

SCIENTIFIC LETTERS

Carcinoid tumor on cystic ovarian teratoma[☆]



Tumor carcinoide sobre teratoma ovárico quístico

Ovarian carcinoid tumors are extremely rare tumors very frequently occurring on a cystic teratoma. They may develop carcinoid syndrome in the absence of liver metastases by avoiding enterohepatic circulation.

We report the case of a 59-year-old female patient with history of high blood pressure controlled with enalapril and gastroesophageal reflux on long-term treatment with omeprazole and cinitapride who reported almost daily episodes of facial flushing starting two years before. Episodes were self-limited, lasted approximately 5–10 min, followed no time pattern, and were not related to drug or food intake. They were not associated to high or low blood pressure, headache, diarrhea, or bronchospasm, but patient reported palpitations during them. Patient differentiated these episodes from the vasomotor symptoms she had previously experienced after menopause at 52 years of age. These symptoms included a generalized hot sensation not associated to sweating or facial erythema which spontaneously resolved at 55 years (two years before the start of current symptoms). The patient reported no associated constitutional symptoms. Physical examination findings were normal. Measurement of calcitonin levels in blood and metanephrines, normetanephrines and 5-hydroxyindoleacetic acid in urine was requested. Repeatedly high 5-hydroxyindoleacetic acid levels were found, together with a mild, discontinuous elevation in normetanephrines (Table 1). Calcitonin levels were normal. Based on these findings, chromogranin A was tested in plasma, and a value of 265 ng/mL (No. < 134) was reported. Based on the suspicion of a carcinoid tumor, a computed tomography (CT) scan and magnetic resonance imaging of the chest and abdomen were performed, showing a 6 cm

right adnexal lesion reported as a possible teratoma. On the other hand, transabdominal pelvic ultrasonography revealed a 3.5 cm × 4 cm tumor related to the left ovary. Because of heterogeneity of the results, a ¹¹¹In-Pentetreotide scan (Octreoscan®) was requested, showing a tracer hyperuptake site in the left paramedial pelvic region (Fig. 1). In order to relieve symptoms while planning surgery, treatment was started with a somatostatin analogue (lanreotide 60 mg every 28 days by the deep subcutaneous route), which decreased the frequency and severity of episodes. After ruling out cardiac valve involvement by echocardiography, bilateral adnexectomy was performed. Histological examination found a low-grade (G1) insular carcinoid tumor on a mature cystic teratoma in left adnexum with Ki-67 1–2%, low mitotic index, and positive staining for chromogranin and synaptophysin in immunohistochemistry. The right ovary had a mature teratoma with no associated carcinoid tumor. After surgery, flushing episodes disappeared, and 5-hydroxyindoleacetic acid and normetanephrine levels normalized. Octreoscan® and CT performed six months after surgery were normal. Although serum chromogranin A levels markedly decreased, values remained slightly elevated (150–154 ng/dL; No. < 134). Since all other supplemental tests did not suggest tumor recurrence, such increased levels were attributed to a drug interaction. Omeprazole treatment was therefore discontinued three weeks before control laboratory tests, and chromogranin A levels normalized (63.3 and 37 ng/mL; No.: 19.4–98.1). Three years after surgery, patient continues to be symptom-free, and results of supplemental tests have been normal to date.

Carcinoid tumors are uncommon, with an annual incidence of approximately 8 cases per 100,000 population.¹ Only 1–2% of these tumors originate in ovarian tissue,² where they often seat, as in the reported case, on a cystic teratoma or dermoid tumor.³ According to some studies, this confers them a better prognosis as compared to tumors not occurring on a germ cell tumor.⁴

Although symptoms of carcinoid syndrome are highly characteristic, the syndrome only occurs in a small proportion of carcinoid tumors. Insular ovarian carcinoid tumor, the histological subtype of our patient, is most common and is the only one that is associated to carcinoid syndrome in one-third of cases.^{5,6}

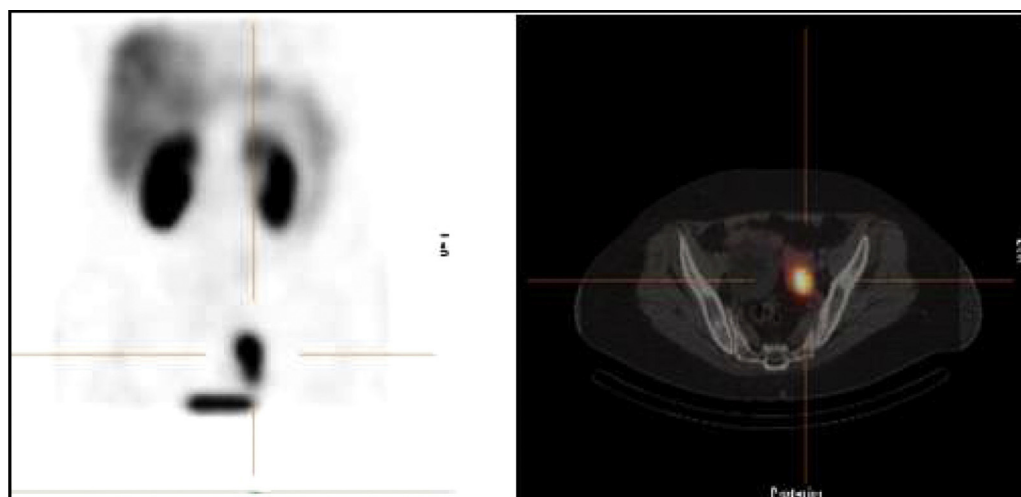
In the reported case, menopause had to be included in differential diagnosis of flushing because of patient

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Table 1 Metanephrine, normetanephrine, and 5-hydroxyindoleacetic acid levels in urine.

	February 2009	June 2009	November 2009	March 2010	December 2010	March 2011
Metanephrines; nmol/mgCr (No.: 0–0.9)	0.9	0.7	0.6	0.8	0.4	0.7
5-OH-indoleacetic acid; nmol/mgCr (No.: 0–34)	49	45	69.9	79	12	13
Normetanephrines; nmol/mgCr (No.: 0–2)	3.2	1.8	2.8	1.6	0.8	1.6

Surgery performed on October 2010.

**Figure 1** Whole body Octreoscan®/abdominal SPECT-CT.

age. Although hot flashes spontaneously disappear in most women a few years after the start of menopause, they may persist in up to 30% of women older than 60 years, and in 9% of those over 70 years of age.⁷ However, hot flashes had disappeared in our patient three years after menopause, and had never been associated to facial erythema as the one she subsequently experienced in the setting of carcinoid syndrome.

Chromogranin A is a protein found in neurosecretory vesicles of neuroendocrine tumor cells. It is currently considered to be the best biochemical marker for follow-up of these tumors because of its high sensitivity.⁸ It is however less specific, and there are various conditions where slight chromogranin A elevations may occur, such as kidney or liver insufficiency. Long-term use of proton pump inhibitors is considered the main cause of increased chromogranin A levels unrelated to a neuroendocrine tumor. Decreased acidity leads to increased gastrin release and enterochromaffin cell hyperplasia, with a resultant increase in chromogranin A. In the case reported, long-term omeprazole treatment hindered interpretation of chromogranin A during follow-up. As recommended by the literature,

omeprazole was discontinued to obtain a reliable value of the marker.⁹

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A hidden cause of virilization in postmenopausal women[☆]



Una causa oculta de virilización en mujeres postmenopáusicas

Virilizing ovarian tumors are very infrequent, representing less than 0.2% of all cases of hyperandrogenism and less than 1% of ovarian tumors.¹ Two women with severe hyperandrogenism who turned out to have a Leydig cell tumor are reported.

Our first patient was a 50-year-old woman with a 5-year history of weight gain of 20 kg, secondary amenorrhea, acne, hirsutism and progressive virilization (male-pattern alopecia, clitoromegaly and deepening of the voice). On physical examination, she revealed moon facies, buffalo hump, thin and wrinkled skin and abdominal purple red striae. Ferriman–Gallwey hirsutism score was 18. Plasma ACTH and cortisol, and urinary free cortisol were increased. Hormonal assessment is summarized in Table 1. Very high testosterone, slightly high androstenedione (4.59 ng/mL, normal 0.3–3.5) but normal dehydroepiandrosterone sulfate (DHEAS) levels (1.25 mcg/mL, normal 0.35–4.3) were detected. FSH and LH levels were 27.4 and 13.4 IU/L respectively (normal range for postmenopause 20–100 IU/L). Dexamethasone suppression tests (1 and 8 mg) were diagnostic of Cushing's disease; magnetic resonance imaging (MRI) revealed a 7 mm microadenoma in the right lateral margin of the pituitary gland, which was resected by transsphenoidal surgery. One month after surgery, she complained of no improvement of her symptoms. Remarkably high testosterone levels, slightly elevated androstenedione (3.89 ng/mL) but normal DHEA-S (2.15 mcg/mL) were found (Table 1). These findings could indicate either an ovarian origin of hyperandrogenism or persistence of Cushing's disease. Although other diagnoses, such as ovarian hyperthecosis, could not be excluded, the rapid onset and very high levels of androgens suggested an ovarian tumor. Pituitary MRI could match with either tumor persistence or postsurgical changes; neck, thorax and abdominal CT scan and pelvic transvaginal ultrasound failed to find any mass. Bilateral laparoscopic oophorectomy was

performed. A pure Leydig cell tumor of 12 mm was found on histological examination of the left ovary. Alpha-inhibin immunohistochemical staining was found to be positive. Total and free testosterone levels returned to the normal range (Table 1), and the patient referred improvement in her voice, hair loss, acne and hirsutism, together with development of hot flushes. As hormonal findings suggested persistent Cushing's disease, MRI was performed showing a focal area of low intensity signal on non-contrast T1 suggesting a remaining microadenoma. Some months later the patient finally agreed to a new transsphenoidal pituitary surgery; unfortunately, the adenoma was not found and hypercortisolism persisted (Table 1). A new MRI revealed a 3 mm microadenoma in the posterolateral right area of the pituitary; Gamma Knife radiosurgery was then delivered, with a maximum irradiation dose of 33.33 Gy. Along the following months the patient lost 10 kg, her general condition improved and hormonal levels finally normalized (Table 1).

The second patient was a 60-year-old woman referred to the Endocrinology clinic due to 5-year complaints of male pattern alopecia, hirsutism and deepened voice. Hormonal evaluation showed increased total (8.58 and 4.86 ng/mL) and free testosterone levels (16 and 13.7 pg/mL); gonadotropin levels were low for postmenopausal state (luteinizing hormone 2.5 IU/L, follicle-stimulating hormone 3.84 IU/L). Other androgens remained within the normal range: androstenedione 2.92 ng/mL, DHEAS 0.81 mcg/mL. A CT scan and transvaginal ultrasound revealed no enlargement or mass in abdomen or pelvis. Considering the differential diagnosis of ovarian hyperthecosis vs ovarian tumor both ovaries were removed. A Leydig cell tumor of 15 mm was found in the right ovary, with positive staining for alpha-inhibin. After surgery, free and total testosterone levels fell to 0.7 pg/mL and 0.22 ng/mL. The physical changes gradually reversed and she suffered hot flushes.

Virilizing ovarian tumors are an unusual cause of hyperandrogenism; however, rapidly worsening signs of virilization in a postmenopausal woman should prompt an urgent diagnostic work-up for an androgen-secreting tumor. Peripheral total testosterone higher than 2 ng/mL (>7 nmol/L), or 3–4 times higher than the upper limit of normal range may be a cut-off level for ovarian neoplasm suspicion.² One study has shown that testosterone level >8.67 nmol/L (2.5 ng/mL) had 100% sensitivity for ovarian neoplasm, together with 98% specificity.³ Our initial differential diagnosis also considered

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