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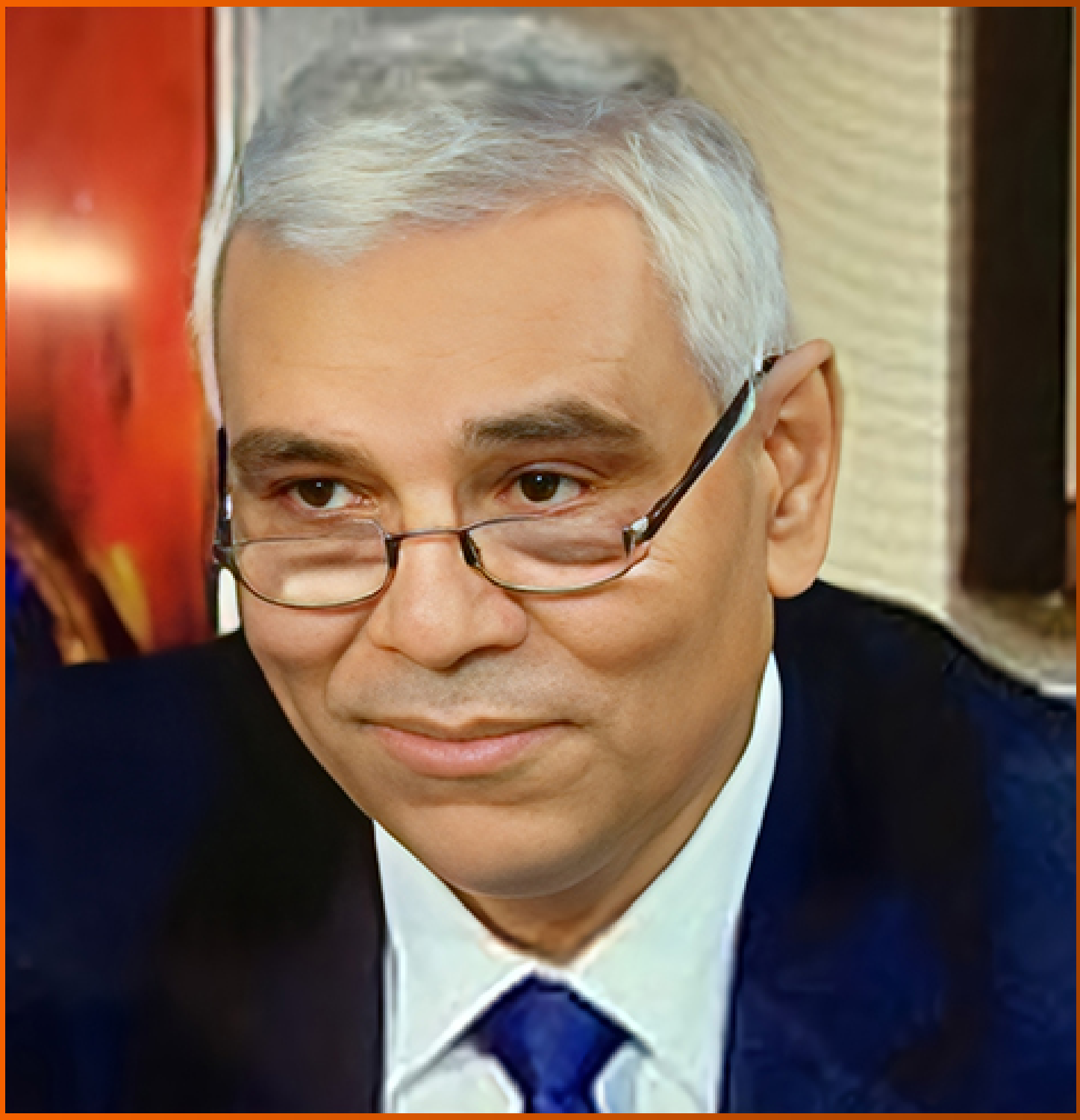

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The primary aim of *World Journal of Obstetrics and Gynecology* (*WJOG*, *World J Obstet Gynecol*) is to provide scholars and readers from various fields of obstetrics and gynecology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJOG mainly publishes articles reporting research results and findings obtained in the field of obstetrics and gynecology and covering a wide range of topics including the diagnosis and treatment of infertility, family planning (including contraception and pregnancy termination), sexual medicine, pediatric and adolescent gynecology, menopausal gynecology, reproductive endocrinology and infertility, and female pelvic medicine and reconstructive surgery.

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CASE REPORT

Therapeutic challenges in metastatic follicular thyroid cancer occurring in pregnancy: A case report

Claudio Spinelli, Beatrice Sanna, Marco Ghionzoli, Elisabetta Micelli

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Abstract

BACKGROUND

Hormones could play a role in the evolution of follicular thyroid cancer (FTC) for which we discuss an unusual presentation of FTC occurring during pregnancy.

CASE SUMMARY

A pregnant woman was admitted with FTC metastasis resulting in a gluteal mass. Preoperative abdominal computed tomography revealed liver metastasis for which the patient underwent total thyroidectomy and liver resection, oral radioiodine therapy and radiotherapy, followed by embolization of the pelvic mass. The patient died of cerebral hemorrhage 16 mo after the initial diagnosis.

CONCLUSION

Human chorionic gonadotropin and estrogen stimulation might have a role in cancer growth, especially during pregnancy. FTC management aims to stop disease progression and overcome hormonal imbalances after thyroidectomy thus reducing fetal complications. It is still under debate whether it is possible to combine optimal timing for treatment to ensure the best possible outcome with reduction of fetal complications and risk of cancer growth.

Key Words: Gluteal pain; Follicular thyroid cancer; Metastases; Pregnancy; Unusual presentation; Case report

Core Tip: We discuss an uncommon presentation of follicular thyroid cancer occurring during pregnancy. Beta human chorionic gonadotropin and estrogens could take part in the progression of thyroid tumors.

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INTRODUCTION

Thyroid cancer is reported as the second most common type of cancer diagnosed during pregnancy, followed by breast cancer[1]. Although the effects of pregnancy on the behavior of this tumor have already been widely discussed, the number of reported cases is too small to draw any conclusions. We assume that beta human chorionic gonadotropin (β-hCG) and estrogens could play a role in the progression and prognosis of the tumor. To date, few reports of follicular thyroid cancer (FTC) causing bone metastases[2-5] (skull[6], mandible[7], maxilla[8], spine[9] and orbit[10]) are described, whereas no cases of gluteus metastases have been reported.

Its management during pregnancy remains challenging. It is crucial to stop the disease progression as well as to overcome the hormonal imbalances after thyroidectomy to avoid fetal complications as a consequence of maternal hypothyroidism[11,12]. The actual standard of care for patients diagnosed with thyroid cancer is a total or near-total thyroidectomy either in the second trimester or after delivery. This treatment is followed by radioactive iodine administration (RAI), contraindicated during pregnancy, as an additional treatment for differentiated thyroid cancer (DTC)[13]. The RAI treatment, with the subsequent total loss of thyroid function and follow-up scintigraphy, is usually postponed to the neonatal period in order to avoid fetal congenital hypothyroidism. A deferred postpartum treatment does not seem to alter the prognosis of thyroid cancer. To our knowledge, patients who undergo postponed surgery should receive thyroid hormone suppression treatment (L-thyroxin) until the definitive surgical treatment[14,15]. It remains controversial to establish whether it is beneficial to postpone the treatment schedule in order to avoid early delivery or if a timely treatment should be mandatory.

CASE PRESENTATION

Chief complaints

Herein we report on an otherwise healthy pregnant woman who came to our attention with hip pain associated with a mass resulting as an FTC metastasis.

History of present illness

A 43-year-old pregnant woman, with no other comorbidities, was admitted at her 30th wk of gestation at our Institution for progressive pain in the right gluteal/iliac region.

History of past illness

Past history showed no smoking or alcohol consumption habits, neither allergies nor history of hypertension, diabetes mellitus, bronchial asthma, tuberculosis or neck swelling.

Personal and family history

No hormonal fertility treatment had ever been performed on the patient who conceived naturally, carrying her first healthy pregnancy.

Physical examination

Physical examination showed a palpable lump of the right gluteus.

Laboratory examinations

Blood tests revealed: thyroglobulin ≥ 10000 (normal value: 3-40 ng/mL), α-FP = 93.4 (normal value: < 6.0 ng/mL), β-hCG = 896 (post-partum) and calcitonin = 15.2 pg/mL (normal value: < 16 pg/mL).

Imaging examinations

The abdominal and pelvic computed tomography (CT) scan and magnetic resonance imaging (Figure 1)

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Figure 1 Magnetic resonance imaging of the lower abdomen and pelvis. Solid formation with osteolytic involvement of the right sacrum, of the sacroiliac synchondrosis and of the contiguous iliac bone was observed.

revealed a solid polylobate mass of 7.3 cm × 7.9 cm × 11 cm with osteolytic involvement of the right portion of the sacrum, of the sacroiliac synchondrosis and of the contiguous iliac bone, extending to the soft tissues of the gluteus. The fetus was delivered *via* cesarean section at 35 wk of gestation without any issue reported concerning his wellbeing. After delivery, a total hysterectomy with bilateral adnexectomy and biopsies of the gluteal mass were performed.

Preoperative ultrasonography and CT scan showed a right thyroid lobe nodule with maximum axial diameter of 12 mm. No enlarged laterocervical, mediastinal, hilar and axillary lymph nodes were found whilst a 5.5 cm solid mass was detected within the liver parenchyma (4th and 8th segments).

FINAL DIAGNOSIS

The histopathological examination confirmed differentiated epithelial follicular neoplasm by morphology and immunohistochemistry (CK+, TTF1+, thyroglobulin +) compatible with FTC metastasis (stage IV). To our knowledge, there have been no previous case reports of FTC in young pregnant patients presenting with gluteal and liver metastasis with no sign of thyroid symptoms.

TREATMENT

Given these findings and the age of the patient, we opted for a total thyroidectomy and liver resection with cholecystectomy (Figure 2).

Because of the complex nature of the disease, 2 mo after the last surgery the patient underwent oral RAI. The first cycle (131-iodine, 3700 MBq dose) did not show the expected improvement. Therefore, it was decided to perform a second round of radioiodine treatment (131-iodine, 5550 MBq dose). Due to the non-resectability of the pelvic mass, 20 d after the RAI treatment, the patient underwent palliative radiotherapy with an external beam on D10 with a total dose of 2000 cGy in 5 fractions. Following radiotherapy, the right gluteal mass displayed an initial reduction with pain relief although after a few months relapsed. Therefore, it was considered to perform a vascular embolization leading to subtotal devascularization of the tumor.

OUTCOME AND FOLLOW-UP

A positron emission tomography (PET)/CT scan performed about 2 mo later showed the failure of this last procedure. Eventually, the patient died of cerebral hemorrhage 16 mo after the initial diagnosis.

DISCUSSION

Amongst all DTCs detected in women during their fertile age, about 10% are diagnosed during pregnancy or shortly after[16]. Female prevalence and increasingly age-specific incidence in women

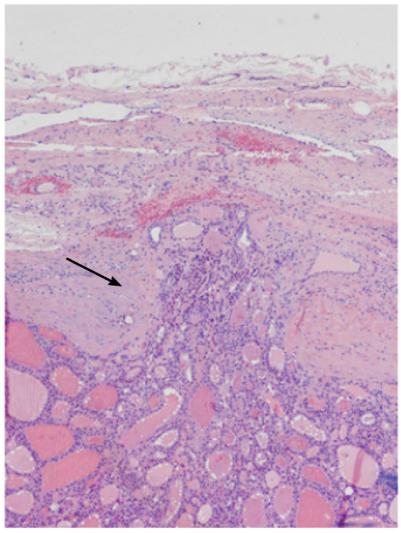

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Figure 2 Follicular thyroid carcinoma. Fibrous capsule invasion (black arrow). The growth pattern is typically micro and/or macrofollicular. No cytonuclear atypia were present. Original magnification for the panel, × 40.

during the child-bearing period suggests a possible role of sexual hormones in the development of thyroid cancer, especially in cases of DTCs (papillary thyroid carcinoma and FTC). However, there is an ongoing debate about the role of pregnancy hormones with regard to the prognosis of DTC[17,18]. The pathophysiological framework of an increased risk of developing thyroid cancer and its progression in pregnant patients is still under debate. β-hCG and estrogen stimulation, increased vascularization and the absence of immune surveillance against cancer may be involved[19]. Hormonal stimulation during pregnancy might escalate the progression of thyroid cancer, suggesting that a more aggressive approach might be required in affected women[20-22]. Thyroid gland size normally increases by 30% during the first and third trimesters of pregnancy, and thyrotropin (TSH) levels fluctuate during pregnancy as they decrease during the first trimester to return to normal range during the following months[23].

β-hCG belongs to the subfamily of glycoprotein hormones, displaying a structural accordance both with TSH and its receptors. This similarity suggests the basis for β-hCG cross-reactivity with the TSH receptor[24]. β-hCG has a stimulating effect on the thyroid gland as it can be noted in gestational trophoblastic diseases that present with high levels of β-hCG and hyperthyroidism. Furthermore, β-hCG is the strongest stimulator of thyroid growth during the first trimester of pregnancy[25]. Therefore, in susceptible thyroid follicular cells (*e.g.*, when *BRAF* and *RAS* mutations or *RET/PTC* and *PAX8-PPAR-γ* rearrangements occur), an excessive β-hCG stimulation may lead to rapid cancer progression[26].

Estrogen levels exert their effects through more complicated mechanisms. They have an indirect effect through increasing the serum thyroxine that binds globulin. A manifestation of their direct effect is estrogen receptor (ER) presentation on thyroid gland cells[27]. ERα and ERβ are intracellular nuclear receptors that exist in normal and neoplastic thyroid cells. When estradiol binds to ERα it enhances cell proliferation. On the contrary, ERβ inhibits these effects and leads to apoptosis[28,29]. Recent studies compared expression of ERα and ERβ in normal thyroid cells and malignant thyroid cells, revealing different levels of expression of ERα and a decreased ERβ activity in the latter[30,31].

The musculoskeletal system represents the most common localization for FTC metastases, which can develop in areas of high blood flow, like the red marrow of the axial skeleton, including the vertebrae (42%-52%), femur (9%-20%), skull (2%-16%) and pelvis (5%-13%)[32]. FTC usually presents itself as a single nodule, which can be either well defined or extensively infiltrating. Lymph node involvement is extremely rare[33]. Magnetic resonance imaging, CT, PET and scintigraphy could complete the diagnostic work-up to reveal metastases[34].

Surgery is the gold standard treatment for FTC. In all patients it is mandatory to balance risks against advantages of thyroid lobectomy with subsequent completion *vs* initial total thyroidectomy[33,35]. Thyroid cancer during pregnancy poses many challenges due to the need to carefully focus on both optimal timing for recommended treatments and the risks of cancer growth. The Endocrine Society recommends thyroidectomy following delivery for pregnancy-related DTC in patients showing no evidence of advanced disease or rapid progression. Meanwhile it is advisable to perform thyroidectomy during the second trimester of pregnancy in complicated cases. Lymph node dissection is not indicated in the absence of palpable lymph nodes[35-39]. Suppressive treatment with levothyroxine therapy is required after surgical treatment. Its aim is to keep TSH levels below 0.1-1 mU/L, with monthly monitoring of TSH and T4 levels.

However, if surgery is performed during pregnancy, levothyroxine therapy should promptly begin after surgery[39,40]. The post-surgical radio-ablation of the residual thyroid tissue facilitates the use of thyroglobulin detection and radioiodine scanning for long-term follow-up. Consequently, for patients at risk of recurrence and for those with known distant metastatic disease, 131I ablation may represent a valid therapeutic strategy[20]. Not all patients benefit from radioiodine therapy, and this treatment is contraindicated in pregnant and in breastfeeding women[30].

The presence of molecular pathway alterations in different DTC (*RET/PTC* rearrangements, *RET* mutations, *BRAF* mutations, *RAS* mutations and VEGFR-2 expression) has allowed the development of new selective drugs. Tyrosine kinase inhibitors are small organic compounds inhibiting tyrosine kinase autophosphorylation and activation; most of them are multikinase inhibitors. Tyrosine kinase inhibitors act on the aforementioned molecular pathways involved in growth, angiogenesis and local and distant spread of DTC and are emerging as a new approach for aggressive thyroid cancer[41].

CONCLUSION

β-hCG and estrogen stimulation might have a role in cancer growth, especially during pregnancy. FTC management aims to stop disease progression and overcome hormonal imbalances after thyroidectomy thus reducing fetal complications. It is still under debate whether it is possible to combine optimal timing for treatment to ensure the best possible outcome with reduction of fetal complications and risk of cancer growth.

FOOTNOTES

Author contributions: Spinelli C, Sanna B and Micelli E participated in conception and design, drafting the article and acquisition of data; Sanna B and Ghionzoli M participated in acquisition of data and analysis and interpretation of data; All of the co-authors interpreted the data, participated in the completion of the article, and approved the final version of the article.

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