Menopausal status and severe pathological conditions: is there a place for bone and neuroendocrine markers?

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ABSTRACT

Introduction. *Menopause involves skeletal losses, which may be accelerated by breast cancer and associated therapy, as aromatase inhibitors.*

Case presentation. *A 67-year old Caucasian female underwent 2 years ago a right mastectomy for breast cancer (invasive ductal carcinoma of mucinous type; 85-90% positive reaction of estrogen receptor). Synchronously, she presented, at computer tomography, a left adrenal hyperplasia, stationary during follow-up. Tamoxifen was continued for two years, then a switch to anastrozole was done for the last four months. On admission, the assays showed a non-secretor adrenal pattern, with negative neuroendocrine markers, including serum serotonin. Bone profile pointed mild hypercalcemia with normal parathormone levels, as well as bone turnover markers and 25-hydroxyvitamin D (negative imagery scan for bone metastases). Dual-Energy X-Ray Absorptiometry (DXA) revealed osteopenia with a mid deterioration of Trabecular Bone Score (TBS) at 1220. Further continuation of aromatase inhibitor is recommended, in association with vitamin D supplementation and monthly oral risendronate, good hydration and serial calcium assays.*

Conclusion. *Modern approach of menopausal breast cancer with aromatase inhibitors increases the speed of age-related bone loss, while detailed imagery may find otherwise unknown artefacts as non-tumour enlargement of adrenal glands. Whether neuroendocrine markers like 5-hydroxytryptamine will find a place in this particular context, apart from traditional bone indices, is still difficult to establish.*

Keywords: breast cancer, osteopenia, serotonin

INTRODUCTION

Menopausal state, either due to a physiological process or surgical intervention, involves a large panel of changes, while the risk of some malignancies is increased (1-3). The management of menopause is complex, being related to a multi-disciplinary team (1-3). Two of the hot topics are represented by high breast cancer incidence after menopause and age-related, as well as estrogen deficiency-associated bone loss, which causes osteoporosis and fragility fractures (4-6).

We aim to introduce a case of a menopausal woman, diagnosed and treated with a mammary malignancy, who was further followed up for

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skeletal status anomalies in a context of unilateral adrenal hyperplasia and an episode of hypercalcemia with normal parathormone levels.

CASE PRESENTATION

This is a 67-year old non-smoking Caucasian female who was admitted after she had suffered twenty four months ago, a total right mastectomy for breast cancer. The surgical excision and anaesthesia procedures went well, without complications. The pathological report showed invasive ductal carcinoma of mucinous type and immunohistochemistry revealed 85-90% positive reaction of estrogen receptor, 80-85% positive reaction of progesterone receptor, negative Cerb B expression, and a value of proliferative index Ki67 of 5-10%. Synchronously, she presented, at computer tomography scan, a left adrenal hyperplasia (an enlargement of the gland that did not associate a well defined mass) and this non-tumoral adrenal aspect was stationary during follow-up. She is known with mild arterial high blood pressure since last decade, which was controlled under adequate drugs. After mammary surgery, therapy with tamoxifen was started and continued for two years, then a switch to anastrozole was done (and she continued it for further four months when she was referred to an endocrinology check-up).

On admission, blood and urinary assays showed a non-secretor adrenal pattern, with negative neuroendocrine markers, including serum serotonin (Table 1). Bone profile pointed mild hypercalcemia with normal parathormone levels, as well as bone turnover markers and 25-hydroxyvitamin D (Table 1). The computer tomography showed stationary aspects without secondary spreading of the malignancy (a similar aspect was described at whole body bone scintigram). Central Dual-Energy X-Ray Absorptiometry (DXA) revealed osteopenia with a mid deterioration of Trabecular Bone Score (TBS) (Figure 1). Further continuation of aromatase inhibitor is recommended, in association with vitamin D supplementation and weekly oral risendronate, good hydration and serial calcium assays.

TABLE 1. *Bone parameters, adrenal profile and neuroendocrine markers on a 67-year old female with non-metastatic mammary breast carcicoma, left adrenal enlargement, and menopausal osteopenia during therapy with aromatase inhibitors*

Parameter	Value	Normal	Units
Neuroendocrine markers			
Serotonin	191	80-400	ng/mL
Chromogranin A	93.5	20-125	ng/mL
Neuron specific enolase	8.51	0-12	Ng/mL
Adrenal profile			
Plasma metanephrines	40.2	10-90	pg/mL
Plasma normetanephrines	173.1	20-200	pg/mL
ACTH (Adrenocorticotrope Hormone)	8.32	3-66	pg/mL
Morning plasma cortisol	14.03	4.82-19.5	µg/dL
Bone indices			
Total serum calcium	10.9	8.5-10.2	mg/dL
Ionic serum calcium	4.51	3.9-4.9	mg/dL
Serum phosphorus	3.2	2.3-4.7	mg/dL
25-hydroxyvitamin D	33.58	30-100	ng/mL
PTH (parathormone)	51.22	15-65	pg/mL
CrossLaps	0.55	0.33-0.782	ng/mL
Osteocalcin	33.24	15-46	ng/mL
P1NP	41.29	15-74	ng/mL
Alkaline phosphatase	118	40-150	U/L
24-hours urinary calcium	0.2	0.07-0.3	g/24 hours

DISCUSSION

This female case reflects a strong link between mammary and bone status. Oncologic disease itself, as well as anti-cancer therapy (for instance, aromatase inhibitors), may deteriorate the skeleton (7). The bone turnover markers are useful for fracture risk assessment, but current guidelines do not routinely recommended their assays, since high inter-individual variations are expected (8). A particular frame is represented by circulating 5-hydroxytryptamine, which serves both as a neuroendocrine marker for neuroendorine neoplasia (NEN) or for breast cancers with neuroendocrine component, as well as atypical bone remodelling indices (9-12). However, controversies still exist in this topic, meaning that it is not well established that non-metastatic NEN cause secondary osteoporosis, neither that routinely assays of blood serotonin will reflect, with high accuracy, its complex skeletal effects (12,13). In this particular case, despite several morbidities as osteopenia and history of mammary carcinoma, the blood bone and neuroendocrine statuses were normal. Hypercalcemia was not confirmed at ionic calcium analysis, neither imagery pointed bone metastases. Most probably, a transient increase of calcium related to hydration status may be involved, since parathromone was normal. The need for paying attention to the skeletal health on menopausal state is well established, but bone loss is accelerated by drugs as anastrozole and a rapid decline is expected unless adequate therapy as vitamin D supplements and

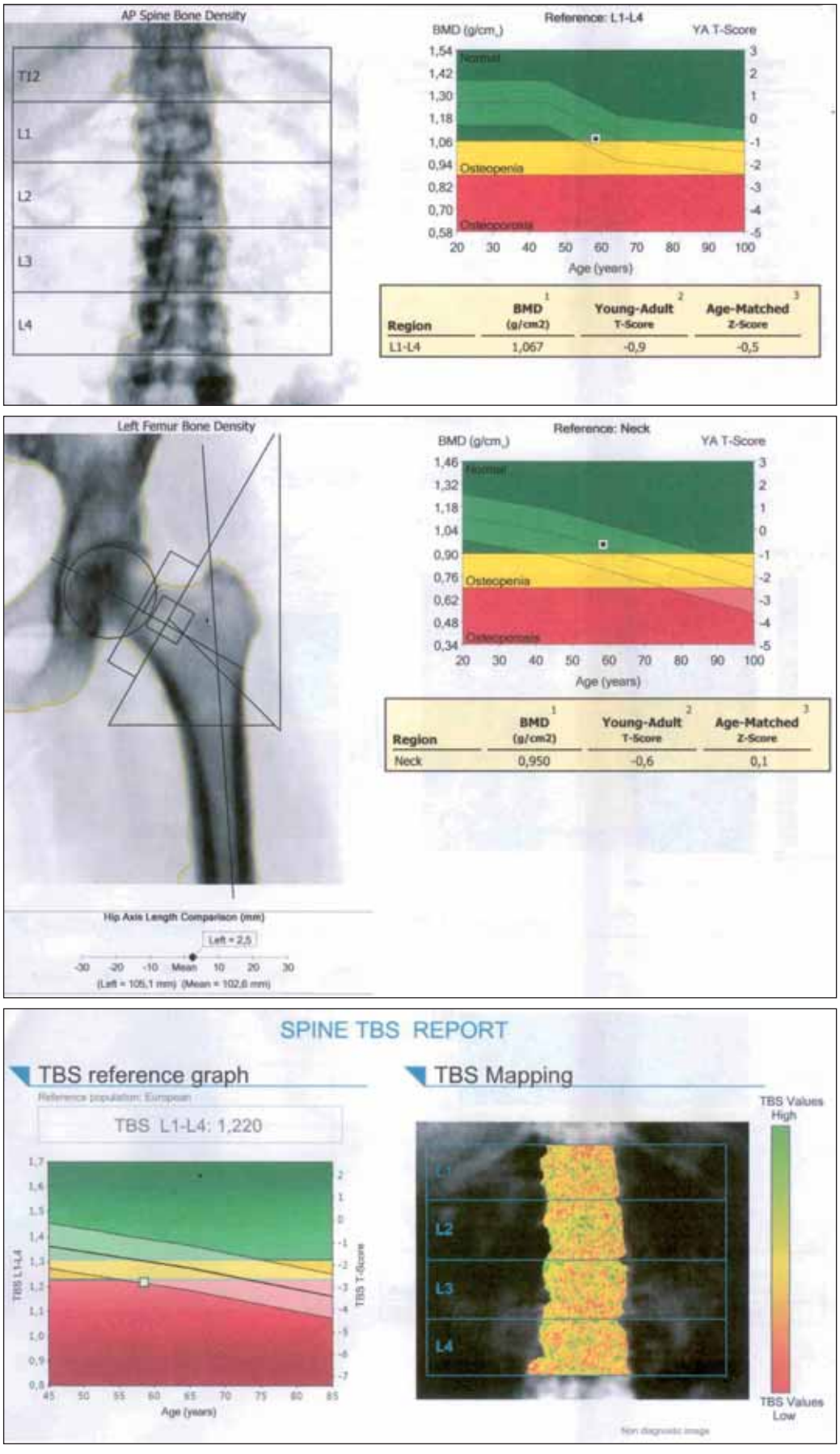

FIGURE 1. *Central DXA (Dual-Energy X-Ray Absorptiometry) showing osteopenia on a 67-year female (menopause at age of 50 years) currently under therapy with aromatase inhibitor for a prior breast cancer. A: Lumbar DXA; B: Femoral neck DXA; C: Lumbar DXA-derived Trabecular Bone Score (TBS)*

bisphosphonates is established, as we did in this case (14). We also provided Trabecular Bone Score (TBS), which is the modern tool to evaluate bone micro-architecture, expected to be deteriorated under anastrozole and also on an age-related pattern (our patient showed a mild decrease at the level of 1220, a normal level been considered above 1350 and a severe deterioration involves a TBS less than 1200) (15).

CONCLUSION

Modern approach of menopausal breast cancer with aromatase inhibitors increases the speed of bone loss, while detailed imagery may find otherwise unknown artefacts, like non-tumour enlargement of adrenal glands. Whether neuroendocrine markers like 5-hydroxytryptamine will find a place in this particular context, apart from traditional bone indices, is still difficult to establish.

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