BMD), the lowest Z-score: -3.8 for her left femoral neck which was compatible with the diagnosis of osteoporosis.

After discussing with endocrinologist, she was admitted to evaluate the severe osteoporosis due to Cushing's syndrome. The screen test with 24-hour urine free cortisol (24-h UFC) was 1298.7 μg/day (normal range: 20.9~292.3 μg/day) and serum ACTH at 8 AM was 68.4 pg/mL (normal reference in our hospital was ≦46 pg/mL). Larger than four times above the upper limit of normal 24-h UFC was documented. Due to positive finding of 24-h

UFC with high serum ACTH level, high-dose dexamethasone suppression test (2mg q6h x 2 days) was performed and the result was positive based on a decrease of more than 50% in serum cortisol and 24-h UFC (Table 2). Pituitary magnetic resonance imaging (MRI) revealed pituitary microadenoma (7 x 5 x 5 mm) in the left-sided pituitary gland (Figure 2). Transsphenoidal surgery for tumor resection due to highly suggestive of pituitary adenoma was performed and the pathological result showed pituitary tissue with positive of immunohistochemical (IHC) study for ACTH and Crooke's hyaline change (Figure 3).

After operation, 8 AM serum cortisol was 1.34 ug/dL (normal reference: 5~23 μg/dL); therefore,

Table 2. High-dose dexamethasone suppression test

	Cortisol (μg/dL)	24-hr UFC (μg/day)
Basal	30.5	1298.7
After high-dose DST	2.05	38.1

DST, dexamethasone suppression test; UFC, urine free cortisol.

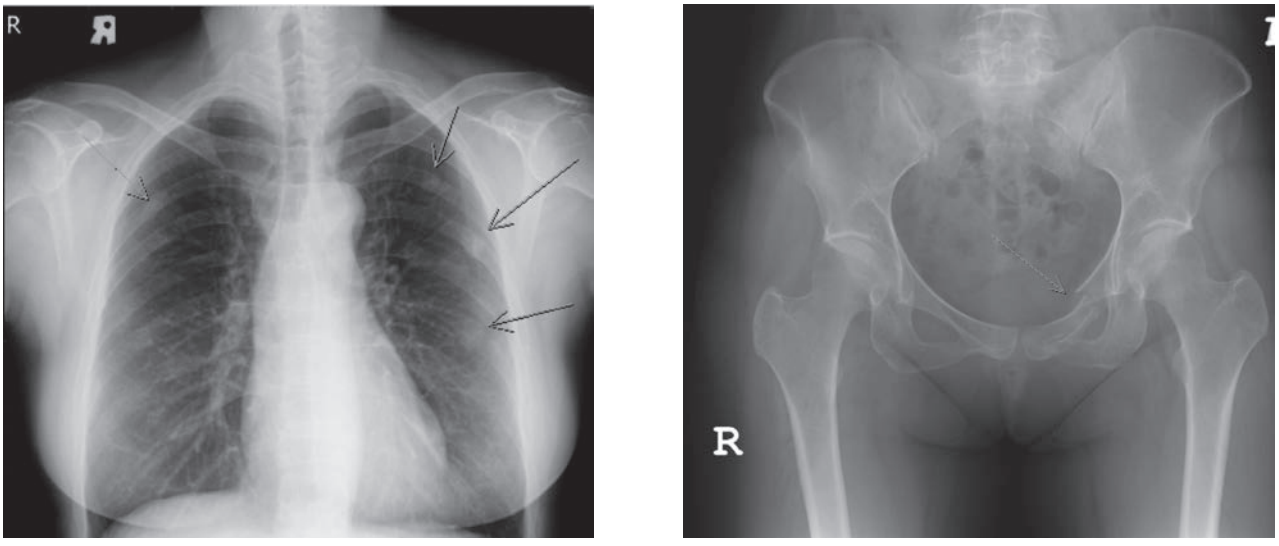

Figure 1. (a) Chest X-ray shows bliateral old ribs fractures. (b) Pelvis X-ray reveals a new fracture of left superior/inferiorpubic ramus.

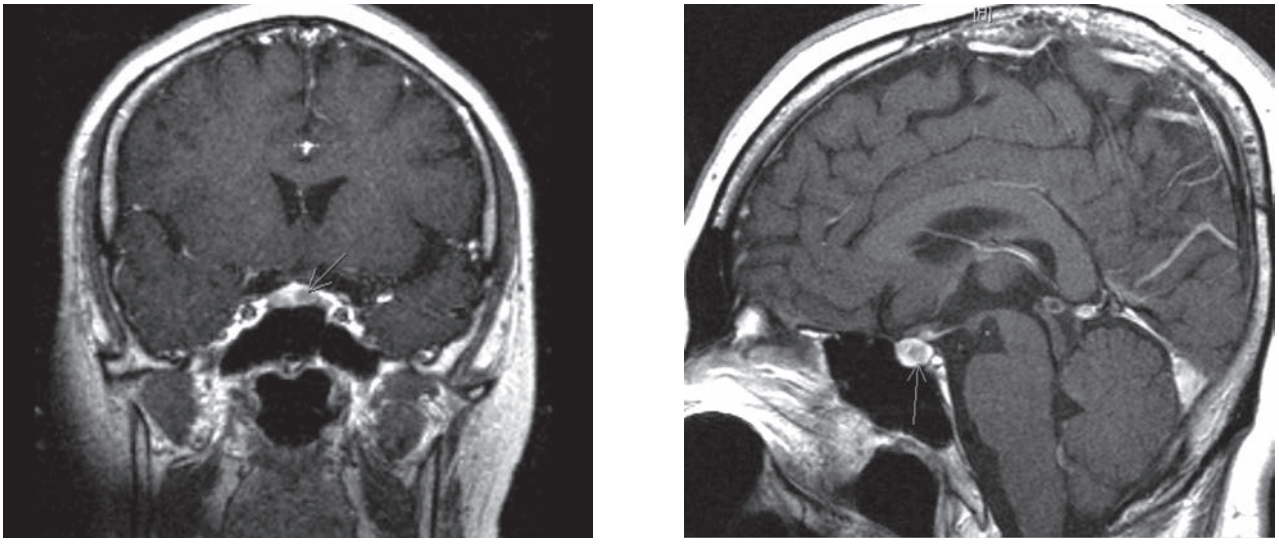

Figure 2. Pituitary MRI revealed microadenoma (7 x 5 x 5 mm) in the left-sided pituitary gland.

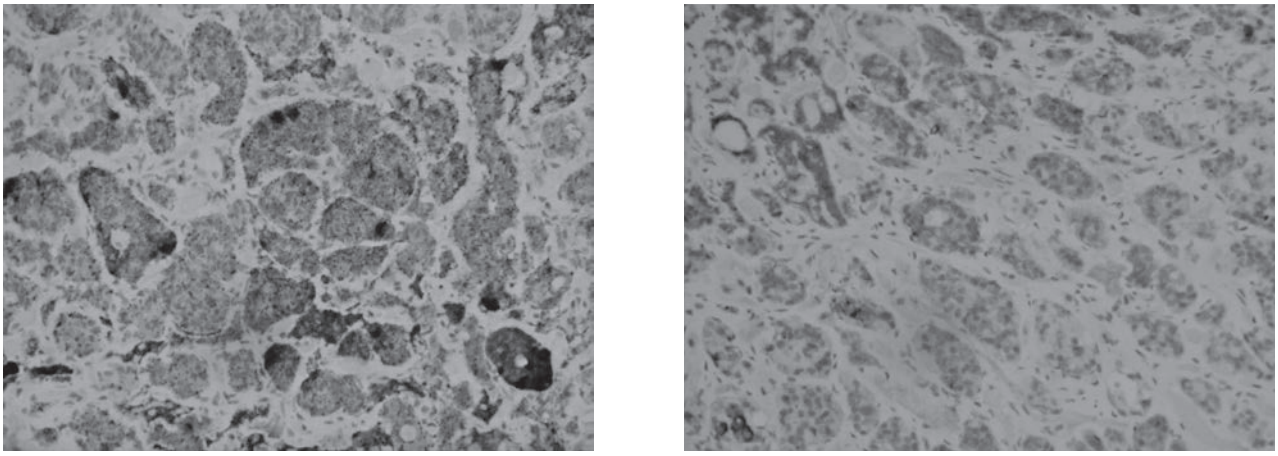

Figure 3. Pathological studies of pituidary adenoma. (a) Immunohistochemistry (IHC) stain for ACTH showed profound cytoplasmic immunoreactivity in the densely granulated cells. (b) Crooke's cells with accumulation of perinuclear cytokeratin highlighted by low molecular weight keratin (CAM5.2) immunostaining.

cortisone acetate 25mg/tab was administered with 2 tablets PC QAM and 1 tablets PC QPM. Due to her stable condition without neurologic deficit and diabetes insipidus, she was discharged. Two months post-operative 24-UFC was 4.5 μg/day and serum ACTH at 8 AM was less than 5.0 pg/mL. Her body weight decreased from 64 to 53 Kg and proximal muscle weakness of four limbs was improved four months after operation. Because of patient's preference, strontium ranelate which has both anti-resorptive and anabolic mechanism was administered to improve her bone mineral density and to prevent her further fragility fracture.

Discussion

Osteoporosis is the most common metabolic bone disease in the world and most patients with osteoporosis are clinically silent until a fracture occurs. In a clinical practice, the fragility fracture which caused by minor injuries, such as falling from a standing height or unnoticed injuries can make the diagnosis of osteoporosis without DXA. DXA is currently the gold standard for the measurement of bone mineral density. However, for premenopausal women, men younger than 50 years and children, Z-score values should be applied instead of T-score and Z-score alone cannot be used to diagnose osteoporosis in premenopausal women[3]. Based on the official position statement of international society for clinical densitometry (ISCD) in 2013, without a fragility fracture, a young woman with BMD below the expected range for age (Z-score $\leq$-2.0) and the risk factors for fracture or secondary causes of osteoporosis, such as administration of glucocorticoid therapy, hypogonadism, or hyperparathyroidism may be defined as premenopausal osteoporosis.

The most patients with osteoporosis were primary osteoporosis, includes postmenopausal osteoporosis and senile osteoporosis. Therefore, premenopausal women with osteoporosis are uncommon and should be studied for a secondary cause, such as estrogen deficiency, glucocorticoid exposure, or hyperparathyroidism[4,5]. According to our patient's history of a fragility fracture, her low Z-score of BMD and documented biochemical studies with pituitary image for Cushing's disease, severe osteoporosis secondary to Cushing's disease was diagnosed. However, the pathologic report for left pituitary lesion revealed pituitary tissue with positive IHC stain for ACTH and Crooke's hyaline change rather than adenoma or hyperplasia.

Crooke's hyaline change, presenting in around 75-80% patients with chronic hypercortisolism of any etiology, means that the normal cortico-

trophs undergo changes with cytoplasmic granules replaced with homogeneous hyaline material[6]. The state of previous hypercortisolism can be confirmed by the presence of any Crooke's hyaline change[7]. If Crooke's hyaline change cells are present, the etiology for hypercortisolism could be pituitary adenoma, ectopic ACTH secretion, primary adrenal lesion or iatrogenic glucocorticoids[8]. According to our patient's clinical history, dynamic biochemical evaluation and imaging study, Cushing's disease was still the most likely diagnosis. The one reason for the diagnosis of Cushing's disease without evidence of ACTH-producing pituitary adenoma or hyperplasia but having pituitary tissue with positive ACTH stain and Crooke's hyaline change was that very small microadenomas can be lost during operation or suction of blood in the surgical field[8]. This reason could explain why our patient was diagnosed with Cushing's disease without evidence of ACTH-producing pituitary adenoma or hyperplasia. Besides, her improvement of clinical manifestation and biochemical remission after surgical intervention also supported our diagnosis.

Although osteoporosis is a common complication of Cushing's syndrome[9]; nevertheless, osteoporotic fractures specific to Cushing's disease is seldom in our clinical practice in Taiwan. Real prevalence of osteoporotic fractures specific to Cushing's disease in Taiwan was unknown. One report ever announced that only two cases were found in five years[10]. Another recent study in Italy, in 81 patients with Cushing's disease (64 women and 17 men), the clinically evident fracture rates were 9% in women and 29% in men[2]. Therefore, the diagnosis of osteoporotic fractures attributed to Cushing's disease needs a high clinical suspicion because most of the symptoms and signs of Cushing's disease, such as obesity, glucose intolerance, hypertension, oligo-or amenorrhea and even osteoporosis were not specific[11]. Hence, osteoporotic fractures with unknown etiology should consult endocrinologist timely based on a clinical suspicion to prevent a delayed diagnosis and treatment of Cushing's syndrome or disease.

The reason for her vitamin D deficiency could be attributed to hypercortisolism because glucocorticoid increases the catabolism of serum 25[OH] D[12, 13]. Although vitamin D deficiency can result in secondary hyperparathyroidism via decreased intestinal calcium absorption and contributes to the cause of osteoporosis, vitamin D deficiency and resistance are still the common causes of osteomalacia[13].

Osteoporosis should not be confused with osteomalacia. In the opinion of osteoporosis, the bone is characterized with porous and brittle ; in the opinion of osteomalacia, the bone is soft. Moreover, significant vitamin D deficiency is usually combined with elevated serum alkaline phosphatase, hypophosphatemia or hypocalcemia and results in characteristic pseudofractures[14]. Although our patient had low serum vitamin D level, she did not have elevated serum alkaline phosphatase, hypophosphatemia, hypocalcemia or pseudofractures. Therefore, her vitamin D deficiency can not mainly account for her severe osteoporosis.

Although newly emerging literatures discussing with treatment of GIOP[1, 15, 16], nearly all of them were focus on GIOP due to exogenous administration of glucocorticoid. Specific discussion for treatment for GIOP due to Cushing's disease was few. Therefore, the most agents for treatment of GIOP due to Cushing's disease such as sclerostin-antibody, denosumab, strontium, teriparatide or selective estrogen receptor modulators, are still lack of data. One relatively specified study for the osteoporotic patient group with Cushing's disease commented that bone impairment and loss of bone mass can recover partially two years after normalization of cortisol levels, either in childhood- or adulthood-onset Cushing's disease; nevertheless, adulthood-onset Cushing's disease could need longer recovery

time or additive therapy to restore bone mass, such as bisphosphonate which can significantly accelerate bone mass recovery[17]. As a result, for our patient with severe osteoporosis due to Cushing's disease, the first priority of treatment was to remove the origin of hormone hypersecretion and pharmacologic therapy to prevent further fracture was the second step. Current recommendations for the treatment of GIOP due to exogenous hypercortisolism can be only partly translated to patients with GIOP due to endogenous Cushing's syndrome[9]. As a result, more studies are still needed to make specific guidelines for these patients.

In summary, a young adult woman with severe osteoporosis due to Cushing's disease was relatively uncommon in our clinical practice. We hope that our experience of this case will remind doctors to be aware of this unusual complication of Cushing's disease.

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一位年輕成年女性罹患因庫欣氏病所導致的嚴重骨鬆骨折：病例報告與文獻回顧

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摘 要

在臨床上大多數的庫欣氏症是導因於醫源性類固醇的使用，而長期使用類固醇會導致骨質疏鬆症的發生進而併發骨鬆性骨折。內生性的類固醇過多症併繼發性的骨鬆骨折在臨床上相對罕見，因此今天我們報告一例35歲年輕女性因為庫欣氏病而導致嚴重骨鬆的病人，希望我們的診斷與治療經驗能提醒各位臨床醫師。