

Endocrine issues and premenopausal breast cancer – case report and review of literature

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ABSTRACT

There is an alarming increasing incidence of PBC (premenopausal breast cancer) in countries with high income due to, on one hand, more accessible screening tools and, on the other hand, potential implications of daily lifestyle habits and endocrine disruptors of modern society on terms of facilitating tumor growth. A more severe prognostic is found in females younger than 40 years old at first detection, with advanced disease at diagnostic, and those with tumors displaying specific immunohistochemistry configuration (and associated gene profile) like ER (estrogen receptor) positive or HEGFR2 (human epidermal growth factor receptor) negative. Recently, particular aspects are reported in terms of PBC therapy: the switch from offering aromatase inhibitors/tamoxifen only in post-menopausal females was done to premenopausal subjects in addition to medication that offers ovarian function suppression (OFS) – as an alternative to classical oophorectomy - for 5 years up to 10 years extension depending on protocol and patient' age at first diagnostic. The main endocrine considerations concerning PBC are: OFS and/or chemotherapy or oophorectomy causing prompt hypogonadism, bone status anomalies due to estrogens deficiency, potential endocrine tumors that are prone to be linked (for instance, a higher risk of cancer in acromegalic patients etc.), cardio-metabolic elements as facilitators of early tumorigenesis, fertility issues on PBC survivals etc. The purpose of the present paper is to introduce several key messages that relate to endocrine implications of PBC starting from a case.

Keywords: breast cancer, menopause, hypogonadism, osteoporosis, acromegaly, adrenal hyperplasia, bone, ovarian suppression, ovarian function suppression, tamoxifen, aromatase inhibitor, goserelin, inidentaloma

INTRODUCTION

Worldwide, mammary cancer represents a condition that associates a complex medical burden due to its epidemiological impact and multidisciplinary implications (1-4). Particular aspects are related to premenopausal breast cancer (PBC), in terms of early detection, familial screening as well as socio-economic and lifestyle implications etc. (5-8). There is an alarming increasing incidence of PBC in countries with high income due to, on one hand, more accessible screening tools and, on the other hand, potential implications of daily

opausal breast cancer (PBC), in terms of early detection, familial screening as well as socio-economic and lifestyle implications etc. (5-8). There is an alarming increasing incidence of PBC in countries with high income due to, on one hand, more accessible screening tools and, on the other hand, potential implications of daily

habits and endocrine disruptors of modern society on terms of facilitating tumor growth (9-12). A more severe prognostic is found in females younger than 40 years old at first detection, and those with advanced disease at diagnostic (and thus a delay of early intervention), as well as those with tumors displaying specific immunohistochemistry configuration (and associated gene profile) like ER (estrogen receptor) positive or HEGFR2 (human epidermal growth factor receptor) negative (13-16). Recently, particular aspects are reported in terms of PBC therapy: the switch from offering aromatase inhibitors (AI) only in post-menopausal females was done to premenopausal subjects in addition to medication that offers ovarian function suppression (OFS) – as an alternative to classical oophorectomy - for 5 years up to 10 years extension depending on protocol and patient' age at first diagnostic (17-20).

The main endocrine considerations concerning PBC are: OFS and/or chemotherapy or oophorectomy causing prompt hypogonadism, bone status anomalies due to estrogens deficiency, potential endocrine tumors that are prone to be linked with mammary cancer (for instance, a higher risk of cancer in acromegalic patients etc.), cardio-metabolic elements as facilitators of early tumorigenesis, fertility issues on PBC survivals etc. (21-24). Adjuvant endocrine therapy includes tamoxifen in low risk patients (or those experiencing intolerance to OFS in association with AI) or combination of therapy in subjects with intermediate or high risk (25-28). Also, another particular aspect, that has an extension to post-menopausal population, we mention the neuroendocrine component of the mammary malignancy or the presence of the tumor in association with different genetic syndromes of high malignancy risk, also underlying non-mammary endocrine and neuroendocrine tumors (29-32).

AIM

The purpose of the present paper is to introduce a case presentation in association with a discussion concerning a few connected key messages that relate to endocrine implications of PBC. The paper is a brief update in relationship to a case report as base of discussion. The endocrine panel of the patient was assessed between 2020 and 2021.

CASE PRESENTATION

At presentation

This is 45-year old female admitted for suspicion of acromegaly due to lingual discomfort, and affirmative development of macroglossia since last year. Clinical examination showed an overweight female. She had menarche at age of 13, one birth, and induced amenor-

rhea since last year. A recent pituitary nuclear magnetic resonance showed a pituitary micro-tumor.

Medical history

The personal medical history includes a diagnostic of PBC and associated breast cancer surgery (ductal in situ carcinoma; ER positive) one year prior to present admission; current therapy with tamoxifen and gosere-lin. She also has a history of a thyroid micro-nodule at the level of right lobe with normal thyroid function.

Biochemistry profile

Routine biochemistry profile was within normal limits (Table 1).

TABLE 1. The biochemistry panel on a 46- year old female with PBC and suspected acromegaly

Parameter	Value	Normal ranges	Units
Uric acid	4.8	2.6-6	mg/dl
ALT (alanine aminotransferase)	14.4	0-31	U/l
AST(aspartate aminotransferase)	13.8	0-32	U/l
Ionic serum calcium	4.21	3.9-4.9	mg/dl
Total serum calcium	9.2	8.4-10.2	mg/dl
Total cholesterol	203	0-200	mg/dl
Alkaline phosphatase	69	40-150	U/l
Serum phosphorus	3	2.3-4.7	mg/dl
Fasting glycaemia	104	70-105	mg/dl
Glycated hemoglobin A1c	5.2	4.8-5.9	%
HDL-cholesterol	66	40-60	mg/dl
LDL-cholesterol	122.8	60-160	mg/dl
Potassium	4.53	3.5-5.1	mmoli/l
Magnesium	2.1	1.6-2.55	mg/dl
Sodium	144	136-145	mmoli/l
Triglycerides	71	0-149	mg/dl
Creatinine	0.73	0.5-1.2	mg/dl

Endocrine profile

The hormonal assays confirmed normal thyroid function with negative thyroid autoimmunity, a vitamin D deficiency as reflected by the low levels of 25-hydroxyvitamin D, central hypogonadism (Table 2).

The investigations for acromegaly ruled out an acromegaly, based on the assessments that were done on admission, but also one year before (Tables 3 and 4).

Computed tomography results

Computed tomography imaging of the abdomen showed liver steatosis; left adrenal hyperplasia (Figures 1 A and B).

As note, the adrenal panel, which is not routinely done in PBC, showed normal morning baseline values of ACTH (adrenocorticotrophic hormone) of 15.89 pg/ml

TABLE 2. Endocrine panel as well as bone turnover markers and neuroendocrine markers on a 46-year old female with PBC under therapy with tamoxifen and goserelin and suspected macroglossia (also, the values from a year prior are introduced)

Parameter	Value (2020)	Value (2021)	Normal ranges	units
TSH (thyroid stimulating hormone)	0.76	1.18	0.5-4.5	μUI/ml
FT4 (free levothyroxine)	13	12.97	9-19	pmol/l
ATPO (Anti-thyroid antibodies)	0.75	1.18	0-5.61	UI/ml
25OHD (25-hydroxyvitamin D)	NA	20.9	30-100	ng/ml
Calcitonin	1	1	5.17-9.82	pg/ml
Serum CrossLaps	0.52	0.48	0.162-0.436	ng/ml
Serum osteocalcin	22.69	27.68	11-43	ng/ml
PTH (parathormone)	NA	52.11	15-65	pg/ml
FSH (follicle stimulating hormone)	NA	2.63	25.8-134.8	mIU/ml
LH (luteinizing hormone)	NA	0.3	7.7-58.5	mIU/ml
Estradiol	NA	16.95	5-138	pg/ml
Total testosterone	4.05	4.26	1.93-7.4	ng/ml
Chromogranin A	39	42.2	20-100	ng/ml
Neuron specific enolase	14.65	14.99	0-16	ng/ml

TABLE 3. IGF 1 values and 24-hour GH (growth hormone) profile show exclusion of acromegaly

2020	
IGF1 (ng/ml); Normal: 69-253 ng/ml	202.6
GH profile/24 hours (ng/ml) Normal: mean < 2.5 ng/ml	1.73 0.13 2.2 0.64
2021	
IGF1(ng/ml); Normal:69-253 ng/ml	118.6
GH profile/24 hours(ng/ml) Normal: mean < 2.5 ng/ml	<0.05 <0.05 0.07 0.07

IGF1 = insulin-like growth factor 1; GH = growth hormone

TABLE 4. GH (growth hormone) during 75 g oral glucose tolerance test confirms exclusion of acromegaly

2020	GH (ng/ml)	1.67	0.64	0.18	0.13	0.08
	glucose (mg/dl)	93	144.4	163.6	110.3	116.7
2021	GH (ng/ml)	0.07	<0.05	0.1	0.06	0.64
	glucose(mg/dl)	84.9	107.2	137.7	128.5	104.8

(normal levels between 3 and 66 pg/ml) and plasma cortisol of 18.62 μg/dl (normal values between 4.82 and 19.5 μg/dl).

Computed tomography imaging of the pituitary gland showed mediosellar pituitary micronodul (Figure 2).

Others evaluations

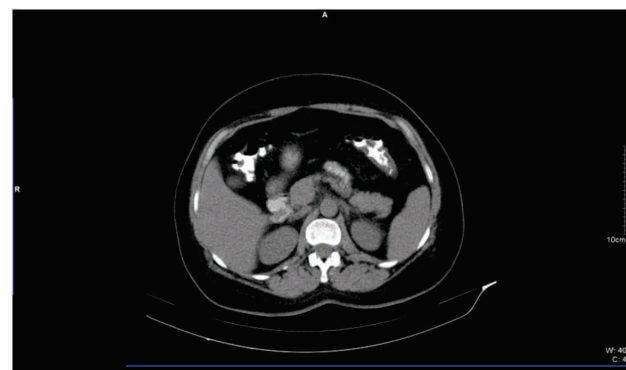
Thyroid ultrasound confirmed a small nodule with stationary aspect (Table 5).

Central DXA (dual energy X-ray absorptiometry) was performed at one year since hypogonadism was induced. Based on lowest T-score which is at lumbar site, the values are suggestive for osteopenia. No prevalent fragility fracture was registered (Table 6).

Despite the fact that the patient complained about macroglossia, this was not confirmed by otorhinolaryngology report (Table 7). However, local accuses might be related to a newly detected hiatal hernia.

Management

The therapy with tamoxifen and goserelin was continued (5-year regime was planned). The patient did



A



B

FIGURE 1. Intravenous contrast computed tomography of the abdomen showing mild left adrenal hyperplasia on a 46-year old female with PBC – **A.** Transverse plane; **1B.** Coronal plan



FIGURE 2. Intravenous contrast computed tomography of the pituitary glands showing a micro-nodule on (Transverse plane)

TABLE 5. Thyroid ultrasound on a 46-year old female with PBC

2020	2021
Right thyroid lobe 1.6 / 1.7 / 4.2 cm, isthmus 0.34 cm, left thyroid lobe: 2 / 1.4 / 4.4 cm, homogeneous, right thyroid lobe with 1/2 inferior to anterior hypo-echoic nodule, intensely vascularized, of 0.98 / 0.65 / 0.73 cm, without local lymphadenopathy	Right thyroid lobe: 1.45 / 1.57 / 4.35 cm; isthmus: 0.32 cm; left thyroid lobe 1.73 / 1.5 / 4.2 cm; right thyroid lobe with 1/2 inferior to anterior spongiform nodule, discreetly vascularized, of 1 / 0.58 / 0.84 cm;

TABLE 6. Central DXA report on a 46-year female with induced hypogonadism since the age of 45

Regions	BMD (g/cm ²)	score T (SD)	score Z(SD)
Lumbar 1-4	1.009	-1.4	-1.7
femoral neck	0.900	-1	-0.6

TABLE 7. 46-year old patient admitted for tongue accuses the feeling of “tongue enlargement” in addition to local discomfort. Acromegaly was not confirmed, the accuses are most probably related to hiatal hernia

2020	2021
Hypo-pharyngeal foreign body sensation and lingual discomfort, dyspnea in supine position, nasal septal deviation, inferior nasal cones hypertrophy, tongue without changes in shape or structure, mobile, normal-looking tongue base.	The patient accuses macroglossia progressively installed during last 2 years. Clinical examination shows: moderately hypertrophied, inferior nasal cones; tongue with dimensions within normal limits, slightly loaded; free oropharyngeal isthmus; normally conformed epiglottis; arytenoid / hyperemic inter-arytenoid mucosa; vocal folds with preserved mobility, free posterior glottis, free oropharyngeal respiratory tract.

not intend to have another pregnancy. Vitamin D supplementation (1,000 UI/day) is initiated. Also, anti-secretor medication for hiatal hernia is recommended. A multidisciplinary lifetime follow-up is required.

DISCUSSIONS

Mammary malignancy with positive ER represents a condition which is closely related with estrogen status

into human body as seen in other circumstances (33,34). This is a case of PBC which was detected by the age of 45 on a patient without known family history of mammary cancer or syndromic context. A part from classical endocrine issues which need to be taken into consideration due to OFS in addition to tamoxifen, the lady was admitted for a suspicion of acromegaly (which finally was not confirmed) starting form potential tongue changes. She was also found with mild vitamin D deficiency and a computed tomography-based diagnostic of unilateral adrenal hyperplasia and a pituitary incidentaloma. These particular aspects need to be discussed.

Acromegaly and risk of malignancy

A patient with mammary cancer may associate a connected endocrine tumor, for instance, a GH producing pituitary adenoma because somatotropin hormone and IGF1 act as promoters of tumorigenesis (35,36,37). Generally, somatotropinoma has a low prevalence in adults, but the condition has a higher morbidity and mortality than general population due to increased risk of cardio-metabolic and even oncologic complications (38,39,40). A patient with acromegaly has a higher lifetime risk of cancer, especially colonic cancer, but, according to some studies, of mammary carcinoma in females, too, thus the importance of mammogram screening in acromegalic women of reproductive age (41,42,43).

GH excess-related macroglossia

GH overproduction induces oral/facial changes which may be extremely severe in some cases as part of classical phenotype; also, the airway interaction aggravates sleep apnea (44,45,46). A part from acromegaly, macroglossia is described in other endocrine conditions like childhood – related severe hypothyroidism (47,48,49).

Adrenal involvement and breast cancer

The present case introduces a non-functioning unilateral adrenal hyperplasia without clinical/hormonal effects. Generally, females diagnosed with breast cancer may associate an adrenal mass, either a metastasis (as isolated metastases which are exceptional at adrenal level or multi-organ metastasis which are found in advanced stages of disease) or an endocrine tumor (secretor or not) (50,51,52). Hereditary syndromes underlying a mammary tumor (including at young ages) and adrenal tumors are: Carney complex, Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome; and potentially, some atypical cases of multiple endocrine neoplasia type 1 or even Cowden syndrome (53-56). In situations with isolated adrenal metastases or secretor

adrenal tumors (adenoma or carcinoma), surgical approach is recommended (57,58). Also, in people over 40 years, there is an increasing incidence of adrenal incidentaloma which required a meticulous follow-up in order to distinct it from an adrenal metastasis, especially in cancer survivals (59).

Thyroid nodules on premenopausal females

A micro-nodule was detected in this case at routine ultrasound examination. 5% up to 50% or even more of general population might have a thyroid nodule detected based on clinical examination and /or anterior cervical ultrasound (females are more frequent, an age-dependent incidence), but generally less than 5% are malign (60,61,62). People with a recent diagnostic of a malignancy are more prone to be detected with a thyroid incidentaloma due to detailed imaging techniques that are performed for staging and follow-up (63,64,65). Ultrasound remains the best screening tool (66,67,68). In a patient with PBC, the risk of thyroid malignancy is exceptional; as mentioned before, some syndromic circumstances might also involve a thyroid neoplasia and breast cancer (69,70,71). Notably, thyroid cancer is among the most frequent malignancies in acromegaly (72,73,74).

Pituitary incidentaloma in subjects with a diagnostic of a malignancy

In this case, the serial assessment that was done for PBC helped the detection of an adrenal incidentaloma. This condition is more often detected in patients under evaluation for a malignancy, including breast cancer, even the tumor remains co-incidental; generally, one in ten persons have such tumor (75,76,77).

Cardio-metabolic risk and mammary malignancy

The mentioned patient with PBC was overweight. High body mass index has been associated with breast cancer, especially in post-menopausal forms (78,79). Cardio-metabolic elements including diabetes mellitus are linked to tumorigenesis *via* insulin resistance, oxidative stress etc. (80,81). However, a high prevalence of both obesity and mammary malignancy may overlap the conditions, while the cause-effect relationship remains multi-factorial (82,83).

Endocrine therapy for PBC

PBC with positive estrogen receptors are treated with chemotherapy and endocrine therapy meaning tamoxifen as adjuvant monotherapy or in combination with luteinizing hormone-releasing hormone agonists (as goserelin was used here) (84). OFS induces an estrogen deficiency status which is helpful to stop tumor growth (85). Negative effects are reflected on bone turnover markers and associated bone loss as reflected by reduced bone mineral density at central DXA (dual X-ray energy absorptiometry) or decreased TBS (trabecular bone score); aggravating circumstances might be chemotherapy or aromatase inhibitors instead of tamoxifen (86,87,88). OFS might help the preservation of fertility since the effect is reversible (89,90).

CONCLUSION

A complex panel of endocrine issues in PBC involves pituitary-ovarian axes as well as bone status, with potential interferences in thyroid and adrenal glands.

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