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Occult Cushing's Syndrome Presenting with Osteoporosis

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Osteoporosis is a frequent complication both of endogenous hypercortisolism and of long-term treatment with corticosteroids, but only rarely is it the major clinical feature with the more characteristic features absent or minimally present. In the two patients presented, hypercortisolism was uncovered only during routine evaluation of osteoporosis. This presentation is probably due to slow progression of the disease and is often associated with so-called black adenoma of the adrenal gland. Secondary causes should be sought in all patients with seemingly "senile" or "postmenopausal" osteoporosis.

Accelerated bone loss with symptomatic vertebral compression or long bone fractures is a well-recognized and frequent complication of long-term corticosteroid therapy (1). In endogenous hypercortisolism (2), osteoporosis is usually detected after the diagnosis has been established in patients with more obvious manifestations, such as amenorrhea, weight gain, or hirsutism. We report two patients who were referred primarily for evaluation of osteoporosis. The usual clinical features of hypercortisolism were absent, and the diagnosis was established only when the urine-free cortisol was measured during the evaluation of osteoporosis.

Case Reports

Case 1

A 52-year-old white woman was referred to Henry Ford Hospital for evaluation of osteoporosis in August 1976. In 1954, she had developed ulcerative colitis during the eighth month of her second pregnancy, followed by postpartum septicemia and pyoderma gangrenosum. Between 1954 and 1961, the ulcerative colitis responded poorly to azulfidine. There were several episodes of acute arthritis of both hands. Corticosteroid therapy was tried but quickly discontinued because of psychotic episodes. In 1961, a total colectomy led to complete resolution of both gastrointestinal and arthritic symptoms. In 1963, after a single episode of right ureteric colic, she passed a stone spontaneously; it was not analysed. In 1971, hypertension was noted for the first time. In May 1976, a traumatic fracture of the right inferior pubic ramus healed well, but the pelvis and lumbar spine were reported as "demineralized" on x-rays. She had felt vaguely unwell for the past several years with nonspecific weakness, lethargy, arthralgias and easy bruising. She denied recent weight gain. The menopause had occurred five years earlier, and she had taken no estrogen replacement.

Physical examination revealed moderate obesity, slightly plethoric face, bruises over both shins, slight wasting of the left thenar eminence and dorsum of both wrists, and an ileostomy. Blood pressure was 180/105 mmHg, height 5'3", weight 142½ lbs.

The x-rays revealed generalized osteoporosis with healed fractures of the right superior and inferior pubic rami without abundant callus. Bone mineral content by photon absorptiometry was 0.513 gm/cm at the proximal site and 0.310 gm/cm at the distal site (−3.50 SD and −5.02 SD, respectively) below the normal mean value adjusted for age, sex, and race). Serum calcium, phosphorus, total protein, alkaline phospatase, BUN and creatinine were all within normal limits. Thyroid function tests were normal. A transiliac crest bone biopsy after double tetracycline labeling showed a moderate decrease in the osteoid surface wth a significant reduction in the osteoblast surface. Total resorption surface, mineral appositional rate, and bone formation rate were within normal limits. Urine-free cortisol excretion obtained as part of the routine workup for osteoporosis was 755 μg/24 hrs. Because of this unexpected finding, the patient was asked to bring old photographs of herself; these indicated evolving, mild Cushing's syndrome. Plasma cortisol was 15.5 μg/dl at 8 a.m. and 16.2 μg/dl at 4 p.m., indicating loss of normal diurnal variation. Two mg of dexamethasone failed to suppress the urine-

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free cortisol excretion (Table I). ^{125}I iodocholesterol scan revealed an adenoma of the right adrenal gland with contralateral suppression of the left adrenal gland. The right adrenal gland was removed; it weighed 8.5 gms and contained a cortical adenoma with black pigment — the so-called black adenoma of the adrenal (3). There was no evidence of micronodular hyperplasia. She required treatement with ACTH for ten months before normal adrenal function was restored. A compression fracture of the L-1 vertebra occurred one month after surgery, but she was subsequently free of backache.

When last seen in January 1980, she had lost the Cushingoid appearance. Her weight was 133 lbs (−9 lbs), height 5'2" (−1"), and there was no significant change in her bone mineral content. Her blood pressure was normal without any antihypertensive therapy. Urine calcium excretion declined progressively (Table I) without further stone episodes.

Case 2

A 62-year-old white man was referred to The Jewish Hospital of St. Louis for evaluation of osteopenia in November 1975. During the previous two years he had sustained several compression fractures of the vertebrae with 6½" loss in height, several fractures of the ribs, and a pathologic fracture of the right inferior pubic ramus and right acetabulum. Ureteric colic due to stones had occurred in 1951, and again in 1961, when a nephrostomy was performed for left hydronephrosis. The stone was composed of calcium oxalate. He did well on a low calcium and oxalate diet, except for one further episode of ureteric colic in 1974. His father and sister also had kidney stones.

On physical examination, none of the usual features of hypercortisolism were present, except for thin and atrophic skin and several purpuric lesions on both hands. Several angiomata were seen on the torso, and the extremities were thin with muscle wasting. Blood pressure was 140/80 mmHg.

X-rays confirmed the old pelvic fractures, compression fractures of the 5th and 11th thoracic and 4th lumbar vertebrae and several rib fractures. Serum calcium, phosphorus, alkaline phosphatase, total protein, BUN, creatinine, fasting blood sugar were all within normal limits. Urine calcium excretion was 333 mg/24 hrs. Immunoreactive parathyroid hormone level was 6 μLEq/ml (normal - 8 μLEq/ml). Plasma cortisol was 14.7 μg/dl at 8 a.m. and 2.3 μg/dl at 4 p.m., which was a normal diurnal change; but urine-free cortisol excretion was 170 and 166 μg/24 hrs. After 2 mg of dexamethasone, urine-free cortisol fell to 64 μg/24 hrs, and after 8 mg to 32 μg/24 hrs (Table II). A transiliac crest bone biopsy showed increased numbers of osteoblasts and osteoclasts; tetracycline uptake was depressed, suggesting diminished new bone formation.

Calciferol 1.25 mg twice weekly and hydrochlorothiazide 50 mg twice daily were started. Later, because of hypercalcemia, the doses were reduced to 1.25 mg weekly and 50 mg three times weekly, respectively. A repeat dexamethasone suppression test confirmed the previous findings, and plasma ACTH was raised (Table II). Because he was a poor operative risk, he was treated with ortho-para DDD (mitotane) 4.5 gms/day for six weeks. The plasma cortisol and urine-free cortisol levels remained elevated. ACTH was 82 pg/ml in the morning and 220 pg/ml in the afternoon. The visual fields were normal.

In September 1976, he was referred to Berkeley California for heavy particle irradiation and was also started on Elipten (α-glutethimide) 250 mg three times a day. After this treatment, his bone pain decreased, he felt better, and was able to move about more easily. Over the next six months, plasma cortisol decreased to 9 μg/dl, urine-free cortisol to 68 μg/24 hrs, and urine calcium 111 mg/24 hrs. There was no recurrence of fractures or kidney stones.

Laboratory Methods

Serum calcium, phosphorus, total protein, alkaline phosphatase, BUN and creatinine were measured by routine autoanalyser methods. Urine calcium was measured by atomic absorption spectrometry (normal <300 mg/24 hrs, for men and <250 mg/24 hrs for women on regular home diet). In Case 1, plasma cortisol and urine-free cortisol were measured by radioimmunoassay (RIA) using a commercially available kit (normal ranges for plasma 7-25 μg/dl (a.m.) and 7-9 μg/dl (p.m.) and for urine 20-90 μg/24 hrs). Plasma ACTH was measured by RIA (Sera Inc, Columbus, Ohio, normal range 15-80 pg/ml). Urine 17 hydroxy steroids were measured by the Porter-Silber method (normal range 4-12 mg/24 hrs). The investigations in Case 2 were performed at different institutions, but the normal ranges were about the same as in Case 1.

Discussion

The usual clinical features of hypercortisolism (both exogenous and endogenous) include marked obesity, moon face, pinkish striae, hypertension, diabetes, and hirsutism. Although common, osteoporosis receives little attention; it can occur in all forms of corticosteroid excess, including the ectopic ACTH syndrome (4).

The effects of hypercortisolism on bone and mineral metabolism are varied both in scope and severity. They include growth retardation in children (5), osteoporosis in adolescents and adults (2,6), with disproportionately greater trabecular bone loss (7), and aseptic necrosis of the femoral or humeral head in adults (8). About 20% of patients with endogenous hypercortisolism have nephrolithiasis (9,10), and they usually have osteoporosis as well (10). Radiographic nephrocalcinosis is rare, but histologic nephrocalcinosis is more common than nephrolithiasis (9). For unknown reasons nephrolithiasis is rare in exogenous hypercortisolism.

The adverse effects of corticosteroid excess on bone and mineral metabolism are mediated by several mechanisms, including decreased intestinal calcium absorption leading to secondary hyperparathyroidism (11), decreased renal

TABLE I
Endocrine Studies
Case 1

		Plasma			Urine		
		Cortisol (μg/dl)		ACTH (pg/ml)	Free Cortisol (μg/24hr)	17-OHCS (mg/24 hr)	Ca (mg/24 hr)
		a.m.	p.m.				
Control	12-13-76	24.1					294
Control	2-2-77	15.5			755		229
Control	3-3-77	18.5					
Control	3-11-77	19.3		49			
6 hr infusion	3-11-77	21.5					
Control	4-2-77	18.3			590		
Control	4-3-77	18.4		53	655	16.4	
Dexame* 2 mg/day	4-4-77	17.5			530	16.3	
Dexame 2 mg/day	4-5-77	19.4		63	624	17.8	
Dexame 8 mg/day	4-6-77	16.2			479	17.9	
Dexame 8 mg/day	4-7-77	15.3			463	18.3	
Metyrapone 750 mg x 6	4-8-77			29		15.8	
day #1	4-9-77					10.3	
day #2	4-10-77			134		15.0	
	4-11-77	12.6	4.3				
Right Adrenalectomy	5-16-77						
	9-20-77			82		6.0	157
ACTH I.M. 40 units	11-20-77						
	11-21-77	10.4	5.5			6.0	
	11-23-77	4.4	2.4				
	11-24-77					7.0	
ACTH I.M. 40 units	11-26-77	2.0	2.9				
	11-27-77	10.4	2.2				
Off ACTH but while on	2-13-78	9.5					46
replacement therapy	1-6-79	21.6	7.0				
	2-14-79						34
	1-22-80						91

* Dexamethasone

tubular reabsorption calcium leading to hypercalciuria (11,12), and decreased bone formation and increased bone resorption (13,14). All these effects contribute to a net negative calcium balance that leads to osteoporosis and, in some patients, to nephrolithiasis.

Both of our patients were referred initially for evaluation of severe osteoporosis and nephrolithiasis. The usual signs of hypercortisolism were minimal or absent, and the diagnosis was made during a routine screening for other causes of osteoporosis. Besides these two cases, five other patients have been reported (4,6,15,16) with skeletal symptoms as the major presenting feature of hypercortisolism (Table III). The duration of skeletal symptoms before the diagnosis of hypercortisolism was two to seven years. Two of the seven patients had nephrolithiasis in addition to severe osteoporosis, and the first patient was initially thought to have primary hyperparathyroidism (15).

Adrenal pathology was available in five of the seven cases. The remaining two patients were thought clinically to have bilateral adrenal hyperplasia. Black or brown pigmentation was found in three, but no mention was made in the other two. "Black adenoma" (or hyperplasia), previously thought to be nonfunctional, is now recognized as a distinct clinical entity which may be associated with either hypercortisolism or aldosteronism (17,18). The deposition of pigment (black, brown, or blue) in the adrenal gland is believed to represent an "exhaustion" or "wear and tear" phenomenon (19) that indicates a long-standing disease pro-

TABLE II
Endocrine Studies
Case 2

		Plasma				Urine		
		Cortisol (μg/dl)		ACTH (pg/ml)		Free Cortisol (μg/24hr)	17-OHCS (mg/24 hr)	Ca (mg/24 hr)
		a.m.	p.m.	a.m.	p.m.			
Control	11-17-75	14.7	2.2			170		333
Control	11-18-75					166		299
Dexame* 2 mg/day	11-19-75					64		
Dexame 2 mg/day	11-20-75					32		
Dexame 8 mg/day	11-21-75					26		
Dexame 8 mg/day	11-22-75					13		
Control	2-11-76	16.0	26.0			314	12.6	
	2-12-76							
Dexame 2 mg/day	2-13-76							
Dexame 2 mg/day	2-14-76	11.5		140			7.3	
Dexame 8 mg/day	2-15-76							
Dexame 8 mg/day	2-16-76	<2.0		60			2.0	
	2-17-76							
Control	2-18-76	20.0		17		1029	2.0	
Metyrapone 750 mg x 6	2-19-76	16.0					30.0	
day #1	2-20-76						18.0	
day #2	2-21-76						18.0	
Control	4-13-76							
Control	4-14-76	15.5	13.7	140	150	553	15.3	
Alpha 1-24 ACTH I.V.	4-15-76							
0 min	(basal)	23.0						
30 min		39.0						
60 min		54.0						
	9-6-76	29.0	26.0	(after overnight 1 mg Dexame suppression)				
	9-7-76	28.7	25.8					
Proton beam irradiation of pituitary	9-10-76							
	10-29-76						107	111
	11-18-76	22						
	12-29-76	23						
	3-17-77	16						
Dexame 1 mg/overnight	3-23-77	15						
	4-18-77	9						
Dexame 1 mg/overnight	4-20-77	8						
	6-8-77	10						
Dexame 1 mg/overnight	6-9-77	6						

* Dexamethasone

cess. This would explain the milder symptoms and signs of hypercortisolism in patients presenting with skeletal manifestations, as well as the frequent finding of pigmented adrenal glands. Apparently, the clinical effects of corticosteroid excess, as of other endocrinopathies, vary with the rate of progression. Rapid progression, as in some patients with the ectopic ACTH syndrome, causes predominant electrolyte disturbance, whereas "normal" progression gives rise to classic Cushing's syndrome, and slow progression to predominant osteoporosis (Table IV).

Physicians should always suspect hypercortisolism in patients with unexplained osteoporosis, especially when the loss of bone is more severe than would be expected for

TABLE III

Seven Patients with Hypercortisolism and Osteoporosis

Case/Age/Sex	Presenting Feature	Duration of Skeletal Symptoms	X-Ray Findings	Initial Clinical Diagnosis	Adrenal Pathology
1/41/M (15)	Back pain, loss of height	2 years	Multiple rib and vertebra compression fractures	Primary hyperparathyroidism	Bilateral micronodular hyperplasia; pigment not mentioned
2/19/M (6)	Chronic back pain	2 years	Vertebral compression fractures	Idiopathic osteoporosis	Micronodular adrenal disease with brown pigment
3/23/F (6)	Spontaneous rib fracture	3 years	Multiple rib fractures	Idiopathic osteoporosis	Micronodular adrenal disease with black pigment
4/46/M (16)	Right hip pain	7 years	Multiple rib fractures, aseptic necrosis of femoral head	Aseptic necrosis of femoral head	Not available; hyperplasia by lab evidence
5/64/F (4)	Back pain, rib fractures, purpuric skin lesions	2 years	Multiple rib and vertebral compression fractures	Metastatic medullary thyroid carcinoma	Bilateral cortical hyperplasia; pigment not mentioned
6/52/F (Case 1)	Back pain, kidney stones	2 years	Healed fracture of right inferior pubic ramus	Postmenopausal osteoporosis and nephrolithiasis	Right adrenal black adenoma
7/62/M (Case 2)	Spontaneous rib fractures, kidney stones	2 years	Multiple fractures of ribs, vertebrae, pubic rami and acetabulum	Idiopathic osteoporosis	Not available; see text

TABLE IV

Relationship Between Progression of the Disease and Clinical Manifestations in Patients with Hypercortisolism

Progression	Clinical Presentation	Adrenal Pathology
Rapid	Hypokalemia	Ectopic ACTH syndromes
"Normal"	Classic Cushing's	"Usual" (adenoma or hyperplasia)
Slow	Osteoporosis and/or nephrolithiasis	Pigmented (adenoma or hyperplasia)

their age and sex. It is important to avoid delay in diagnosis, since osteoporosis in this disease is preventable but not reversible (2). Urine-free cortisol is a more sensitive test than the plasma cortisol, because it is an index of the integrated cortisol secretion rate. This test should be obtained routinely as a part of the evaluation of osteoporosis.

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