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CASE REPORT

MENOPAUSAL OSTEOPOROSIS IN PATIENTS WITH BILATERAL ADRENAL TUMORS

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Summary

Introduction: Bilateral adrenal tumors have a wide area of etiologies but most of the cases are actually incompletely known. In some situations a persistent mild hypercortisolemia associates subclinical Cushing's syndrome. Menopausal subjects with adrenal masses might be admitted for osteoporosis with a dual component: the lack of estrogens and elevated plasma cortisol. Metabolic improvement after adrenalectomy involves also the skeleton. However there are cases when surgery is refused and further close follow-up including bone is needed. We introduce 2 cases with a long medical history of both osteoporosis and bilateral adrenal tumors which suggest a potential connection between these two conditions.
Cases: A 63-year female is known since the age of 60 with a right adrenal tumor associating a low plasma ACTH and partial suppression of cortisol after dexamethasone test. At age of 62 a second tumor at the level of left adrenal was identified. Since the age of 58 she was found with osteoporosis and specific therapy was offered to her, associating the indication of continuing it once the persistent cortisolemia was identified (and surgery refused by the patient). A 70-year female was treated 8 years with oral bisphosphonates for menopausal osteoporosis (menopause was at 45 years). At age of 68 she was accidentally found with a left adrenal tumor of 2 cm. Despite improvement of Bone Mineral Density to a lumbar L1-4 T-score of -2.3 SD, endocrine profile was consistent for mild endogen glucocorticoid secretion so anti-osteoporotic therapy was continued. 1 year later, the suppression of ACTH was stationary while CT scan revealed a second tumor (on the right) of 1.19 by 0.79 cm.
Conclusion: Persistent mild hypercortisolemia- associated bilateral adrenal tumors might change the decision of therapy in cases with long term menopausal or age-related osteoporosis

Résumé

Ostéoporose de ménopause chez les patients atteints de tumeurs des glandes surrénales bilatérales

Introduction: Les tumeurs surrénales bilatérales ont une vaste zone d'étiologies mais la plupart des cas sont effectivement incomplètement connus. Dans certaines situations, une hypercortisolémie persistante légère associe le syndrome Cushing subclinique. Les sujets ménopauses avec des masses surrénales peuvent être admis à l'ostéoporose avec une double composante: le manque d'oestrogènes et de cortisol plasmatique élevé. L'amélioration métabolique après adrenalectomie implique également le squelette. Cependant, il y a des cas où la chirurgie est refusée et un suivi plus proche incluant l'os est nécessaire. Nous présentons 2 cas avec une longue histoire de l'anamnèse à la fois de l'ostéoporose et des tumeurs bilatérales surrénales qui suggèrent un lien potentiel entre ces deux conditions.
Les cas: Une femme de 63 ans est connue depuis l'âge de 60 ans avec une tumeur surrénale droite associant un ACTH plasmatique faible et partiellement suppression de cortisol après le test de la dexaméthasone. A l'âge de 62 une tumeur seconde au niveau de la surrénale gauche a été identifiée. Depuis l'âge de 58 ans elle a été trouvée avec l'ostéoporose et la thérapie spécifique lui a été offerte, associant l'indication de sa poursuite dès que le cortisolémie persistante a été identifiée (et la chirurgie refusée par le patient). Une femme de 70 ans a été traitée pendant 8 ans avec des bisphosphonates par voie orale pour la ménopause (ménopause à 45 ans). À l'âge de 68, elle a été accidentellement trouvée avec une tumeur surrénale gauche de 2 cm. Malgré l'amélioration de la densité minérale osseuse au niveau lombaire L1-4 T-score de -2,3 SD, profil endocrinien était compatible pour les formes légères de la sécrétion endogène de glucocorticoïdes de sorte que la thérapie

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especially if adrenalectomy is not performed. Which is the exact component of bone loss caused by abnormal adrenal profile is difficult to establish but an individual decision is required.

Abbreviations: IV = intravenous, cm = centimeter, μg = microgram, CT = computed tomography, BMD = Bone Mineral Density, ACTH = Adrenocorticotropic Hormone, DXM = Dexamethasone

Key words: osteoporosis, adrenal tumor, bilateral adrenal masses

antiostéoporotique a été poursuivie. 1 année plus tard, la suppression de l'ACTH était stationnaire tandis que la CT a révélé une seconde tumeur (à droite) de 1,19 par 0,79 cm.

Conclusion: L'hypercortisolémie - associée aux tumeurs surrénales bilatérales pourraient changer la décision de la thérapie dans les cas avec ostéoporose de la ménopause ou liés à l'âge, surtout si la surrénalectomie n'est pas effectuée. Laquelle est la composante exacte de la perte osseuse causée par le profil surrénal anormal est difficile à établir, mais une décision individuelle s'impose.

Mots clefs: ostéoporose, tumeur surrénale, tumeurs surrénales bilatérales

Introduction

Bilateral adrenal tumors associate a wide area of potential etiologies but, apart from classical syndromes as seen in Multiple Endocrine Neoplasia Syndrome type 2, familial pheocromocytoma, bilateral adrenal hyperplasia, Carney syndrome, bilateral adrenal masses (including associated hyperplasia) causes are still incompletely known. (1,2,3,4,5) Generally, one out of ten adrenal tumors (or even less) tend to correlate a bilateral condition. (6) Adrenal venous sampling is useful in selected cases but it is not available in many centers. (7) In some situations a persistent mild hypercortisolemia may associate the incomplete Cushing's syndrome phenotype or subclinical pattern. Menopausal subjects with adrenal masses might be admitted for osteoporosis with a dual component: the lack of estrogens and sustained small increase of plasma cortisol. (8,9) Metabolic improvement after adrenal surgery involves also skeletal status. However, there are cases when adrenalectomy is refused by the patient and further close follow-up including the bone is needed. (8,9)

Objective

We introduce two female cases with a long medical history involving both osteoporosis and adrenal tumors which suggest a potential connection between these two conditions.

Material and Methods

This is a case series report. Central Dual-Energy X-Ray Absorptiometry (GE Lunar Prodigy) was performed providing Bone Mineral Density (BMD). Calculated T-score based on BMD allowed the diagnosis of osteoporosis. (10) The adrenal profile was evaluated based on imagery and endocrine tests. The informed written consent was obtained from both patients. The females were diagnosed and treated during years in different secondary and tertiary Endocrine Romanian Centers.

Results

Case 1

A 63-year old smoker female is known since the age of 60 with a right adrenal tumor which was accidentaly indentified while performing a routine abdominal ultrasound. At age of 62 a second tumor at the level of left adrenal was identified. Since the age of 58 she was found with osteoporosis and specific therapy was offered to her.

The medical family history includes: mother with ischemic coronary heart disease; a brother and father with duodenal ulcer.

The personal medical history associates: duodenal ulcer, renal kidney stones, mild multi-nodular goiter with normal thyroid function, hypercholesterolemia. She had spontaneous menopause at age of 47 and no further hormonal replacement therapy was given to her.

Because of prior gastrointestinal condition the patient was treated with Ibandronat IV (intravenous) every 3 months together with daily orally vitamin D supplements. Annual DXA check-up pointed a BMD improvement so the therapy was continued for 3 years. (Table 1) No fracture

Age (years)	58		59		60		61		62		63
Lumbar L2 -4 BMD (g/sqcm)	0.852	Ibandronate IV	0.856	Ibandronate IV	0.857	Ibandronate IV		Drug holiday		Ibandronate IV	0.888
T-score (SD)	-2.9		-2.8		-2.7						-2.4
Z-score (SD)	-1.9		-1.7		-1.4						-1.6
CT max diam of the right adrenal tumor (cm)									3.1		3.25
CT max diam of the left adrenal tumor (cm)									N		1.37

Table 1 - The medical history of osteoporosis (based on lumbar DXA results) and abdominal computed tomography on a menopausal woman

BMD = Bone Mineral Density; CT max diam = maximum diameter of the adrenal tumor at IV contrast computed tomography examination; N=normal aspect

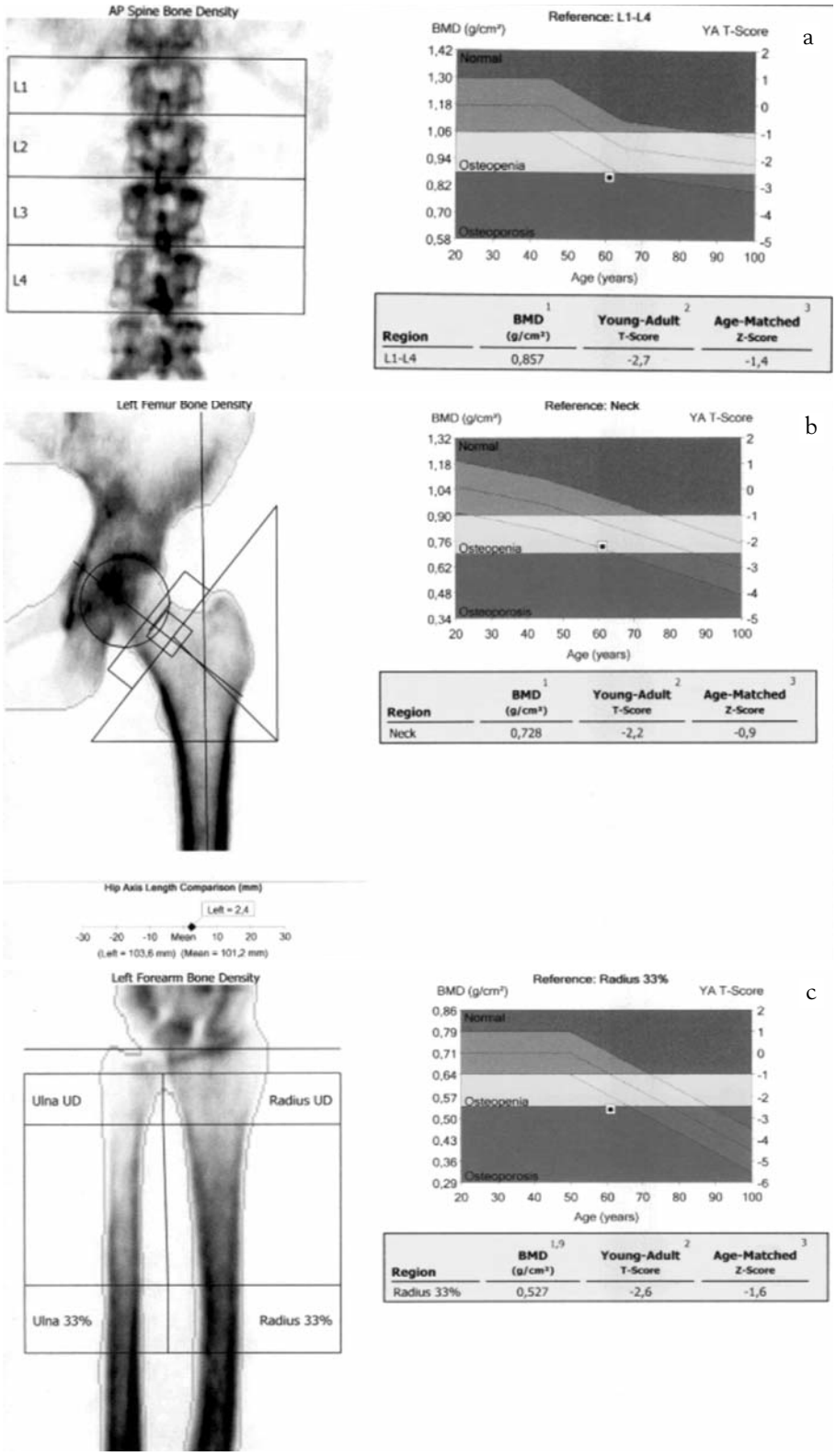

Figure 1 - Central DXA at lumbar, hip and distal radius (non-dominant forearm) on a 60-year female (menopausal age at 47 years)

a. Lumbar DXA

b. Left Hip DXA

c. Left Distal Radius DXA

was registered (including at profile X-Ray scan at the level of thoracic and lumbar spine). (Fig. 1) A year of drug holiday was recommended noting the good clinical outcome. At age of 62, the renal ultrasound was indicated in order to evaluate the status of previous stones and pointed a right adrenal mass. IV contrast computed tomography (CT) confirmed a solid tumor of 2.9 by 2.5 by 3.1 centimeter (cm) with negative spontaneous density of -13 Hounsfield Units. Normal left adrenal tumor and kidney aspect was also described. The endocrine tests showed low-normal ACTH (Adrenocorticotropic Hormone) of 8.48 µg/dL (Normal levels between 3 and 66 pg/mL), morning

plasma cortisol of 27.31 μd/dL (Normal levels between 6.2 and 19.4 μd/dL). The suppression test for 2 days of 2 milligram Dexamethasone (DXM) revealed a mild secretion: morning plasma cortisol of 2.13 μd/dL (Normal ranges of less than 1.8 μg/dL). No other adrenal excess was identified. Surgery was recommended but the patient refused it. However, anti-osteoporotic therapy was re-introduced (IV Ibandronate every 3 months) together with vitamin D supplements because of mild persistent hypercortisolemia. One year later, the hormonal profile was similar while the CT scan showed a right adrenal mass of 2.63 by 2.79 by 3.25 cm (of oval shape, well delimited, contacting the inferior cave vein, and the fifth and sixth liver segments) but also a newly discovered left adrenal tumor of 0.99 by 1.37 by 1.01 cm. (Fig. 2) The lumbar DXA showed an improvement of BMD. Further close follow-up is recommended.

Case 2

A 70-year old smoker female associates hypercholesterolemia and duodenal ulcer; she was treated for almost 8 years with orally Ibandronate (150 mg per months) with vitamin D and calcium supplements for menopausal osteoporosis (the menopausal age is 45 years). At age of 68 she was accidentally found with a left adrenal tumor of 2 cm (first at ultrasound and then confirmed at CT examination). After 8 years of therapy a consistent improvement of BMD showed a lumbar L1-4 T-score of -2.3 SD (BMD of 0.905 g/sqcm, Z-score of -0.8 SD; hip BMD of 0.881 g/sqcm, T-score of -1 SD, Z-score of 0.3 SD; femoral neck BMD of 0.884 g/sqcm, T-score of -1.1SD, Z-score of 0.4 SD). The endocrine profile was consistent for mild endogen glucocorticoid secretion. (Table 2) Surgery was refused by the patient thus anti-osteoporotic therapy was continued (35 mg weekly Risendronate per os). One year later, the suppression of ACTH was stationary while the CT scan revealed the left adrenal of 1.38 by 1.91 cm and another contra-lateral of 1.19 by 0.79 cm. (Table 2) She was further followed-up with an adrenal status quo. (Table 2) DXA showed a less good outcome based on lumbar T-score of -2.6 SD (BMD of 0.873 g/sqcm, Z-score of -1.1 SD; femoral neck: T-score of -1.1 SD, BMD of 0.889 g/sqcm, Z-score of 0.4 SD; total hip T-score of -1.1SD, BMD of 0.871 g/sqcm, Z-score of 0.2SD thus one more year of bisphosphonate was recommended.

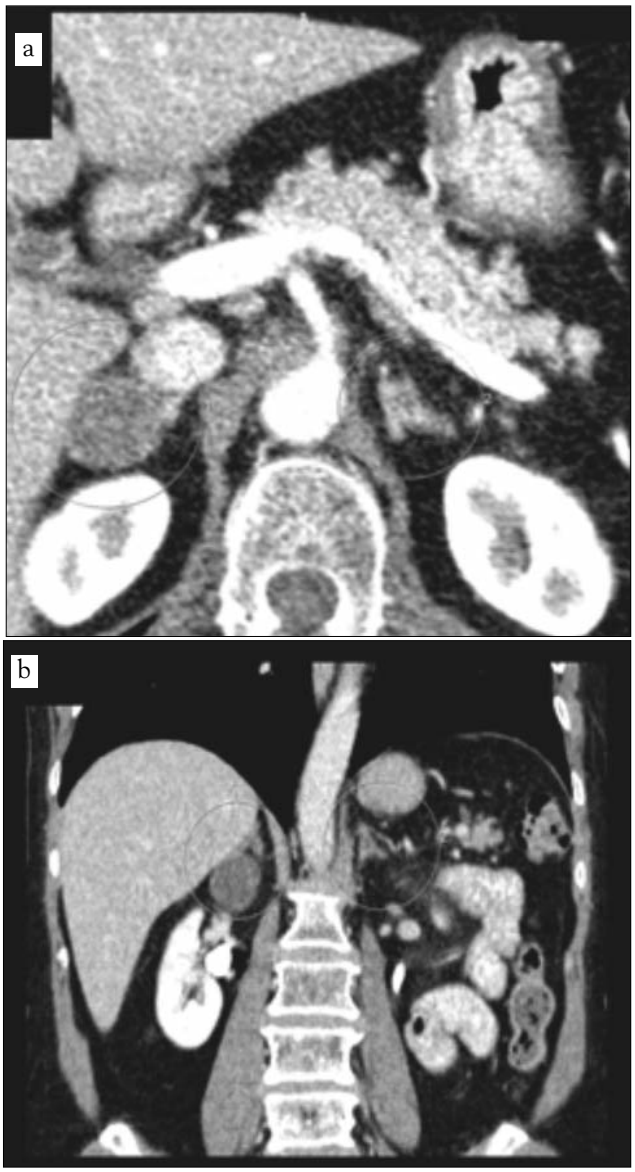

Figure 2 - IV contrast Computed Tomography on a female aged of 63 with bilateral adrenal tumors, mild persistent hypercortisolemia and treated osteoporosis

a. Transversal plane; b. Coronal plane

DISCUSSION

A few aspects are necessary to be discussed in correlation with these two cases.

First, it is the idea of an adrenal incidentaloma (including bilateral synchronous or asynchronous incidentalomas) starting from an accidental abdominal ultrasound, for instance, related to a prior kidney stones condition. (11) The term of "incidentaloma" was aggressively extended during the last years based on largely use and progress of different imagery scans. Both of the patients had an abdominal ultrasound done mostly related to phosphor-calcium metabolism disturbances.

Second, the mild persistent endogenous production of glucocorticoids or subclinical Cushing's syndrome is positive in both cases based on low or low-normal ACTH and non-inhibition of plasma cortisol after low-dose DXM suppression test. (12) However, the results were not precisely stationary during years of follow-up and no classical phenotype with arterial hypertension or diabetes mellitus was actually registered in neither of cases. (13) Osteoporosis, on the other hand, might have a more severe outcome or a less response to therapy in correlation with the adrenal condition (which is probable for the second case). (14) After adrenal surgery, some of the metabolic disturbances are corrected but there is not a specific pattern. (15,16)

Because of the previous renal lithiasis history, the first subject did not tolerate the ingestion of calcium supple-

Table 2 - Persistent hypercortisolemia on a female patient with bilateral adrenal tumors and previously treated osteoporosis

BMD = Bone Mineral Density; CT max diam = maximum diameter of the adrenal tumor at IV contrast computed tomography examination; N = normal aspect; DXM = Dexamethasone; NA = not available; ACTH = Adrenocorticotropic Hormone

Age (years)	68		69		70	
Lumbar L2-4 BMD (g/sqcm)	0.905	Risendronate 35 mg per week	NA	Risendronate 35 mg per week	0.873	Risendronate 35 mg per week
T-score (SD)	-2.3		NA		-2.6	
Z-score (SD)	-1		NA		-1.1	
CT max diam of the right adrenal tumor (cm)	N		1.19		1.18	
CT max diam of the left adrenal tumor (cm)	2		1.91		1.34	
Baseline ACTH (pg/mL) N: 3-66 pg/mL	1		5.1		7.1	
Morning Plasma Cortisol (µg/dL) N: 6.2 and 19.4 µd/dL	16		14.7		29.2	
Plasma Cortisol after DXM 2days*2mg (µg/dL) (N:<1.8.4 µd/dL)	1.13		NA		1.6	

ments. The type of anti-osteoporotic drugs was chosen based on digestive profile of the women rather than adrenal hyper secretion. A drug holiday was considered useful in the first case but the identification of cortico-adrenal disturbances (in the absence of surgery) indicated resumption of bisphosphonate. (17) The second case introduced the idea of how long to treat menopausal or age-related osteoporosis. Even new theories reduced the useful indication to 3-5 years; currently the idea of treating for "how long it is necessary" based on individual risk profile assessment is applied here. (18)

Third, as limits of our series cases we mention the lack of tumor pathological confirmation (because no surgery was done) and a deficiency of least significant change data which are not provided by DXA machine we had to assess.

Conclusion

Persistent mild hypercortisolemia- associated bilateral adrenal tumors might change the decision of therapy in cases with long term menopausal or age-related osteoporosis especially if adrenalectomy is not performed. Which is the exact component of bone loss caused by abnormal adrenal profile is difficult to establish but an individual decision is required.

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Conflict of interest: none

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