Hurthle Cell Thyroid Carcinoma During Pregnancy: A Case Presentation and Literature Review

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Introduction

Thyroid carcinoma (TC), the most common endocrine malignancy, has been shown to affect women more than men in a 3:1 ratio and is also more common per capita in pregnant women than in the general female population.[1] Prevalence of TC has also been shown to increase with increasing parity.[2] There are obvious ethical concerns about fetal effects of maternal treatment for TC, however most cases of TC during pregnancy are actually diagnosed post-partum.[1] Given that these patients are by default of child-bearing age, concerns about post-partum treatment still exist due to potential effects of radiation on the gonads and overall fertility.[3]

Follicular carcinoma (FC) and papillary carcinoma (PC) are collectively considered differentiated thyroid carcinoma (DTC). More specifically, Hurthle cell carcinoma (HCC) is considered a variant of follicular carcinoma which contains Hurthle cells: follicular derived epithelial cells which are large, polygonal cells with distinct borders, eosinophilic granular cytoplasm, a large hyperchromatic nucleus, and a prominent nucleolus.[8] (figure 1) Their cytoplasm contains around 5000 mitochondria, whereas a typical eosinophil contains around 30.[8] This makes the cytoplasm highly acidophilic, and as such the official World Health Organization designation of Hurthle cells is “oncocytic cells” (oncocytic cells are epithelial cells with acidophilic cytoplasm).[8]

DTC during pregnancy is well documented in the literature; however, the vast majority of DTC cases are papillary. There is very little documentation of other types of thyroid carcinoma during pregnancy, and although management of all DTC is similar, there are important distinctions for consideration, such as PC’s predilection for nodal metastases as opposed to hematogenous spread, whereas FC has the opposite tendency.[6] As such, a higher index of suspicion may be required for diagnosis of FC, as fine needle aspiration or biopsy and evaluation of regional lymph nodes is less likely to reveal malignant tissue than in the case of PC. Patients with FC have been shown to present at a higher age, have lower carcinoma related survival, and have more frequent distant metastases and less frequent nodal metastases than their papillary carcinoma counterparts. [6]

Overall survival for HCC has been shown to be around 95% at 1 year, 85% at 5 years, and 75% at 10 years.[9] Overall survival for FC has been shown to be around 100% at 1 year, 95% at five years, and 85% at 10 years.[9] Overall survival for PC is around 100% at 1 year, and still over 95% at 5 and ten years.[10] Although HCC is generally considered more aggressive than typical DTC, survival rates have not been shown to be statistically significantly different than those for pure follicular carcinoma ($p=0.47$).[9] Even so, stage I,II, III, and IV 5 year relative survival for PC is 100%, 100%, 93%, and 51% respectively whereas FC is 100%, 100%, 71%, and 50% respectively.[11] This demonstrates a significant difference in survival once the cancer has extended past the thyroid capsule (stage III or greater). This data is compiled in tables 1 and 2.

Case

A 29 year old white female G2 P2002 underwent a normal prenatal course for a second pregnancy and gave birth to a term male infant via uncomplicated spontaneous vaginal delivery. Shortly after discharge home from the hospital, the infant became jaundiced and was diagnosed with hemolytic disease of the newborn after readmission to the hospital. The infant was treated and discharged with instructions to follow up with a pediatrician. During a two month follow up, the patient asked the pediatrician to look at a “lump” on her neck, which he diagnosed as non-descript right sided thyroid mass and instructed the patient to seek medical care for this mass.

She sought the care of her primary care physician, who agreed with the pediatrician. He ordered a thyroid ultrasound with fine needle aspiration (FNA), which revealed a solid appearing mass with a small amount of fluid. Aspirate revealed only follicular cells. The patient subsequently saw a head and neck surgeon and underwent removal of the right lobe of the thyroid. Frozen section during the procedure yielded a preliminary diagnosis of "benign." The patient was discharged home after an uncomplicated surgery. Permanent section analysis yielded a final diagnosis of "follicular adenoma" with no areas of the mass breaching the capsule. However, the pathologist noted two areas where the mass seemed to invade vasculature, which prompted him to send the slides to a nearby quaternary care center specializing in endocrine pathology. After two weeks of evaluation with special staining, a final diagnosis of angioinvasive Hurthle cell carcinoma was made.

The patient subsequently underwent a second procedure for removal of the remainder of thyroid tissue with exploration of the surrounding tissue for palpable lymph nodes. The patient also underwent lymph node ultrasonography, which revealed possible tumor in the patient's right-sided lymph nodes. After healing from her uncomplicated operation, the patient was referred to a nuclear medicine physician for evaluation of any remaining local or metastatic spread. Four months after diagnosis she underwent high dose radioactive iodine ablation of residual thyroid tissue and possibly two lymph nodes. She was required to wait 6 months after cessation of therapy to breastfeed due to concern of uptake of RAI by mammary glands. The mother sought follow-up care from a thyroid malignancy specialist about an hour away in a quaternary referral center. Subsequent cervical ultrasounds and lab values have been negative for recurrence.

Discussion

According to the American Thyroid Association (ATA), thyroid function testing during pregnancy must be interpreted differently.[5] The most commonly used tests are TSH and free T4 (FT4). Both FT4 and thyroid binding globulin (TBG) increase by 6-8 weeks gestation and remain high during pregnancy.[5] This results in an apparent "decrease" of FT4 on standard lab testing. TSH decreases during the first trimester as well due to the thyrotropic activity of hCG.[5] Albumin concentration tends to decrease as gestation progresses as well. All of these changes combine to make standard thyroid assays unreliable, and as such it is recommended that consideration be given to the analytical method for measuring FT4 concentration.[5] Detailed description of such methods is beyond the scope of this paper. It is also recommended to take into consideration that TSH is often below the traditional "normal" lower limit of 0.4 mIU/L.[5]

The ATA recommends that all pregnant women with a thyroid mass undergo a complete history and physical, serum TSH measurement, and neck ultrasounography. Fine needle aspiration of the thyroid or neck lymph nodes has not been shown to carry any additional risk in any trimester, and any masses which have suspicious features on ultrasound should be considered for FNA.[5] Though surgery for thyroid carcinoma during the second trimester has not been shown to carry additional risk for mother or fetus, it is recommended that surgery for all DTC be delayed until the post partum period due to the fact that outcomes for women diagnosed during pregnancy and treated post partum are similar to those for non-pregnant patients.[5] Skill of the surgeon has also been shown to be a significant factor in outcomes for pregnant or post-partum patients undergoing thyroid surgery.[2] An algorithm for workup of thyroid masses during pregnancy is shown in Figure 2.

As mentioned earlier, many patients may express concern about the impact of radioactive iodine ablation on fertility and future pregnancy. A 2011 study by Sioka and Fotopoulos demonstrated that while there are transient effects on the gonads from RAI therapy, subsequent pregnancies are safe with no significant effects on offspring.[3] Levothroxine dosing should be stabilized after RAI before subsequent pregnancy is attempted.[5] It has also been demonstrated that further therapy besides RAI ablation is seldom needed in patients whom

thyroglobulin continues to decline, as RAI has been shown to provide long term efficacy even in cases of widely metastatic cancer.[4] It should be noted that RAI therapy is an absolute contraindication to breastfeeding.[7]

This case reinforces three important points. First, many physicians in training tend to notice the physiologic enlargement of the thyroid during pregnancy, and subsequently order a barrage of tests to discover that they are all normal, possibly causing these physicians to have a tendency to ignore the pregnant patient's thyroid from that point onward. As such, true pathologic masses tend to go unnoticed until post-partum checkups (as was the case with this patient). Second, many pathologists may be quick to note that the difference between benign and malignant thyroid nodules is difficult to distinguish as finding capsular invasion in a specimen can be difficult. However, this difficult distinction makes a great deal of difference in treatment. Third, this case also highlights the aforementioned difficulty in diagnosing Hurthle cell carcinoma as compared with the more common papillary, as well as the difficulty (or impossibility) in distinguishing malignant HCC from a benign follicular adenoma on FNA. Such cases are underreported in the literature (the authors were unable to find any such case report), and as such it is assumed that the rarity of this diagnosis compared to one of papillary or ordinary follicular carcinoma contributes to said diagnostic difficulty. As mentioned before, a high index of suspicion is needed to make this diagnosis, and it is the goal of this paper to raise awareness that the diagnosis of Hurthle cell carcinoma in the pregnant or post-partum patient should hold a legitimate place in the differential. Treatment options and decisions should always involve a joint discussion between the patient, the obstetrician, pathologist, and surgeon.

Table 1: Overall survival of Differentiated Thyroid Carcinoma variants

	1 year	**5 year**	**10 year**
Papillary Carcinoma	100%	95%	95%
Follicular Carcinoma	100%	95%	85%
Hurthle Cell Carcinoma	95%	85%	75%

Table 2: Stage specific survival of Papillary Carcinoma vs. Follicular Carcinoma

	Stage I	**Stage II**	**Stage III**	**Stage IV**
Papillary Carcinoma	100%	100%	93%	51%
Follicular Carcinoma	100%	100%	71%	50%

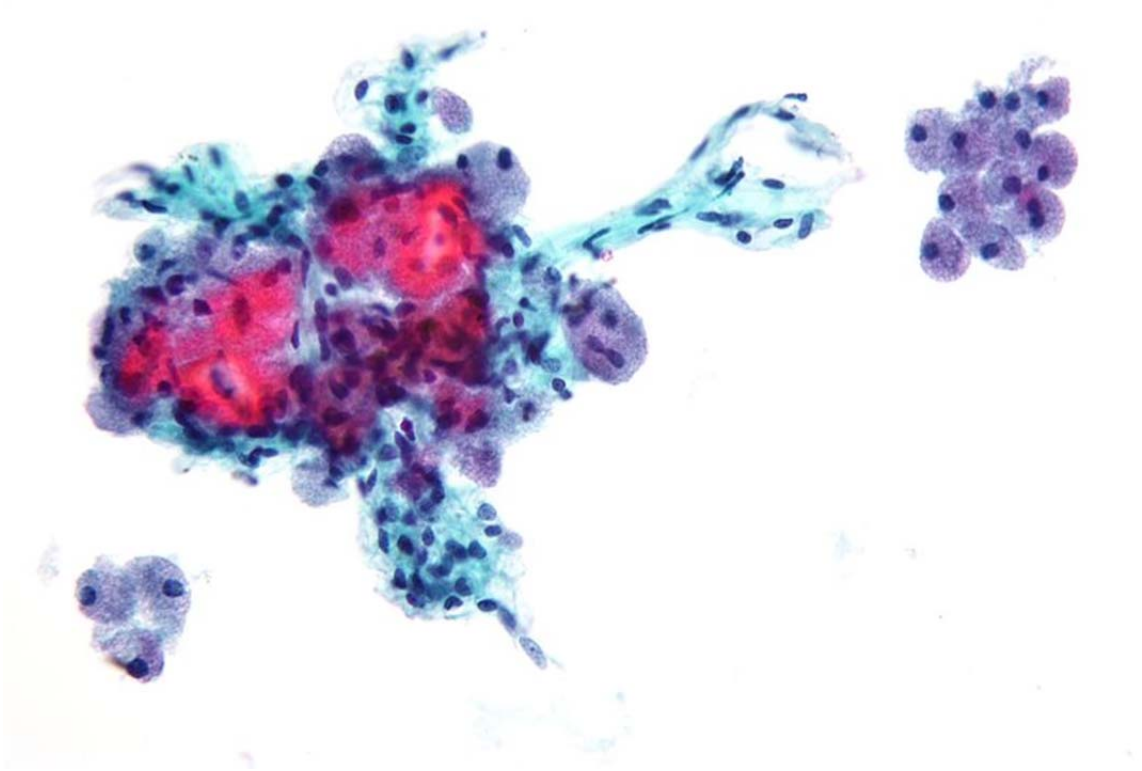

Figure 1: Hurthle cells arranged in clusters. Note granular cytoplasm and prominent nucleolus.[13]

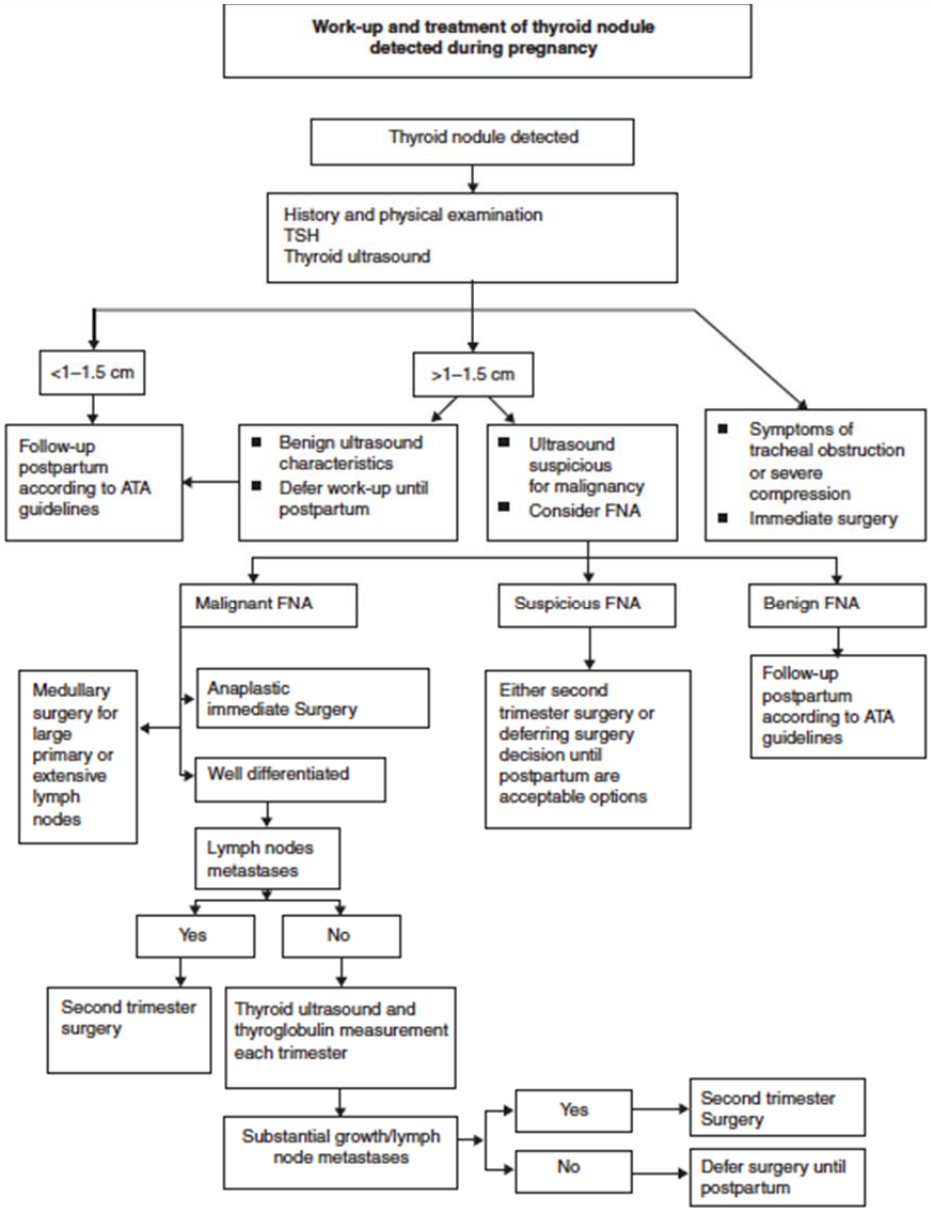

Figure 2. An algorithm for the work-up and treatment of a thyroid nodule detected during pregnancy.[5]

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