

CASE REPORT

Well-differentiated neuroendocrine tumor and osteoporosis: incidental findings?

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Abstract

The neuroendocrine tumors (NETs) have an increased incidence related to the age. Secondary osteoporosis might be found in patients with bone metastases and in those with NETs associated Cushing's disease or primary hyperparathyroidism. Primary osteoporosis might be found in postmenopausal women, but in case with non-metastatic NET as G1 NET it is difficult to establish the NET contribution to the bone loss. We present the case of a 53-year-old female accidentally diagnosed with G1 lung NET after surgery of the tumor. The immunohistochemistry pointed positive reaction for CHROMO, SYN and negative for CK7 and TTF1, and a Ki67 of 1–2% (well-differentiated neuroendocrine tumor). The central Dual X-Ray Absorptiometry (DXA) showed osteoporosis based on a T-score of -3. The patient had normal neuroendocrine markers and she was asymptomatic. She remained so for one year and the only therapy provided was weekly alendronate with adequate vitamin D and calcium supplements. Based on the pathological and immunohistochemistry profile, the low risk NET was diagnosed. We encourage the skeletal status assessment as central DXA in postmenopausal women with NETs, regardless clinical evidence of bone loss. The future will provide more epidemiological and pathogenic connections between the two dynamic fields of medicine as neuroendocrine tumors and osteoporosis.

Keywords: neuroendocrine tumor, osteoporosis, lung carcinoid.

Introduction

The neuroendocrine tumors (NETs) field is aggressively extending while the tools to case finding strategy are adequately performing, including the histological and immunohistochemistry methods of diagnosis and classification, so that larger cohorts of patients are diagnosed with NETs. The incidence of NETs is age-related [1]. Thus, common diseases with similar age-pattern might be seen in these patients as cardiovascular and metabolic complications like high blood pressure, type 2 diabetes mellitus, and atheromatosis or osteoporosis (especially in postmenopausal women) [2]. Whether there is an incidental finding or common pathogenic pathways are displayed is difficult to be established.

The advanced neuroendocrine tumors as G3 NETs typically associate bone metastases that might interfere with bone mineral density (BMD) as provided by central Dual X-Ray Absorptiometry (DXA) [3, 4]. The bone metabolism disturbances in NETs include the PTHrP production by the metastases or tumors itself, the bone invasion (both causing hypercalcemia) [5]. Also, some atypical multiple endocrine neoplasia syndromes relate NETs to primary hyperparathyroidism. The primary

osteoporosis related to postmenopausal status or to age-related BMD decline might be found in NETs, especially in those cases without bone metastases as G1 NET. The epidemiological connection between osteoporosis and NETs with typically good long-term prognosis becomes more obvious in years since menopause. It is still difficult to establish in women after menopause presenting neuroendocrine tumors whether the bone loss (osteoporosis) is primary (related to estrogen deprivation) or it has a secondary component (secondary osteoporosis) related to the neuroendocrine carcinoma itself.

The advantages of the pathological report in association with immunochemistry profile include an extensive use of the neuroendocrine tumors diagnosis (classification), mostly seen during the last decades. This might be regarded in connection with osteoporosis domain, especially postmenopausal osteoporosis, a traditional field of interest where many epidemiological data are registered during the last years. Whether these two distinct aspects of medicine, respective the neuroendocrine tumors and the primary osteoporosis are connected throughout pathogenic common pathways is still an open question up to this moment.

Our aim is to present a female case diagnosed with a well-differentiated neuroendocrine tumor and soon after this diagnosis, she was found with osteoporosis.

☞ Patient, Methods and Results

A 53-year-old female patient was accidentally found at X-ray scan (and then confirmed at Computed Tomography) with a lung tumor at the left superior lobe of 2.5 by 2.8 cm. The resection of the tumor was

performed in November 2011. The adequate diagnosis was not possible before surgery, only after surgery, based on the pathological exam which pointed a typical lung carcinoid (Figure 1). The immunochemistry revealed a positive reaction for CHROMO (Figure 2). The synaptophysin was positive (Figure 3). CK7 was negative in the tumor cells and positive in normal pulmonary epithelium and TTF1 negative reaction. The Ki67 levels were 1–2% (Figure 4).

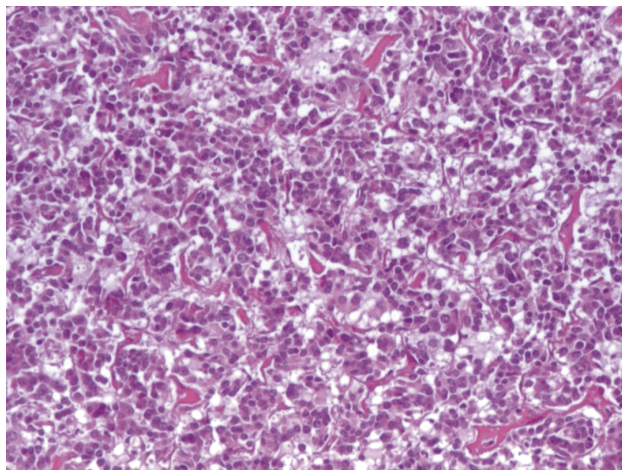


Figure 1 – Pathological exam of typical carcinoid (HE staining, ×100).

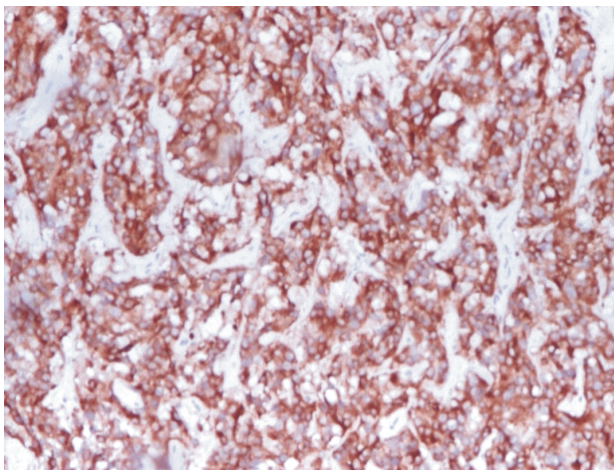


Figure 2 – Immunohistochemistry: positive chromogranin A (×100).

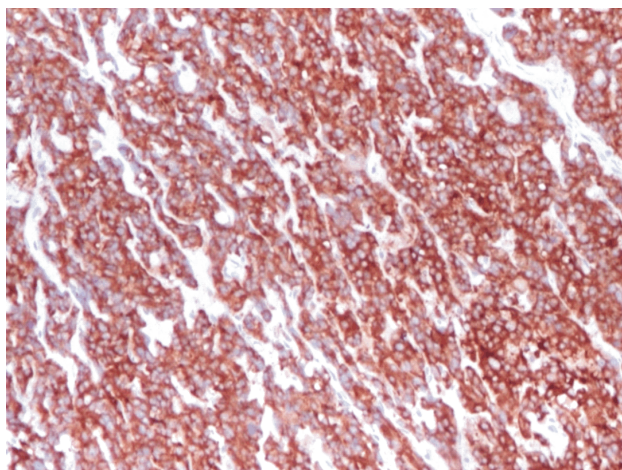


Figure 3 – Immunohistochemistry: positive synaptophysin (×100).

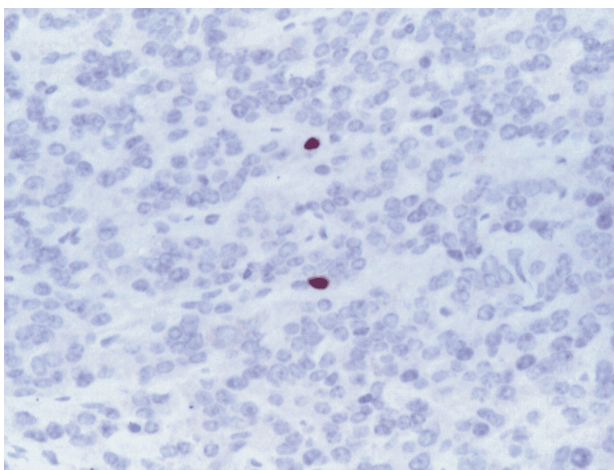


Figure 4 – Immunohistochemistry: G1 NET, Ki67 of 1–2% (×200).

Based on these aspects, a G1 NET was diagnosed (well-differentiated neuroendocrine tumor). The neuroendocrine markers after surgery were normal, respective serum chromogranin of 81 ng/mL (normal levels between 40 and 100 ng/mL), serum serotonin of 369 ng/mL (normal levels between 40 and 450 ng/mL), blood neuronal specific enolase of 8.81 ng/mL (normal levels between 0 and 12 ng/mL), urinary 5-hydroxy-indole acetic acid of 6.4 mg/24 h (normal levels between 1 and 10 mg/24 h) (Table 1).

The endocrine evaluation after the surgery included a central DXA scan, because the patient had surgical menopause at age of 46 years for a benign uterine fibroma. Osteoporosis was diagnosed based on the lumbar DXA analysis: bone mineral density (BMD) was 0.823 g/cm², T-score was -3, Z-score was -1.6. The femoral neck,

respective total hip DXA revealed less affected areas: bone mineral density of 0.719 g/cm², respective 0.806 g/cm²; T-score of -2.3, respective -1.6; and Z-score of -0.9, respective of -0.5.

Mild hyperprolactinemia (of 38 ng/mL, with normal levels <20 ng/mL) was registered after the lung surgery and then remitted within one month. Based on the pathological profile, the patient was followed-up for the neuroendocrine tumor using the neuroendocrine markers and the annual computed tomography. Weekly alendronate therapy was started for osteoporosis, together with vitamin D and calcium supplements. After one year, the patient remained asymptomatic, the neuroendocrine markers were normal but the BMD did not significantly improve (Table 1). She will be followed-up for the G1 NET, while treatment for osteoporosis is still recommended.

Table 1 – The neuroendocrine markers and central DXA at baseline and after follow-up

	January 2012	January 2013	Normal
The neuroendocrine markers			
Serotonin [ng/mL]	369	236	40–450
Chromogranin A [ng/mL]	81	75	40–100
Urinary 5-hydroxy-indole acetic acid [mg/24 h]	6.4	5	1–10
Neuronal Specific Enolase [ng/mL]	8.81	7.85	0–12
Central DXA			
Lumbar	BMD [g/cm ²]	0.823	0.817
	T-score	-3	-3
	Z-score	-1.6	-1.9
Femoral neck	BMD [g/cm ²]	0.719	0.742
	T-score	-2.3	-2.1
	Z-score	-0.9	-0.9
Total hip	BMD [g/cm ²]	0.806	0.815
	T-score	-1.6	-1.5
	Z-score	-0.5	-0.6

Discussion

The pathological exam and the immunochemistry profile provided the G1 NET diagnosis for this case. Based on this report, a very good prognosis is registered. The newly diagnosed osteoporosis might be considered primary or postmenopausal in this particular situation but it is still a matter of debate if the carcinoid tumor might act through cytokines, kinins, and growth factors on bone loss. Experimental data and very few from humans pointed the bone loss caused by excess of serotonin [6]. The relationship between serotonin metabolism interferences as seen in anti-depressives user and fragility fracture risk is known [7]. In our case, the serum serotonin was normal and remained so for more than one year after surgery for the primary tumor. Up to this moment, NETs, as they are showed in relationship to the pathological phenotype, are not listed in classical causes of bone loss, and eventually osteoporosis.

Data from literature are very few relating the neuroendocrine field and primary osteoporosis. This issue is not completely solved yet, as many other aspects (like dedifferentiation) related to the continuing developing neuroendocrine tumors domain [8]. The epidemiological data are very few. Recently, the FDA report connected osteoporosis to the neuroendocrine carcinoma in 87 013 people with osteoporosis and 0.01% of them had NETs, all of them aged over 60 years. Also, the frequency of the NETs is increased over the last decade [9].

There are no specific guidelines in order to evaluate the decreased BMD in patients with NETs. The screening for primary osteoporosis in postmenopausal women is related to the patients' age, the years since menopause, or the number of clinical risk factors or prevalent fragility fractures. Among these, the neuroendocrine tumors have no specific place in order to indicate the screening for

osteoporosis in women after menopause. Except for postmenopausal (primary) osteoporosis, secondary osteoporosis is seen in NETs associated Cushing's disease [10]. Finding of such skeletal anomalies causes supplementary cost in patients with NETs [11]. The bone assessment and the pathological exam in NETs needs a multidisciplinary approach and we hope that the future will highlight more connections between these interesting fields.

Conclusions

The field of osteoporosis may be related to the neuroendocrine tumors domain but up to this moment, no specific recommendation of bone loss evaluation in patients diagnosed with carcinoid neoplasia is included in clinical practice guidelines. Our case highlights the value of the pathological report in the diagnosis of the G1 neuroendocrine tumor but also it opens new dimensions to the possible neuroendocrine tumors associated diseases as low bone mineral density. Postmenopausal osteoporosis in a patient with well-differentiated neuroendocrine tumor might be seen as an epidemiological overlap but pathological and pathogenic common pathways might be involved.

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