

74576-C.docx

Name of Journal: *World Journal of Obstetrics and Gynecology*

Manuscript NO: 74576

Manuscript Type: CASE REPORT

Therapeutic challenges in metastatic follicular thyroid cancer occurring in pregnancy:

A case report

Spinelli C *et al.* Follicular thyroid cancer during pregnancy

Claudio Spinelli, Beatrice Sanna, Marco Ghionzoli, Elisabetta Micelli

Abstract

BACKGROUND

Hormones could ⁵ play a role in the evolution of follicular thyroid cancer (FTC) for which we discuss an unusual presentation of FTC occurred during pregnancy.

CASE SUMMARY

A pregnant woman was admitted with FTC metastasis resulting in 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

Spinelli C, Sanna B, Ghionzoli M, Micelli E. Therapeutic challenges in metastatic follicular thyroid cancer occurring in pregnancy: A case report. *World J Obstet Gynecol* 2022; In press

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

INTRODUCTION

Thyroid cancer is reported as the second most common type of cancer diagnosed during pregnancy, following breast cancer^[1]. Despite the effects of pregnancy on the behavior of this tumor have been already widely discussed, the number of reported cases is too small to draw any conclusion: 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 both 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 a FTC metastasis.

History of present illness

A 43-year old pregnant woman, with no other comorbidities, was admitted at her 30th week 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, no 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), Calcitonin = 15.2 pg/mL (normal value: < 16 pg/mL).

Imaging examinations

The abdominal and pelvic computed tomography (CT) scan and magnetic resonance imaging (MRI) (Figure 1) revealed a solid polylobate mass of $7.3 \times 7.9 \times 11$ cm with osteolytic involvement of the right portion of the sacrum, of the sacroiliac synchondrosis and 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 (US) 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 with 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, two months 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 (RT) with an external beam on D10 with a total dose of 2000 cGy in 5 fractions. Following RT, the right gluteal mass displayed an initial reduction with an essential 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

⁹ A positron emission tomography (PET)/CT scan performed about two months later showed the failure of this last procedure. Eventually, the patient died of cerebral hemorrhage 16 mo after the initial diagnosis.

DISCUSSION

Amongst all DCTs 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 during child-bearing period, suggests a possible role of sexual hormones in the development of thyroid cancer, especially in case 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, an 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 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 receptors presentation on thyroid gland cells^[27]. ER α and ER β are intracellular nuclear receptors that exist in normal and neoplastic thyroid cells. When Estradiol binds to ER α it enhances cell proliferation, on the contrary ER β inhibits these effects and leads to apoptosis^[28,29]. Recent studies compared expression of ER α and ER β in normal thyroid cells and malignant thyroid cells, revealing different levels of expression of ER α and a decreased ER β 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]. MRI, 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 (LT4) 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, LT4 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 pathways 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 (TKIs) are small organic compounds inhibiting tyrosine kinases auto-phosphorylation and activation, most of them are multikinase inhibitors. TKIs act on the aforementioned molecular pathways involved in growth, angiogenesis, 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.

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