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Opinions Vary on How to Evaluate and Treat Possible Cases of TSH-Producing Pituitary Tumors

Stephen W. Spaulding

van Varsseveld NC, Bisschop PH, Biermasz NR, Pereira AM, Fliers E, Drent ML. A long-term follow-up study of eighteen patients with thyrotropin-secreting pituitary adenomas. Clin Endocrinol (Oxf). July 15, 2013 [Epub ahead of print]. doi:10.1111/cen.12290

SUMMARY

Background

The rising incidence of TSH-producing pituitary tumors (TSHomas) probably reflects the increased reliability and sensitivity of TSH assays and improvements in pituitary imaging. Cases are being uncovered in patients originally diagnosed as having Graves' disease or toxic nodular goiter after they display recalcitrance to medical treatment. If a case has only subtle symptoms of hyperthyroidism, it may be diagnosed only after signs or symptoms of pituitary tumor develop. Doctors treating patients with hyperprolactinemia or acromegaly—which are present in about 25% of cases of TSHoma—may overlook thyroid problems. The key diagnostic laboratory feature of a TSHoma is a persistently inappropriate level of TSH in the face of elevated thyroid hormone levels, but this combination is also found in patients with reduced sensitivity to the actions of thyroid hormone, with minor mutations in the TSH receptor that reduce its sensitivity to TSH, or with defects in associated pathways. Surgical treatment of TSHomas is frequently unsuccessful, particularly in macroadenomas, which tend to be fibrotic. The authors of the current paper previously reported on a patient with a macroadenoma who was apparently cured after 4 years of treatment with a somatostatin analog (SSA). In the current report, they review the outcomes of 18 patients given various treatments for TSHomas; almost all had been given SSAs, and 3 have been treated only with SSAs. The authors findings are compared with some recent guidelines published by the European Thyroid Association (ETA) (1).

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Methods

Between 1989 and 2011, a total of 18 cases with at least biochemical hyperthyroidism along with inappropriate TSH levels were studied in one of three academic centers in the Netherlands. Any patient who had been taking octreotide was not tested until the drug had been discontinued for 4 weeks. Records were reviewed to document each patient's initial clinical signs and symptoms and their initial biochemical and CT or MRI data. Data on mutational analysis of thyroid hormone receptor (TR) β; dynamic testing with T_3, octreotide, or TRH; as well as histologic and immunohistochemical findings were checked. Tests on other pituitary/target organs and the use of hormones or endocrine antagonists were also recorded. Student's t-test was used for analysis of continuous variables, while Fisher's exact test was used for categorical variables.

Results

Twelve of the 18 patients were men. The mean age at diagnosis was 48 years, and the median period of follow-up was 7 years (range, 1 to 21). Three had undergone partial thyroidectomy, while 2 had previously undergone block-and-replace therapy. Symptoms had generally had been present for more than 6 months: 16 had at least one symptom of thyrotoxicosis, 6 had headache, and 4 had visual-field defects. The basal TSH was above the upper limit in 8 patients and was inappropriately normal in the remaining 10. Five patients had microadenomas, whereas 13 had macroadenomas (9 had suprasellar extension [5 involving the optic chiasm], 10 had parasellar extension, and 10 had infrasellar extension). Pretreatment free T_4 was high in all 14 cases tested, total T_4 was high in 6 of 8 tested, total T_3 in 10 of 12, and free T_3 in 2 of 2. The rise in TSH after the administration of TRH was blunted in 10 of 13. In the one case tested, L-T_3 (200 µg) suppressed the TSH by slightly more than 50%. Short-term administration of octreotide (subcutaneously or intravenously) suppressed the TSH by more than 50% in 5 of 5 cases. The level of glycoprotein hormone α-subunit was above normal in 7 of 11 (after correcting for sex and for age of females). The level of sex-hormone–binding globulin (SHBG) was high in 5 of 12. Two patients with macroadenomas oversecreted prolactin (PRL), and another 2 patients with macroadenomas oversecreted growth hormone (GH), while an additional patient with a macroadenoma oversecreted both PRL and GH (2 of the 3 patients with GH oversecretion had frank symptoms of acromegaly).

The therapy chosen was based on the characteristics of each individual case and on the treatments available at the time of diagnosis. Three patients were treated only with SSA, based on their initial responses to SSA and on patient preference. Of these 3, 1 patient (previously reported) was apparently cured, 1 had partial shrinkage of a macroadenoma and remains euthyroid on SSA, and 1 needed RAI for a concurrent toxic nodular goiter, but now is euthyroid on SSA. One of these patients also required a cholecystectomy after being on SSA for 3 years.

Surgery was performed on 14 patients; 2 remain apparently cured, and 6 were initially in remission off medical treatment, but half of them had recurrences (as much as 2½ years later), although the residua of their tumors did not change in size. Seven of the patients were given SSA before surgery, 6 of them became euthyroid before surgery, including 2 who had tumor shrinkage and 1 who had tumor progression. The other 7 patients underwent tumor resection without SSA pretreatment; 1 was apparently cured, 1 is in remission off medical treatment, while the remaining 5 are continuing to take SSAs. Two patients are taking methimazole; 1 had mild hyperthyroidism with an empty sella, and psychological symptoms developed in 1 after only a single injection of SSA. Radiation was used in 2 patients with incompletely resected macroadenomas, but after more than 13 years of follow-up, their TSH levels remain elevated. One is euthyroid while taking cabergoline for high GH, and the other remains euthyroid while taking SSA. One patient refused any treatment; his TSH and thyroid hormone levels remain elevated, and he is being followed closely.

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Opinions Vary on How to Evaluate and Treat Possible Cases of TSH-Producing Pituitary Tumors

Stephen W. Spaulding

Conclusions

Patients with large TSH-secreting macroadenomas presenting with extrasellar extension can have an excellent response to treatment with SSAs. In view of the frequently disappointing results with surgery and radiotherapy, the authors suggest that primary therapy with SSA might be considered for virtually all patients, except those with evidence of compression of the optic chiasm.

ANALYSIS AND COMMENTARY

Upon finding that a patient's TSH level is inappropriate in the face of high thyroid hormone levels, one must rule out assay artifacts such those as can occur when nondialysis assays of free T_4 and free T_3 are used or antimouse antibodies or certain binding-protein abnormalities are present. One must also recognize that many physiological and pathological conditions can transiently alter the level of TSH until counter-regulatory pathways adjust (2).

The recent ETA guidelines (1) reviewed tests used in the differential diagnosis of TSHomas, and strongly recommended using both a suppression and a stimulation test, since neither test is very sensitive or specific. They stated that the TSH response to TRH stimulation is "blunted" in 90% of TSHomas, while the TSH response to T_3 never shows "complete inhibition" in TSHomas. In the current study, blunted TSH responses to TRH were found in only 10 of the 13 (77%) cases tested. In comparison, in cases of resistance to thyroid hormone, which are some 30 times more common than TSHomas, one expects a normal or exaggerated TSH response to TRH. Alas, TRH is no longer available in the United States. One needs to use caution when contemplating a T_3-suppression test, particularly in the elderly or in those with possible cardiovascular disease. In the current study, the T_3-suppression test was used only once: 200 µg suppressed the TSH level by more than 50%. Certainly, if one uses the formal three-step 9-day T_3-suppression test, it would seem to be important to assess more than the just the TSH response; perhaps serum markers like cholesterol, creatine kinase, SHBG, and ferritin should also be assessed. The responses in patients with TSHomas may be smaller than what is observed in normal subjects who haven't been chronically exposed to above-normal thyroid hormone levels. In comparison, in cases of thyroid hormone resistance, responses to T_3 are not generally observed.

Clinically, patients with TSHomas can have almost any of the symptoms of thyrotoxicosis. In comparison, in cases of resistance to thyroid hormone, about 50% of patients have an increased resting pulse, 40% will have a goiter, and 10% will be hyperactive. Sequencing the TRβ gene will uncover a mutation in about 85% of cases thyroid hormone resistance, although the same mutation may have different clinical manifestations in different patients, possibly reflecting genetic variability in other factors that interact with the receptor. Patients with thyroid hormone resistance have a positive family history about 75% of the time, whereas familial TSHomas are rare but have been observed, particularly in families with multiple endocrine neoplasia type 1. Another disease included in the differential diagnosis is a recessive mutation in SBP2, the gene required for synthesis of selenoproteins, including the deiodinases. These patients have a high serum T_4, low T_3, high rT_3, and normal or slightly elevated serum TSH. Finally, some patients with a mild loss-of-function mutation in the TSH receptor can have an elevated serum TSH level, but be euthyroid; these patients generally lack a goiter or signs of hyperthyroidism or hypothyroidism.

The recent ETA guidelines, in reviewing therapy for TSHomas, strongly recommend surgical adenomectomy as the first-line treatment, with complete cure being expected for most microadenomas but being less likely in macroadenomas (1). Postsurgical complications, although not specifically addressed in the

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ETA guidelines, were observed in 3 of 14 patients in the current series, although no patient developed panhypopituitarism. The ETA guidelines, however, do state that SSAs reduce TSH levels in almost all cases, produce euthyroidism in 90%, goiter reduction in 30%, and reduce pituitary tumor mass in 40%, although in the current study only two tumors shrank after SSA treatment. The results of the current paper provide some support for using SSAs as primary therapy for some patients with TSHomas, but it bears noting that tachyphylaxis and glucose intolerance can also be side effects of SSAs. In the future, chimeric drugs that selectively target cells that express specific combinations of somatostatin and dopamine receptor types may provide another avenue for treating TSHomas that become resistant to octreotide (3).

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How Effective Are Clinical Guidelines for Hypothyroidism in Pregnancy in Clinical Practice?

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Granfors M, Akerud H, Berglund A, Skogö J, Sundström-Poromaa I, Wikström A-K. Thyroid testing and management of hypothyroidism during pregnancy: a population-based study. J Clin Endocrinol Metab 2013;98:2687-92. Epub May 20, 2013.

SUMMARY

Background

Recently, guidelines for the management of thyroid diseases in pregnancy (the Endocrine Society [1] and the ATA [2]) were published as well as a survey of European endocrinologists on the treatment and screening of hypothyroidism in pregnancy. The objective of the authors was to assess the integration of international guidelines into local guidelines and also into clinical practice.

Methods

Antenatal care in Sweden is standardized, free of charge, and decentralized to 41 maternity care areas. Within each maternity care area, a consultant in obstetrics is responsible for the development and implementation of guidelines. Twenty-nine different written guidelines were available for thyroid testing and management of thyroid disease. All districts recommended thyroid-function testing based on targeted case finding in high-risk women. A total of 5254 pregnant women delivered in a 3-year period (2009–2011). The guidelines were analyzed with respect to four different aspects: (1) the degree of adherence to the Endocrine Society Guidelines, (2) recommended thyroid-function tests, (3) the trimester-specific TSH upper reference limit for intervention with levothyroxine, and (4) the trimester-specific TSH upper reference limit for monitoring women undergoing treatment with levothyroxine.

Results

All but one district had guidelines on the subject. All local guidelines included fewer than the 10 reasons for thyroid testing recommended by the Endocrine Society Guidelines. Of the local guidelines, only 17.2% recommended thyroid testing solely with TSH. Most guidelines recommended additional types of thyroid-function tests (free T_4 [75.9%], TPOAb [37.9%], free T_3 [6.9%], and TSH receptor antibodies [6.9%]). Approximately 50% of the local guidelines advocated intervention with levothyroxine when first-trimester TSH exceeded 2.5 mIU/L, which was in accordance with the Endocrine Society Guidelines. In the follow-up, the thyroid-testing rate was 20%, with an 18.5% overall frequency of women with trimester-specific elevated TSH. More than half of the women (50.9%) who were on levothyroxine treatment at conception had an elevated TSH level. The TSH upper reference limits recommended by the local guidelines were significantly lower than those recommended by the Endocrine Society Guidelines. Only 3 of the 29 local guidelines were completely consistent with the international guidelines with respect to TSH trimester-specific upper reference limits for women with ongoing levothyroxine treatment. For women already undergoing levothyroxine treatment at conception, none of the local guidelines contained a recommendation for increasing the L-T_4 dose by 4 to 6 weeks of gestation. Most of the 163 women who were undergoing levothyroxine treatment at the time of conception were tested in the

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first trimester of pregnancy (91.4%). In only 4 of those 163 women was the dose of levothyroxine increased at an early stage of pregnancy before a thyroid test. Personal and family histories of thyroid disease were the most common reason for thyroid testing in the first trimester (28.9% and 43.6%, respectively); symptoms and clinical signs were the most common reasons for thyroid testing in the second and third trimesters (42.1% and 56.4%, respectively).

Conclusions

The authors concluded that the local guidelines are variable and poorly compliant with international guidelines. Performance of thyroid testing was not optimal, and rates of elevated TSH at testing were extremely high in subgroups.

ANALYSIS AND COMMENTARY

An article based on Danish nationwide registers that was just published (3) reported that both maternal hyperthyroidism and hypothyroidism were associated with increased risk of preterm birth and other maternal and obstetric complications. The study confirmed data published in the past three decades; in addition, the deleterious effect of maternal thyroid disease, active or inactive (such as women with a previous history of Graves' hyperthyroidism and persistent elevation of TSHRAb), on the fetus, newborn, and offspring is well known to the medical community. Several studies have also shown that controlling thyroid dysfunction in early pregnancy, before the third trimester, may avoid many of these complications (4-8). In order to assist the health care professional in the care of women in their childbearing years, the Endocrine Society published in 2007 recommendations for detecting women at higher risk for thyroid disease early in pregnancy, thyroid tests reference ranges in different trimesters of pregnancy and proper management of thyroid dysfunction (1). The guidelines were revised and published (9) along with similar recommendations by the American Thyroid Association (2). One clinical situation not well recognized in the medical community is the 30% to 50% increase in thyroid-gland secretion in early pregnancy, which was reported as early as 1990 (10). As the clinical corollary, serum TSH in the hypothyroid range early in pregnancy is consistently reported in about 50% of women on replacement levothyroxine therapy. The observations by Granfors et al. in a country with excellent organization in women's health show that consistency in the diagnosis and management of thyroid disease in pregnancy is lacking; even their own written guidelines, although similar in context to the ones published by the Endocrine Society and the ATA, differ from clinic to clinic. Because the outcomes of these pregnancies were not reported, it is impossible to determine the clinical significance of the lack of medical consistency in diagnosis and treatment. As mentioned in a previous analysis, better education for both medical practitioners and patients may hopefully improve obstetrical and medical outcomes in pregnant women affected by thyroid disease (11).

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Higher Environmental Exposure to Perchlorate and Thiocyanate, in Combination with Low Urinary Iodine, Is Associated with Decreased Thyroid Hormone Levels

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Steinmaus C, Miller MD, Cushing L, Blount BC, Smith AH. Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-08. Environ Res 2013;123:17-24. Epub March 7, 2013.

SUMMARY

Background

Perchlorate and thiocyanate are competitive inhibitors of the sodium–iodide symporter (NIS); therefore, there has been concern that environmental exposures might be associated with decreased thyroid function. In analyses of data from the National Health and Nutrition Examination Survey (NHANES 2001-2002), Blount and colleagues found that among women with urinary iodine values <100 µg/L, urinary perchlorate concentrations were positively associated with serum TSH and inversely associated with serum T_4 values (1). In the 2007-2008 NHANES data set, urinary perchlorate was inversely associated with total T_4 and free T_3, although urine iodine and thiocyanate were not included in regression models (2). The combined effects of perchlorate, thiocyanate, and iodine on thyroid function had not previously been assessed using the NHANES 2007-2008 database.

Methods

This cross-sectional study used data from NHANES 2007-2008. Urinary perchlorate, thiocyanate, iodine, and creatinine concentrations and serum T_4, free T_4, TSH, T_3, and TPO and Tg antibodies were measured in the majority of study participants. Covariates included sex, age, and urine specific gravity. Other potential factors were considered in a stepwise fashion but were not incorporated into final models if they did not change results, including race/ethnicity, educational level, income, serum albumin, 24-hour caloric intake, body-mass index, hours of fasting prior to sample collection, pregnancy status, menopausal status, self-reported history of thyroid disease, antithyroid antibody positivity, current lactation, and use of medications that might affect thyroid function (such as levothyroxine, antithyroid drugs, amiodarone, beta blockers, lithium, and estrogen). Analyses used weighting to account for the complex NHANES sampling design. Participants were categorized into three groups: group A (the reference group: urinary perchlorate and thiocyanate in the lowest tertile and urinary iodine ≥100 µg/L); group B (urinary perchlorate and thiocyanate in the middle tertile and urinary iodine ≥100 µg/L); and group C (urinary perchlorate and thiocyanate in the upper tertile and urinary iodine <100 µg/L).

Results

In adjusted models, serum total T_4 was 2.5% lower in the 1952 individuals with urinary thiocyanate concentrations in the highest tertile as compared with the 1915 individuals with concentrations in the lowest tertile. Serum total T_4 was 5.0% lower in the 1939 individuals with urinary perchlorate concentrations in the highest tertile as compared to the 2084 with concentrations in the lowest tertile. There were 390 participants in group A, 553 in group B, and 64 in group C. After adjustment for age, sex, and urine specific gravity, free thyroxine was 2.8% lower in group B and 7.1% lower

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in group C as compared with group A. Similarly, after adjustment for age, sex, and urine specific gravity, total thyroxine was 5.1% lower in group B and 12.9% lower in group C as compared with group A. Urinary perchlorate, thiocyanate, and iodine concentrations were not associated with serum TSH.

Conclusions

Exposure to higher environmental levels of both perchlorate and thiocyanate, in combination with low urinary iodine levels, was associated with lower serum free and total thyroxine levels.

ANALYSIS AND COMMENTARY

A major strength of this study design was the ability to examine multiple environmental exposures simultaneously rather than studying a single exposure in isolation. These data suggest that exposure to more than one NIS inhibitor may have additive effects, as previously observed in in vitro studies (3). Limitations include the cross-sectional design and the use of a single spot urinary iodine value as a proxy for dietary iodine status. More studies are needed to better understand why inverse associations have been found between environmental NIS inhibitor exposures and thyroid function in the NHANES population, but not in pregnancy and occupational cohorts (4,5). The Environmental Protection Agency has recently decided to regulate the permissible amounts of perchlorate in U.S. drinking water because of concerns about thyroidal disruption. However, better data are still needed to inform public health policy, given inconsistencies between previous studies. Ideally, future prospective studies will include vulnerable populations, will ascertain a wide variety of potential confounders, and will assess the combined effects of a wide range of exposures to multiple potential thyroidal disruptors.

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Taking Levothyroxine with Breakfast May Be Satisfactory for Many Patients

Jerome M. Hershman

Perez CL, Araki FS, Graf H, de Carvalho GA. Serum thyrotropin levels following levothyroxine administration at breakfast. Thyroid 2013;23:779-84. Epub June 21, 2013.

SUMMARY

Background

Many patients take their levothyroxine (L-T_4) tablet with breakfast because they do not have time to wait 30 to 60 minutes, as recommended, to avoid the possible interference of absorption caused by food. Does this make a difference for most people? The current study addresses this question.

Methods

This prospective, randomized, controlled, crossover study, conducted in Brazil, evaluated patients with primary hypothyroidism who were receiving L-T_4 either while fasting or during breakfast. The study included 45 patients with primary hypothyroidism who had normal serum TSH (0.5 to 3.5 mU/L) on their usual dose of L-T_4. Patients were excluded if they were pregnant or lactating, had serious chronic disease, were taking medication that could interfere with absorption or metabolism of L-T_4, or had malabsorptive disorders such as celiac disease. Only two brands of L-T_4 were used. Patients were randomly assigned to take a single brand at their customary dose for 90 days either after an overnight fast and 1 hour of fasting after taking L-T_4 before breakfast (group 1) or at the start of breakfast (group 2). Then each patient crossed over to the other regimen for 90 days. Thyroid function tests were performed at baseline and at 45, 90, 135, and 180 days, as was a clinical evaluation. Patients reported food intake at breakfast, and the nutritional and caloric content of the meals were assessed.

Results

Forty-five patients met the inclusion criteria and underwent randomization, but only 42 completed the protocol. Twenty started taking L-T_4 in the fasting state and 22 started by taking it with breakfast. The mean age was 46 years, and 90% were women. The mean (±SD) duration of hypothyroidism was 85±64 months and the mean baseline serum TSH was 1.7±1.3 mU/l.

Patients consumed approximately 381 kcal during breakfast, 58% carbohydrate, 28% protein, and 14% fat. The most consumed food items were coffee, sugar, milk, biscuits, and fruit.

When the TSH data at the end of each 3-month period from both groups were analyzed together, TSH was higher when L-T_4 was taken during breakfast (2.9±2.8), as compared with taking it with conventional fasting for 1 hour after ingestion (1.9±1.8) (P = 0.028). At the end of both treatment periods, some patients had elevated TSH levels: 6 (14%) had elevated TSH when they took L-T_4 on an empty stomach and 10 (24%) had elevated TSH when they took L-T_4 during breakfast. Specific food preferences and calculated caloric intake did not explain the elevated serum TSH levels. With regard to patient preference, 41% preferred the fasting administration because they were used to it, 33% preferred the breakfast regimen, and 26% indicated no preference.

Conclusions

Levothyroxine administration with breakfast could be an alternative regimen for patients who have adherence difficulties because of the need for delaying intake, but this regimen is more likely to cause variability in the TSH level.

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Taking Levothyroxine with Breakfast May Be Satisfactory for Many Patients

Jerome M. Hershman

ANALYSIS AND COMMENTARY

Variation of serum TSH levels in treated hypothyroid patients is often a cause of frustration to patients and physicians. Previous studies have differed with regard to whether it is preferable to take L-T_4 after an overnight fast and then waiting 30 to 60 minutes before breakfast or to take it before sleep (1, 2), as discussed in Clinical Thyroidology in April 2011 (3). After Wenzel showed that L-T_4 absorption was reduced by simultaneous food intake (4), withholding L-T_4 ingestion for 30 to 60 minutes has been strongly advised for better absorption of the hormone. Nevertheless, there are many patients who find this very inconvenient. If a patient does not want to take it before sleep because of a late meal, what should be done? I have found that many patients have reliable and normal serum TSH levels despite taking L-T_4 with breakfast, so I do not recommend that they change this pattern of ingestion.

The data of this study may be interpreted to show that taking L-T_4 with breakfast is reasonable. However, the data also clearly show that mean TSH levels are higher when L-T_4 is ingested with breakfast as compared with the conventional fasting regimen. More importantly, elevated serum TSH levels are probably more likely to occur when the dose is taken with breakfast. In patients who should have a precise serum TSH level, such as pregnant women or those with thyroid cancer, it is preferable to use the fasting or before-sleep regimen. But in the usual patient who has hypothyroidism, maintenance of a pattern that produces a normal serum TSH, whether L-T_4 is ingested with fasting or with breakfast, probably makes no difference.

As I stated in 2011 (3), I would like to get your thoughts about this common problem of the optimal time for L-T_4 ingestion.

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Repeated Dental X-Rays Without Neck Shielding Predispose to Thyroid Cancer

Jerome M. Hershman

Neta G, Rajaraman P, Berrington de Gonzalez A, Doody MM, Alexander BH, Preston D, Simon SL, Melo D, Miller J, Freedman DM, Linet MS, Sigurdson AJ. A prospective study of medical diagnostic radiography and risk of thyroid cancer. Am J Epidemiol 2013;177:800-9. Epub March 15, 2013; doi: 10.1093/aje/kws315.

SUMMARY

Background

Exposure to ionizing radiation at a young age is a well-established risk factor for thyroid cancer. Currently, diagnostic x-ray procedures are a leading source of exposure to ionizing radiation in the United States. The purpose of this study was to determine the risk of thyroid cancer in relation to various diagnostic radiation procedures.

Methods

The US Radiologic Technologists Study is a nationwide prospective cohort study of 146,022 radiologic technologists. It includes extensive data on self-reported personal medical histories of diagnostic imaging procedures collected at baseline in 1982 before the development of thyroid cancer. The present investigation focused on 75,494 technologists who responded to the first questionnaire and to additional questionnaires in 1994-1998 and 2003-2005. The diagnostic x-ray procedures that potentially involve radiation exposure to the thyroid gland included x-rays of the skull, cervical spine, head and neck, chest, and thoracic and lumbar spine; dental x-rays; mammograms; barium swallow examinations; angiograms; and upper gastrointestinal tract series. The estimated radiation dose to the thyroid from a full-mouth dental x-ray examination is estimated at 0.7 mGy, from a panoramic dental x-ray examination 0.4 mGy, and from a bitewing x-ray examination <0.1 mGy.

The investigators adjusted for the estimated occupational radiation exposure to the thyroid gland. They estimated the risk of thyroid cancer related to each of the 11 radiologic diagnostic procedures by using multivariate Cox proportional-hazards models.

Results

There were 75,243 noncases (controls) and 251 thyroid cancer cases, of which 187 were papillary. The mean age at study entry was 38 years, and all subjects were older than age 22 at entry into the study. Cases were more likely to be female, nonsmokers, and obese.

Dental x-rays were associated with an increased risk of all types of thyroid cancer (hazard ratio [HR], 1.13 per 10 radiographs; 95% CI , 1.01 to 1.26) and with the subgroup of papillary thyroid cancer (PTC) (HR, 1.18 per 10 radiographs; 95% CI, 1.04 to 1.33). The increase in thyroid cancer risk from dental x-rays was associated with exposure before 1970, but there was no evidence that the increased risk was associated with childhood or adolescent exposure. No other diagnostic radiation exposure was associated with an increased risk of thyroid cancer. An increased number and frequency of dental x-ray examinations was associated with an increased risk of thyroid cancer, including PTC. In addition, radiotherapy to the head was associated with a 2.7-fold increased risk of thyroid cancer (HR, 2.74; 95% CI, 1.52 to 4.95).

Conclusions

Repeated dental x-ray examinations before 1970 increased the risk for thyroid cancer.

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Repeated Dental X-Rays Without Neck Shielding Predispose to Thyroid Cancer

Jerome M. Hershman

ANALYSIS AND COMMENTARY

This carefully performed epidemiologic case–control study by a group with considerable experience in this area is very convincing because the subjects, radiologic technologists, were very sophisticated with regard to radiation exposure. It is interesting that procedures—such as chest CT, which gives 15.5 mGy to the thyroid, and cervical spine x-rays, which give 4.0 mGy—were not associated with the risk of thyroid cancer. The explanation is probably that these procedures were not done repeatedly or were not done when the subjects were young. A case–control study in Kuwait with a much smaller control group also concluded that dental x-ray examinations increased the risk of thyroid cancer with an odds ratio of 2.1 (95% CI, 1.3 to 3.1) (1). A Swedish case–control series of women with PTC also reported that more than 10 dental x-ray examinations increased the odds ratio to 3.5 (95% CI, 1.6 to 7.6) (2).

My dentist for over 20 years (the daughter of an endocrinologist) has used a lead apron with a thyroid shield when she takes my dental x-rays. The current recommendation by the American Dental Association stresses the need for shielding of the thyroid during dental x-ray examinations (3). Last year, the American Thyroid Association made a comprehensive recommendation about shielding during dental x-rays (http://thyroid.org/american-thyroid-association-ata-issues-policy-statement-on-minimizing-radiation-exposure-from-medical-dental-diagnostics). Take heed and advise your patients about this preventive measure.

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Clin Thyroidol 2013;25:203–204.

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Male Sex is Not an Independent Prognostic Factor for Thyroid Cancer

Jerome M. Hershman

Nilubol N, Zhang L, Kebebew E. Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin. Thyroid 2013;23:695-702. Epub May 28, 2013; doi: 10.1089/thy.2012.0269.

SUMMARY

Background

Thyroid cancers in men have usually been regarded as having a worse prognosis than thyroid cancers in women. The data to substantiate that sex is an important factor in the prognosis of thyroid cancer may be misinterpreted when other clinical factors are not considered. The current study focuses on sex as a prognostic factor in an analysis of over 60,000 cases of differentiated thyroid cancer in the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

The study included 61,523 adult patients with non-medullary thyroid cancer in the SEER database from 1988 to 2007. The patients were divided into four groups based on tumor histopathology: group 1 had moderately differentiated thyroid cancer (DTC), group 2 had papillary thyroid cancer (PTC) with Hürthle cells, group 3 had poorly differentiated DTC (columnar, insular, tall-cell variants), and group 4 had undifferentiated thyroid cancer. The variables analyzed were age (<45 and >45 years), sex, and race, histology (groups 1 to 4), greatest dimension of the primary cancer, extrathyroidal extension, cervical lymph-node metastasis, distant metastasis, types of surgery, radiotherapy (none, radioisotopes, external radiotherapy, combined radioisotopes and external-beam radiation therapy, and disease-specific survival (DSS).

Results

The mean follow-up time was 54 months. At the time of diagnosis, 61.2% of men were >45 years of age, as compared with 49.7% of women (P<0.01). Men had significantly more aggressive histologic subtypes of DTC and undifferentiated thyroid cancer. Moreover, men had significantly more advanced disease at presentation: larger primary tumor size (P<0.01), higher rates of extrathyroidal extension (P<0.01), regional lymph-node metastasis (P<0.01), and distant metastasis (P<0.01). Stratified by histology, there was a strong association between men and larger tumor size (P<0.01) and more advanced stage at presentation. Men had shorter DSS than women, regardless of age. Although univariate analysis showed that sex was a significant prognostic factor associated with disease-specific survival (DSS) (P<0.01), sex was not an independent prognostic factor associated with DSS by multivariate analysis.

Conclusions

Men with thyroid cancer are more likely to present with more advanced disease, aggressive histologic subtypes, and older age, but male sex is not an independent prognostic factor for DSS.

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Male Sex is Not an Independent Prognostic Factor for Thyroid Cancer

Jerome M. Hershman

ANALYSIS AND COMMENTARY

The excellent analysis by these authors shows that the worse survival of men with DTC is attributed to more advanced disease at the time of presentation. The authors suggest that more aggressive screening of men to detect thyroid cancer at an earlier stage would improve their outcomes, and this seems very reasonable. The worse outcome of men with thyroid cancer has influenced the evaluation of thyroid nodules to the point at which, all other factors being equal, male sex is in the minds of many endocrinologists a factor that enters into the decision for surgical removal. However, the data of the authors shows that survival of men is related to traditional risk factors and not male sex.

Others have concluded that sex is not an independent risk factor in DTC in multivariate analysis in smaller cohorts (1,2). At this time, it is still unclear whether men have intrinsically more aggressive disease or whether the reduced DSS is due to delayed diagnosis. When men present with localized disease, their survival is the same as that in women, a factor that reinforces the conclusion that sex is not an independent factor for DSS.

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Clin Thyroidol 2013;25:205–207.

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The Phenotypes of TRα1 Mutations Can Greatly Vary

Albert G. Burger

Van Mullem AA, Chrysis D, Eythimiadou A, Chroni E, Tsatsoulis A, de Rijke YB, Visser WE, Visser TJ, Peeters RP. Clinical phenotype of a new type of thyroid hormone resistance caused by a mutation of the TRα1 receptor: consequences of LT_4 treatment. J Clin Endocrinol Metab 2013;98:3029-38. Epub April 30, 2013.

SUMMARY

Background

Since the description of T_3 receptors in 1987, many patients with T_3-receptor mutations have been described. These mutations were restricted to $T_3\beta$ receptor (TRβ) (1-3). It was only in 2012 that the first human case of a dominant mutation of the α1 receptor (TRα1) was described (4). The patient had clinically hypothyroidism, was mildly mentally retarded, was of short stature, and had skeletal dysplasias, while the predominant symptom was severe constipation. This is to be expected, since the intestine is highly endowed with TRα1. Biologically, the thyroid parameters were characterized by a normal serum TSH, a decreased free T_4 and increased T_3 and free T_3. In the present article, the authors review the cases of a daughter and her father who were affected by the mutation. The girl, the index case, has been followed clinically since the age of 6 years.

Methods

In vitro, the mutation was tested by functional analyses in cell cultures transfected with mutant TRα1 and/or nonmutant TRα1. The index patient was treated from the ages of 6 to 11 years with thyroxine. At the age of 8½ years, growth hormone treatment was begun. At age 11, thyroxine treatment was stopped for 35 days. While off treatment with thyroxine, and 7 months after restarting thyroxine, clinical analyses were performed. Thyroxine treatment for the father was also withdrawn for 35 days.

Results

In vitro, the mutated receptor was not only inactive but, in addition, it completely inhibited the activation of the normal TRα1 by T_3. The mutation is therefore of the dominant negative type. It also affected the functional activity of TRα1, but this could be overcome by higher T_3 doses.

The genetic analysis of the index case and her father revealed a heterozygotic mutation with an insertion of thymine at codon 397 (F397fs406X). The index patient had moderately impaired cognitive function; her mental age was retarded by 4 to 5 years. She was of short stature. Her pulse rate when off treatment was 88 beats per minute. The blood pressure and electrocardiogram were normal. Her pubertal age was 12. At the age of 3 years the patient was considered to have clinical hypothyroidism because of symptoms such as macroglossia, omphalocele, and congenital hip dislocation (5).

In the index patient and her father, thyroid hormone levels, when off thyroxine treatment, showed high serum T_3 and free T_3, a normal serum TSH, and a borderline decreased T_4 and free T_4. The T_3:T_4 ratio was clearly increased. When on thyroxine treatment, the index patient's serum T_4 levels normalized, as did the T_3:T_4 ratio, but serum TSH decreased to suppressed levels of 0.1 mU/L Before and after the interruption of thyroxine treatment, total and LDL cholesterol levels were clearly elevated despite high serum T_3 levels.

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Without thyroxine treatment, insulin-like growth factor I (IGF-I) levels tended to decrease and thyroxine treatment corrected the cholesterol and IGF-I values. In the index patient and her father, moderate constipation was present during thyroxine withdrawal but was corrected with treatment. The pulse rate in the index patient increased to 94 beats per minute while on thyroxine treatment.

Conclusions

Heterozygotic dominant negative mutations of TRα1 should be considered in a slightly retarded child with short stature and high serum T_3 levels but borderline low total and free T_4 levels. Serum TSH is not informative. When thyroxine treatment was withdrawn, constipation recurred but not in as severe a form as in the first case described. This indicates that the phenotype can be variable. Thyroxine treatment stimulated the TRβ-mediated effects (such as deiodinase type I, sex-hormone–binding globulin (SHBG), and TSH inhibition). Constipation is likely to be related to the mutated intestinal TRα1; unexpectedly, it seemed to respond to thyroxine treatment. The short period of thyroxine withdrawal did not allow obtain any information on possible cognitive effects of thyroxine.

ANALYSIS AND COMMENTARY

It is obvious that such cases should be discovered at birth in order for T_4 treatment to be started immediately. Only then would it be possible to see whether thyroxine has any beneficial effects on the most crucial of all TRα–mediated actions, that on brain development. Such treatment will, however, come with the price of overstimulating TRβ-dependent effects, such as TSH inhibition and stimulation of deiodinase type 1 activity; other effects, such as those on cholesterol and SHBG, are of minor consequence. Deiodinase type 1 activity is strongly dependent on TRβ-related effects, and this explains the high serum T_3 levels. Thus, it has been proposed to add PTU to the thyroxine to specifically inhibit deiodinase type I activity.

The thyroid hormone values (low T_4 and increased T_3) together with normal serum TSH should not be mistaken for other pathologies. Iodine deficiency and dyshormogenesis would have similar T_4 and T_3 levels, but serum TSH levels would be in the high normal range or increased. In the syndrome of resistance to TRβ, both T_4 and T_3 will be increased, while serum TSH is normal or slightly increased.

Most neonatal screening programs measure either serum TSH or T_4. In this particular situation, TSH screening will miss the mutation, as in the case of central hypothyroidism. Most children come to the attention of the pediatrician much later, when parents get worried about delayed development. Because of the nature of the mutation, a dominant negative one, treatment with thyroxine may be fraught with difficulties, even though these authors report that constipation, probably an α-dependent manifestation, was improved. In order to enhance the chances of an early diagnosis, a large-scale prospective study measuring both T_4 and TSH may be welcome.

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Clin Thyroidol 2013;25:208–211.

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An Atypical Case of a Slowly Progressive Undifferentiated Thyroid Carcinoma

Wendy Sacks

CASE PRESENTATION

A 69 year old woman was found to have hypothyroidism and a goiter on preoperative evaluation before foot surgery in 2010. She was otherwise well and had no family history of thyroid disease. She was referred for endocrinologic evaluation when the goiter enlarged significantly over a one month period, and within 6 months, she reported new onset of dysphagia and neck discomfort. Ultrasound and CT scan (Fig. 1) of the neck showed an enlarged and heterogeneous thyroid gland, particularly involving the right lobe which extended inferiorly into the superior mediastinum. There was mild tracheal shift to the left and possibly mild tracheal narrowing. This patient went for thyroidectomy 6 months after initial presentation. The operative report described the gland as adherent to both recurrent laryngeal nerves (RLN), trachea and esophagus with involvement of strap muscles and the right internal jugular vein. The thyroid weighted 67 grams. Surgical pathology reported multifocal undifferentiated thyroid carcinoma with multiple foci of lymphovascular invasion, extracapsular tumor extension and an incidental microscopic nodule with follicular variant papillary thyroid carcinoma (Figs. 2, 3). Three central neck lymph nodes were replaced by undifferentiated thyroid cancer. Immunostains were strongly positive for thyroglobulin, TTF-1, and vimentin confirming the thyroid origin of the tumor. The slides were sent for expert opinion to Dr. Juan Rosai who categorized the tumor as undifferentiated rather than poorly differentiated stating, "it is worse looking than usual poorly differentiated carcinoma, although clearly epithelial and not as sarcomatoid as anaplastic carcinoma." The patient has had persistent postoperative hypocalcemia and required a tracheostomy due to RLN injury. One month after surgery her thyroglobulin (Tg) was 3,000ng/mL with negative TgAb).

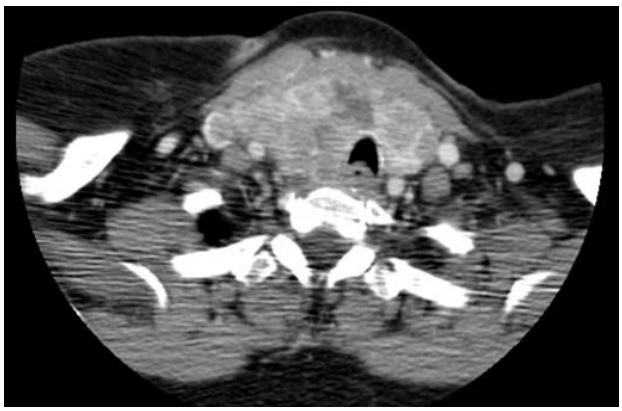

Figure 1: CT scan performed prior to thyroidectomy. Enlarged and heterogeneous thyroid gland, particularly involving right lobe. Thyroid gland extends inferiorly into superior mediastinum. Trachea is shifted to the left.

Postoperatively, a PET/CT scan (Fig. 4) showed hypermetabolic uptake in the thyroid bed, right cervical lymph nodes and multiple lung nodules. She was treated aggressively for Stage IVC (T_4b,N1,M1) anaplastic carcinoma with postoperative external beam radiation (EBRT) to the head and neck followed by chemotherapy. EBRT included 68 Gy in 34 fractions directed to residual gross disease in her neck and 50 Gy in 25 fractions to uninvolved areas within the radiation field in the bilateral neck and upper thorax from the chin down to aortic arch. She then received 6 cycles of taxol and carboplatin. CT imaging after treatment demonstrated shrinkage of multiple small lung nodules and near-complete resolution of a right paratracheal soft tissue mass as well as right middle lobe lung nodule.

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One year after surgery, EBRT, and chemotherapy, her Tg was 143ng/mL (negative TgAb) and the largest lung metastasis measured 5mm. By 15 months after the initial treatment, the Tg increased to 197ng/mL and repeat PET/CT imaging of the lungs demonstrated an increase in number, size and FDG avidity of the lung nodules. The patient was then referred for radioiodine treatment (RAI) with 200 mCi. The reasons for use of RAI were 1) the spectrum of pathology, including remnants of FV-PTC in addition to undifferentiated histology, 2) Tg continued to be produced suggestive that there is a component of differentiated thyroid carcinoma within the tumor, and 3) overall treatment options were limited. The post-treatment whole body scan demonstrated uptake in the neck, but not in the lungs. Interestingly, over the following 6 months, her Tg decreased to 64 ng/mL and lung nodules also decreased in size from 7 mm to 5mm.

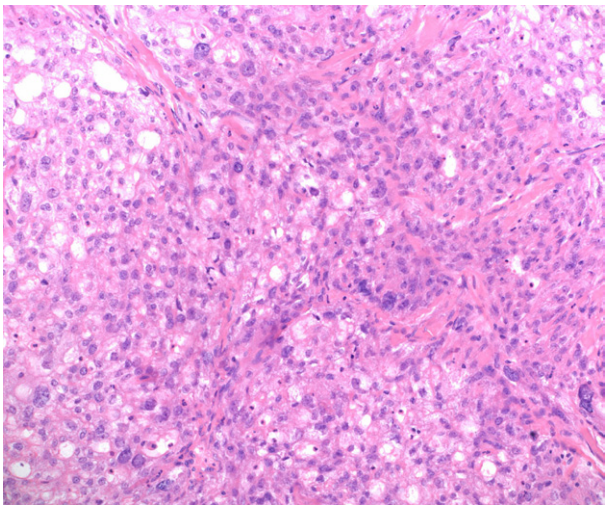

Figure 2. Papillary thyroid carcinoma showing a papillary architecture with nuclear clearing and overlapping (H&E, x100), which is a part of the tumor of the anaplastic thyroid carcinoma showing in Fig 3.

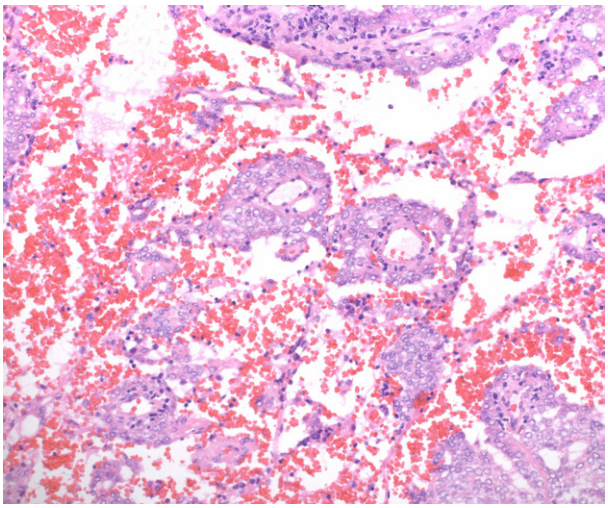

Figure 3. Anaplastic thyroid carcinoma showing a giant cell type with nuclear pleomorphism and marked cytologic atypia (H&E, x200).

Serial imaging every 3 months since the Tg nadir has revealed lung metastases that have increased in size up to 8 mm from 5 mm in the prior year. FDG uptake was not seen on repeat PET imaging which may have been due to poor preparation. Additionally, the Tg increased to 347ng/mL.

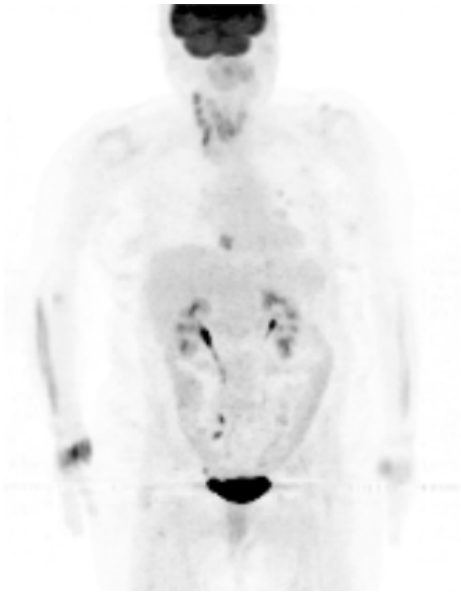

Figure 4: Postoperative PET scan. Hypermetabolic uptake in region of thyroid bed, extensive enlarged lymph nodes in right carotid space (involving level II, III, and IV regions) and extending inferiorly into superior mediastinum. Uptake within inferior right jugular vein and extending into right superior vena cava (may be related to tumor involvement). Multiple nodules are in lungs with many demonstrating metabolic activity. These nodules are highly suspicious for metastases.

ANALYSIS AND COMMENTARY

While anaplastic thyroid carcinoma (ATC) is not common, comprising just 1-2% of thyroid cancers, it has a dismal prognosis and accounts for up to 39% of thyroid cancer deaths with a median survival of 6 months (1). The peak incidence of ATC occurs in the sixth and seventh decades of life with a female/male ratio of 5 to 1 (2). Most patients with ATC present with a rapidly enlarging anterior neck mass accompanied with dysphagia (40%), voice change (40%), and stridor (24%). ATC is usually advanced at the time of diagnosis with up to 50% of patients having distant metastases at the time of diagnosis (2). On the one hand, our patient had a classic initial presentation of ATC with a rapidly enlarging mass, dysphagia, and distant metastases. On the other hand, the biological behavior of her malignancy is not typical since she is still alive and asymptomatic 3 years after diagnosis. While the tumor pathology is consistent with an undifferentiated carcinoma, clinically, there has been relatively slow progression of disease. In addition, her tumor (or at least a part of the tumor) has demonstrated a response to radioactive iodine, also uncommon for ATC. It suggests that her cancer arose as a dedifferentiation from a pre-existing more well-differentiated tumor. ATC may derive "de novo" or from pre-existing papillary or follicular thyroid carcinoma. Gene mutations seen in well-differentiated thyroid cancers such as BRAF and RAS are also seen in ATC. Other mutations contributing to the molecular pathogenesis of ATC include p53, catenin (cadherin-associated protein), beta 1, PIK3CA, AXIN1, PTEN, APC genes and chromosomal abnormalities (3). Genetic alterations in the p53 tumor suppressor gene on chromosome 17p are the most frequent mutation in ATC (55%) resulting in tumor growth, angiogenesis and dedifferentiation. These molecular markers hold promise as potential therapeutic targets.

The American Thyroid Association guidelines for the management of anaplastic thyroid carcinoma stress the importance of discussing with the patient the overall goals and preferences of therapy since treatment for ATC can have many significant side effects. (4) An aggressive multidisciplinary team approach with multimodal therapy is a reasonable option. A recent publication assessed overall survival in a cohort of 2742 ATC patients from the National Cancer Database (5). Patients who received intensive therapy including surgery, radiation and chemotherapy had the longest median overall survival in Stages IVA (11.2 months), IVB (9.9 months) and IVC (4.9 months) when compared to those who did not receive multiple treatment modalities. Although the results demonstrate a significant difference, the actual length of prolonged survival was marginal.

Summary

Our patient is an otherwise healthy 69 year-old woman with ATC who has expressed a strong desire to pursue all treatment modalities available to treat her cancer. While she remains asymptomatic, her disease is progressing, albeit more slowly than a typical ATC. She has already undertaken multiple treatment modalities including surgery, external beam radiation therapy, systemic chemotherapy and RAI treatment. Current therapeutic options are limited. A second dose of RAI may treat the better-differentiated part of her disease, but likely will not slow the progression of the RAI resistant tumor. In a phase II clinical trial using sorafenib for ATC, 2 of 20 patients (10%) responded to the drug and 5 of 20 patients (25%) showed stable disease for median duration of 4 months (range 3-11 months) (6). Rosove reports that a 51 year old male patient with a BRAF V600E positive ATC treated with vemurafenib demonstrated a dramatic regression of metastases (7). These drugs are off-label options for our patient; ideally, identifying the specific gene alterations in her tumor may permit targeting it with one or more chemotherapeutic agents against the tyrosine kinase signaling pathway and/or the neoangiogenesis signaling cascade. Unfortunately, this is not yet possible.

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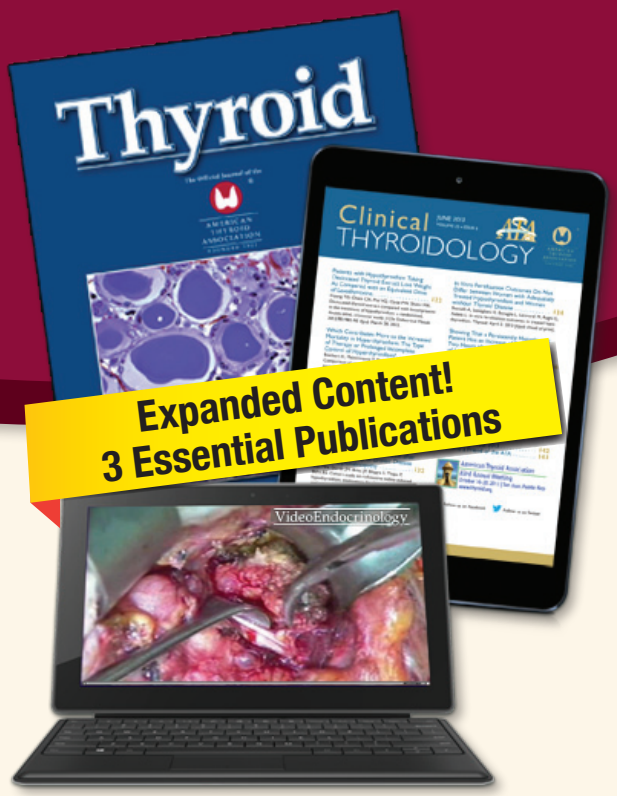

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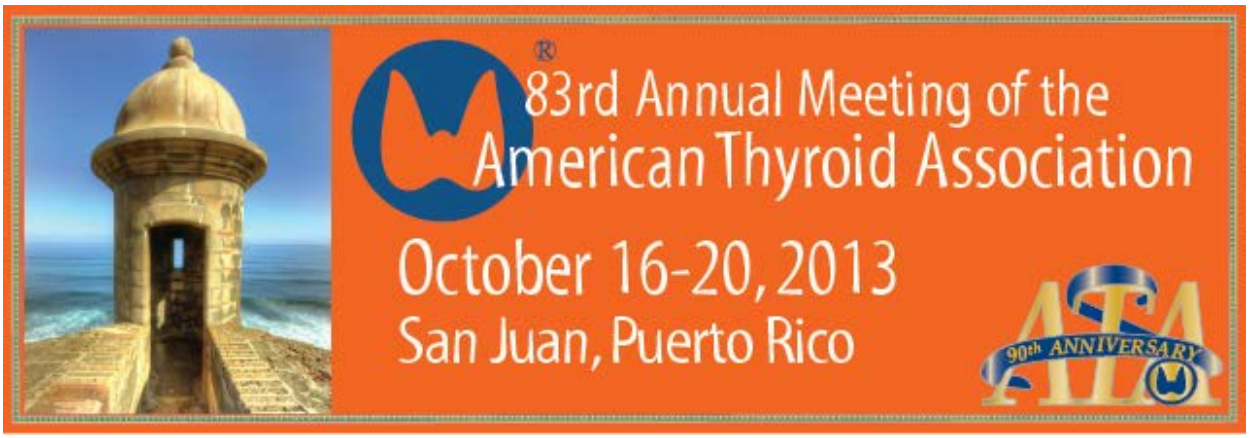

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The American Thyroid Association (ATA) is a nonprofit medical society composed of physicians and scientists who specialize in the research and treatment of thyroid diseases. Dedicated to improving the lives of the millions of Americans of all ages living with thyroid problems, we are strongly committed to serving as a resource for these patients and the public and to promoting the prevention, treatment, and cure of thyroid-related diseases.

With extensive online resources for thyroid patients, families, and the general public at *www.thyroid.org*, each year we reach thousands of people who have come to rely on us for health information they can trust.

- Answers to frequently asked questions, or FAQs;
- Brochures on specific thyroid diseases;
- A database of ATA members called "Find a Thyroid Specialist";
- A toll-free telephone number with referrals to patient education materials and support groups; and
- Links to the ATA Alliance for Patient Education: organizations that provide support for understanding and coping with thyroid disease and its treatments.

Visit *www.thyroid.org* and become a *Friend of the ATA*.