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CASE REPORT

Repeated vertebral compression fractures in young adult may imply functional adrenal tumor

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Abstract

BACKGROUND: Patients with adrenal Cushing's syndrome (ACS) typically present with central obesity, hirsutism, hypertension, or glucose intolerance, which can be easily identified by a clinical physician. However, recognizing those with subclinical CS or those with less common symptoms and signs is challenging to the subspecialist, which can lead to delayed diagnosis and treatment. We report a case who presented with repeated vertebral fractures in 6 months. Typical physical appearance of CS was not shown so that suspicions were not raised until severe osteoporosis was demonstrated from bone marrow density study. From our case report, endocrine tests and image survey should always be considered in young patients with repeat vertebral fractures.

CASE PRESENTATION: A 48-year-old man presented with severe back pain for 3 months. Second and fifth lumbar spine (L2 and L5) vertebral compression fractures were noted from X-ray and magnetic resonance imaging (MRI), and vertebroplasty was performed by orthopedic surgeons. After 1 month, a newly developed compression fracture of the ninth to twelfth thoracic spine and L4–L5 were noted. Severe osteoporosis was noted from the hip bone mineral density test, and he was referred to an endocrinologist for analysis. Serial endocrine tests confirmed hypercortisolism, and subsequent abdomen MRI showed a left adrenal tumor. ACS was diagnosed. Left laparoscopic adrenalectomy was performed, and the patient received cortisol supplement for 12 months. Thereafter, no new fractures were identified.

CONCLUSIONS: ACS should be considered and carefully verified in middle-aged adults who present with severe osteoporosis and repeated vertebral compression fracture.

Abbreviations:

ACS	- Adrenal Cushing's syndrome	BMD	- Bone marrow density
T	- Thoracic spine	CT	- Computed tomography
L	- Lumbar spine	CS	- Cushing's syndrome
MRI	- Magnetic resonance imaging		

INTRODUCTION

The classical symptoms reported in patients with Cushing's syndrome (CS) include central obesity, rounded face, plethora, hirsutism, hypertension, and glucose intolerance. Patients with these symptoms are easily identified by clinical practitioner so that survey for CS can be initiated promptly. However, recognizing patients with subclinical CS who presented with infrequent symptoms and signs is challenging, and treatment will be delayed. Pathological fracture over vertebra, rib, and pubic bone as the primary presentation of adrenal Cushing's syndrome (ACS) was recorded in only few case reports. Adrenalectomy remains the first-line treatment for functional adrenal tumors, and adrenal insufficiency usually develops postoperatively. Glucocorticoid supplement is advised in all patients after surgery, but only few patients require long-term glucocorticoid supplement.

CASE PRESENTATION

A 48-year-old man, a computer numerical control milling engineer, was in relatively good health and performed independent activities of daily living well. His body weight and height were 70 kilogram and 165 centimeter, respectively. Five years ago, he was diagnosed with type 2 diabetes mellitus with HbA1C 8.3. Oral hypoglycemic agent Linagliptin 5 milligram once a day and Glimepiride 1000 milligram twice a day were given initially, then were changed to Insulin Aspart 15 unit once daily in the morning and 10 unit once daily in the evening. He also had hypertension and received Propranolol 10 milligram twice a day, Spironolactone 25 milligram once a day, and Doxazosin 4 milligram once a day at the cardiovascular clinic. Three months before his visit to our clinic, he fell down at work, and second and fifth lumbar spine (L2, L5) compression fractures were discovered from the X-ray (Supplementary Figure 1.a). Lumbar spine magnetic resonance imaging (MRI) revealed L2 and L5 compression fracture with anterior compression of the cauda equina, as well as severe spondylosis and mild kyphoscoliosis of the lower thoracic-lumbar(T-L) spine. Due to his severe back pain and sciatica, L1 and L3 posterior instrumentation and L2 kyphoplasty were performed (Supplementary Figure 1.b).

One month later, severe back pain developed again, and he quit his job due to his limited ability to work. He experienced a spasm of intolerable back pain one day and went to the emergency room for evaluation. The whole spine MRI showed partial compression fractures of the ninth to twelfth thoracic spine (T9–T12) and to the L4–L5 vertebrae (Figure 1.a). T10-L1 kyphoplasty was performed and the screw implant from the earlier surgery was removed (Figure 1.b). However, 1 month later, compression fractures of the T5–T8 were found (Figure 1.c). The Bone marrow density (BMD) study of the right hip showed a T score of −2.6, interpreted as severe osteoporosis.

The patient was then referred to the metabolic clinic. On physical examination, no moon face, buffalo hump, skin pigmentation, axillary, or pubic hair loss were noticed. The areola was pink. He reported recent erectile dysfunction for 2 months, and he took folk therapy without notable improvement. Serial hormone studies showed an elevated level of serum cortisol (Table 1.). A low-dose dexamethasone suppression test (dexamethasone 0.5 mg Q6H for 48 hours) was performed, and the serum cortisol at 8 a.m. was 29.07 ug/dL. CS

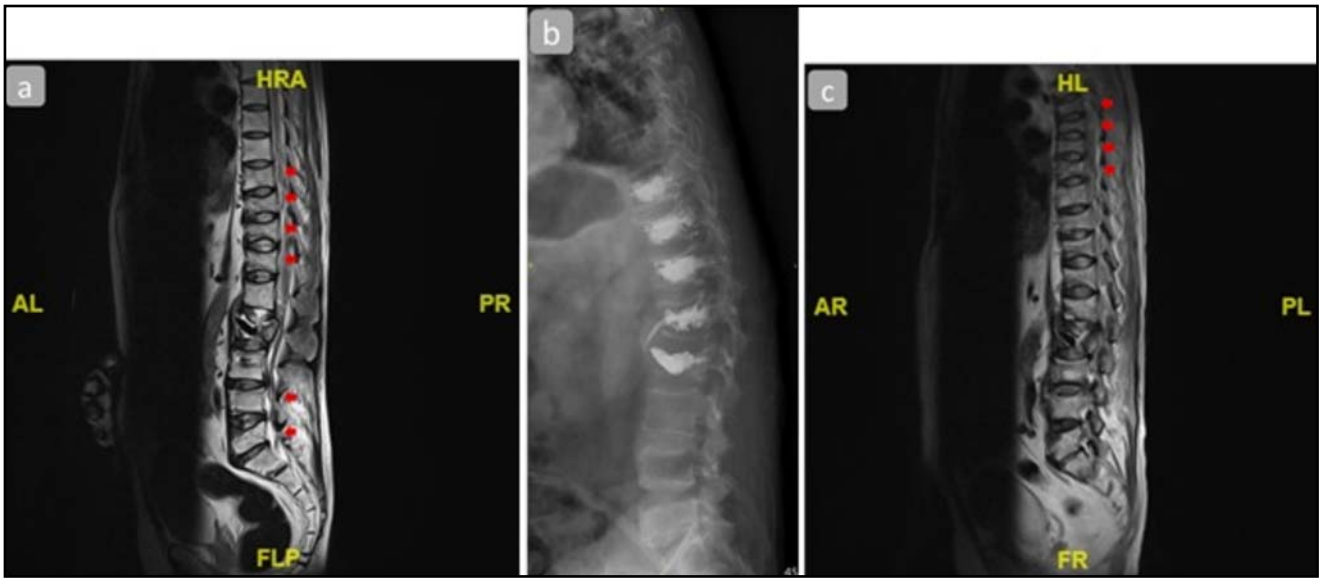
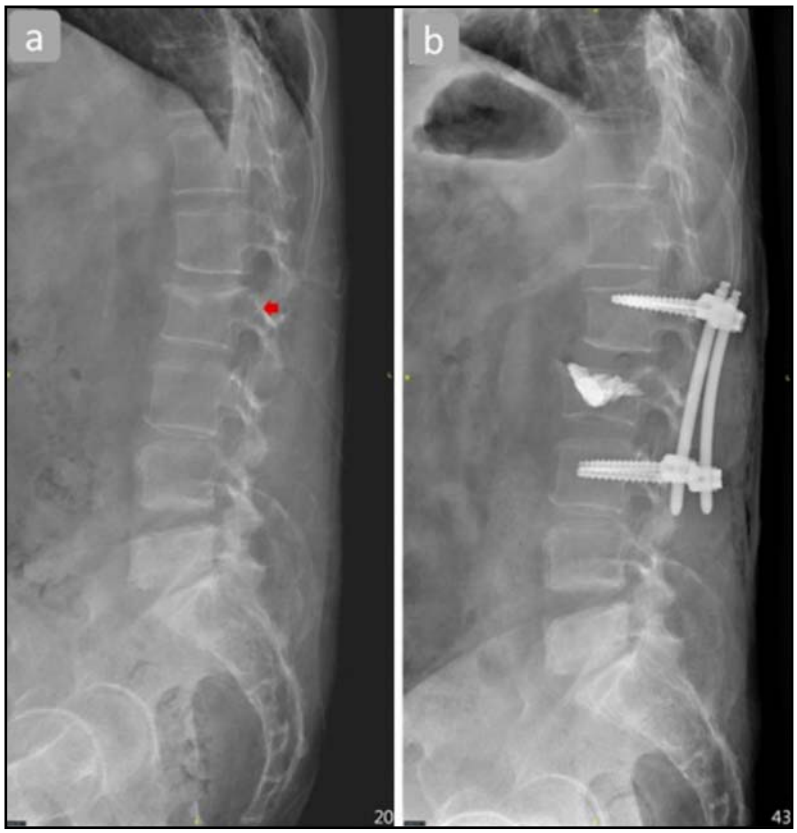


Fig. 1. Whole spine T2-weighted (T2W) image sagittal view showed partial compression fractures of the T9-T12, L4 and L5 (a: red arrow). T10-L1 kyphoplasty was performed and the screw implant from the earlier surgery was removed (b). One month later, followed whole spine T2W image showed new T5-T8 compression fractures (c: red arrow).
T: Thoracic spine, L: Lumbar spine



Suppl. Fig. 1. Lumbar spine lateral view showed second lumbar spine (L2) compression fracture (a: red arrow). L1 and L3 posterior instrumentation and L2 kyphoplasty were performed (b)
L: Lumbar spine

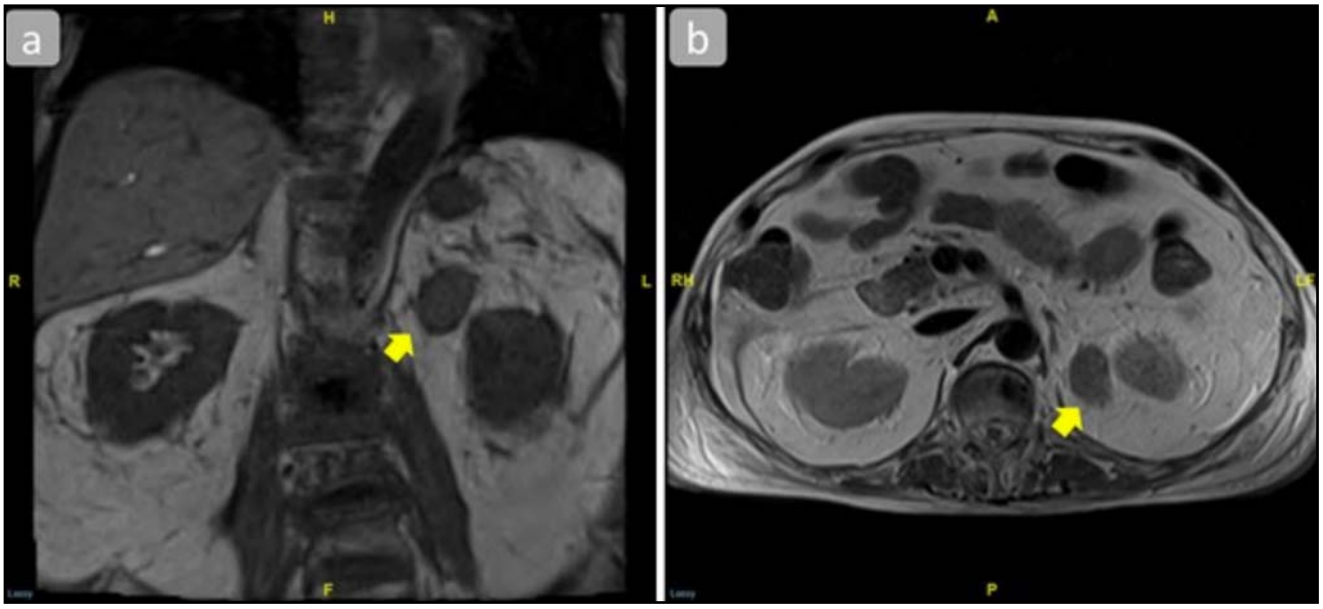
was diagnosed. Findings were noted for a lower level of testosterone with decreased follicle-stimulating hormone and luteinizing hormone levels warranted a diagnosis of secondary hypogonadism. Sella MRI was performed, and no pituitary lesion was found. An abdominal MRI was arranged, revealing a 3.8 × 2.8 × 3.6 cm ovoid mass at the medial limb of the left adrenal gland (Supplementary Figure 2.). ACS was diagnosed. Left laparoscopic adrenalectomy was performed, and the pathology reported cortical adenoma.

Serum ACTH and cortisol level was followed at 1, 3, 6, 12, 18, and 24 months postoperatively. Adrenal insufficiency was observed during follow-up (Supplementary Table 1.). He was prescribed with oral cortisone 37.5 mg per day. For CS-related hypogonadism, testosterone replacement therapy was administered. Denosumab 60 mg injection every 6 months was administered. Thereafter, no new compression fracture was noticed during the 5-year follow-up.

DISCUSSION

CS is described as the result of prolonged exposure to excess glucocorticoids. The excess glucocorticoid could be caused by iatrogenic glucocorticoid supplementation, pituitary ACTH overproduction, ectopic ACTH stimulation, or overproduction of cortisol from a functional adrenal tumor. (Stratakis, 2008, Orth, 1995) Globally, the annual incidence of endogenous CS is 3.2 per million person-years. (Wengander *et al.* 2019) The annual incidence of adrenal CS in Korea has been reported as 1.5 per million person-years. (Ahn *et al.* 2021) The common symptoms and signs of CS are obesity, round face, buffalo hump, abdominal striae, hypertension, and depression. Osteoporosis is a relatively uncommon sign of CS, with variable incidence and reported in 35%–65% of cases. (Tóth & Grossman, 2013, Kawamata *et al.* 2008) Lower BMD and deleterious cortical bone microstructure have been reported of the lumbar spine, femoral neck, and shaft. (dos Santos *et al.* 2015) Bone loss and fracture seem to occur much frequently in adrenal than pituitary CS. (Ohmori *et al.* 2003) A common fracture site was reported of the vertebrae and ribs; other fracture sites, such as pubic bone, have been reported. (Yoshihara *et al.* 2007, Salcuni *et al.* 2015, Lee *et al.* 2014, Arduc *et al.* 2014) However, the correlation of osteoporotic fracture and subclinical Cushing's syndrome is debatable. (Chiodini *et al.* 2008)

The Endocrine Society's Clinical Practice Guidelines suggest consideration of CS if vertebral osteoporosis happened in non-elderly adults. The initial workup includes 2 measurements of 24-hour urinary-free cortisol excretion and either an overnight 1 mg Dexamethasone suppression test or a low-dose Dexamethasone (2 mg/day for 48 hours) suppression test. (Nieman *et al.* 2008) The next step is to determine if CS is ACTH-dependent, by measuring the serum ACTH level between 11:00 p.m. and 12:00 a.m. (Weitzman *et al.* 1971) Once a low plasma ACTH



Suppl. Fig. 2. Adrenal MRI showed one 3.8 × 2.8 × 3.6cm ovoid mass at the medial limb of the left adrenal gland with iso signal intensity in T1W (a: yellow arrow) and T2W image (b: yellow arrow)
MRI: Magnetic resonance imaging

concentration (< 5pg/mL) is identified in a patient with hypercortisolemic, ACTH-independent CS can be determined. (Invitti *et al.* 1999) Following this, a thin-section computed tomography (CT) of the adrenal glands should be performed. A lower unenhanced CT attenuation value (< 10 Hounsfield unit) is usually seen in adrenal adenomas, whereas the presence of necrosis, hemorrhage, and calcification increase the suspicion of carcinoma. On delayed contrast-enhanced CT, the absolute washout of contrast exceeded 50%, which is indicative of benign adenoma. (Blake *et al.* 2006, Pena *et al.* 2000) Other image modalities, such as MRI (T1, T2, chemical shift, and fat-suppression refinement), functional nuclear medicine imaging, and scintigraphy can be used as optimal imaging approaches when the lesion cannot be characterized by CT. (Ilias *et al.* 2007)

Among functional cortical adenoma in the adrenal gland, surgery should always be considered. Open adrenalectomy was the gold standard of treatment; however, laparoscopic adrenalectomy has recently been shown to be equal in mortality but superior in reducing postoperative pain level, morbidity, and length of hospital stay. (Thomas *et al.* 2016) Exceptions are that if any evidence for metastatic carcinoma, adrenal vein, or vena cava involvement is found intraoperatively, conversion to an open approach is suggested. (Stefanidis *et al.* 2013)

Following surgery, patients with both overt ACS and subclinical ACS may experience insufficient cortisol secretion, detected by plasma cortisol levels on the 3rd postoperative day. All patients require postoperative glucocorticoid replacement, but most patients even-

Tab. 1. The hormone levels of the patient and reference values before Dexamethasone suppression

Hormone	Value	Reference	Hormone	Value	Reference
TSH (uIU/mL)	0.113	0.4-4.0	IgF-I (ng/mL)	48.7	113-326
Free T4 (ng/dL)	1.36	0.8-2.0	1.25-(OH)2-D	26.1	25.1-66.1
Intact PTH (pg/mL)	56.2	8-76	25-(OH)-D	10.5	32
FSH (mIU/mL)	1.7	2.2-10	Prolactin (ng/mL)	39.8	< 20
LH (mIU/mL)	1.1	1.8-8.4	Testosterone (ng/dL)	37.7	400-600
ACTH (pg/mL)	8.22	10-60	Cortisol (8 am)(ug/dL)	28.12	4.75-23.27
After Dexamethasone suppression					
Hormone	Value	Reference	Hormone	Value	Reference
ACTH (pg/mL)	10.4	10-60	Cortisol (8 am)(ug/dL)	29.07	4.75-23.27

TSH: thyroid stimulating hormone, T: thyroid hormone, PTH: parathyroid hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone, IgF-1: insulin-like growth factor-1

Suppl. Tab. 1. The hormone changes of the patient post adrenalectomy*

Hormone	Post operation					
	1M	3M	6M	12M	18M	24M
ACTH (pg/mL)	13.41	12.74	15.57	105.3	60.02	18.78
Cortisol (ug/dL)	1.77	0.77	0.56	2.15	2.08	1.15

M: month
*Patient receive cortisone 37.5 mg once a day

tually discontinue glucocorticoid supplementation. (Raffaelli *et al.* 2017)

To our acknowledgement, osteoporotic fractures as the main presentation in subclinical CS was uncommon and were described only in few case reports. (Yoshihara, Okubo, 2007, Salcuni, Morelli, 2015, Lee, Je, 2014, Arduc, Dogan, 2014) We reported a middle-aged male case with ACS who experience multiple vertebral compression fractures in 6 months. Further cohort studies are needed to demonstrate the correlation of osteoporotic fractures and subclinical ACS.

CONCLUSIONS

We reported a case of a 48-year-old man with a functional adrenal tumor who presented with recurrent pathological vertebral fractures over a 6-month period. ACS should be considered and carefully verified in all middle-aged and younger patients with severe osteoporosis and repeated vertebral compression fractures.

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