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SCIENTIFIC LETTERS

## A thyroid nodule overtreated twice

### Nódulo tiroideo sobretratado dos veces

*Dear Editor,*

In the last few decades, there has been an epidemic of thyroid cancer in the U.S. and the rest of the world. Overdiagnosis of thyroid cancer contributes mostly to the high incidence of thyroid cancer.[1] Overtreatment of thyroid nodule is another common, but less recognized form of healthcare waste and contributes to patient morbidity. Even when an appropriate diagnostic approach is followed, treatment of thyroid nodule with clinical, sonographic, and cytological characteristics suggestive or suspicious of thyroid cancer may be overzealous or unnecessary in selected cases.[2] Apparent or superficial adherence to treatment guidelines may not be sufficient to avoid overtreatment, which is illustrated in the case presented here.

A 45-year-old female consulted in July 2016 for a second opinion on management of thyroid cancer. In 2011, at age 40, she had an enlarging right thyroid nodule, a few centimeters in diameter. Thyroid ultrasound examination was not performed. The nodule was needle-biopsied and cytology showed a follicular lesion. In 2012, at age 41, she underwent right hemithyroidectomy at an outside hospital. Histological examination of the surgical specimen showed a 3.2-cm encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), without extrathyroidal extension or capsular or angiolymphatic invasion. One perithyroidal lymph node was resected which was negative for metastasis. The tissue slides were also reviewed at our institution which agreed with the diagnosis. She underwent completion thyroidectomy 2 months later. Histological examination of the left thyroid lobe did not find any cancerous lesions. Radioactive iodine (RAI) ablation was considered but not performed due to the patient's chronic renal insufficiency (see below). She was given levothyroxine 150–175 mcg daily. During the next 3 years, her thyroglobulin (Tg) and Tg antibody (TgAb) levels remained undetectable with normal TSH levels. Neck ultrasound examination did not find suspicious lesions. Besides this problem, her main remaining medical history was chronic renal insufficiency of unknown cause. She had been on hemodialysis since age 35 (2006). She underwent deceased-donor renal transplantation at age 44 in 2015. She received one dose of rabbit anti-thymocyte globulin intraoperatively, and prednisone and mycophenolate postoperatively. Two weeks after the renal transplantation, TSH level was 1.8 mU/L, Tg undetectable, and TgAb 2 IU/mL (lowest detection level 1 IU/mL). The newly positive TgAb level was considered to be evidence of PTC recurrence. She underwent recombinant TSH (Thyrogen)-stimulated RAI ablation in early 2016. While under Thyrogen stimulation, Tg level was 1.3 ng/mL while TgAb were undetectable. Post RAI scan showed neck and anterior mediastinum uptake. Three months later, neck ultrasound found a 1-cm complex nodule in the right thyroid bed; at that time TgAb were 1 IU/mL (lowest detection level 0.9 IU/mL). The nodule was biopsied and cytology did not find PTC cells; the cells were negative for TTF-1 but positive for PTH immunostaining, suggesting parathyroid tissue. Due to the detectable TgAb, the patient was believed to have persistent PTC at an unknown location. She was given levothyroxine 175 mcg, resulting in suppressed TSH (0.01 mIU/L) and elevated FT4 (1.9 ng/dL, range 0.8–1.8).

When the patient was seen in our clinic in July 2016, she felt well without symptoms of hyperthyroidism. She denied dyspnea, dysphagia, or hoarseness. She had never been exposed to neck radiation and had no family history of thyroid cancer. As the renomenclature of EFVPTC to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) had already been published online in April 2016,[3] the patient was reassured that, in retrospect, she did not have thyroid cancer in the first place. The slightly elevated TgAb levels were likely caused by the immunomodulating therapy she received during and after renal transplantation. She was recommended to decrease levothyroxine dose to target normal TSH levels and to do annual physical examination of the thyroid bed. Six months later, her Tg and TgAb levels were both undetectable (lowest detection level of TgAb 0.9 IU/mL).

The patient presented here underwent appropriate workup for a growing thyroid nodule. As needle biopsy of the nodule showed a follicular lesion which carries a malignant rate of 15–30%,[4] it is reasonable to perform right hemithyroidectomy to remove the nodule, although molecular studies of the biopsied tissue may add value in refining the risk of malignant thyroid nodule.[5] After surgical pathology demonstrated EFVPTC in this patient, it was controversial to do completion thyroidectomy. Even before the renaming of EFVPTC to NIFTP, strong evidence already suggested that EFVPTC has largely indolent behaviors.[6,7] For example, a study in 2006 showed that all 43 patients with EFVPTC without invasion did not have lymph node

or remote metastasis and had no recurrence even after hemithyroidectomy.[7] At least in hindsight, right hemithyroidectomy was a sufficient therapy for this patient. The use of ''cancer'' in the name of EFVPTC may have led to the perception that EFVPTC is, after all, cancer, so that a full-blown thyroid cancer therapy including total thyroidectomy and RAI ablation is needed.[6] The patient described here indeed would have undergone RAI ablation right after completion thyroidectomy had she not been on hemodialysis. Unfortunately, she could not escape from the unnecessary RAI therapy due to a second mistake in her care.

The patient initially had no evidence of thyroid or thyroid cancer tissue after completion thyroidectomy, as shown by the undetectable Tg and TgAb levels and negative neck ultrasound findings. The slightly elevated TgAb level and normal Tg level 2 weeks after renal transplantation were overzealously interpreted as evidence of thyroid cancer recurrence or metastasis. As TgAb interferes with Tg measurement and causes inaccurate Tg results, and increased TgAb levels or de novo appearance of detectable TgAb levels during follow-up of thyroid cancer suggest thyroid cancer recurrence, TgAb measurement is important for monitoring thyroid cancer recurrence and progression[8] There are a few caveats, however, in the interpretation a positive TgAb result, such as effects of different assays and random laboratory variations. An increasingly realized issue in the use of TgAb as a surrogate of thyroid cancer recurrence is the unpredictable effects of immunomodulating drugs which may stimulate or suppress TgAb levels.[9] Interferon and cancer vaccine have each been shown to stimulate TgAb developments. It is recommended that TgAb should not be measured until 6 months after the use immunomodulating drugs.[9] This patient received rabbit anti-thymocyte globulin, prednisone, and mycophenolate intra- and post-operatively; 2 weeks later, TgAb was measured and became slightly positive de novo. Although none of the 3 immunomodulating drugs has been reported to stimulate TgAb development, rabbit anti-thymocyte globulin has been reported to stimulate development of heterophilic antibodies which may interfere with TgAb measurement.[10] The de novo development of slightly elevated TgAb 2 weeks after renal transplantation is thus likely attributable to the use of immunomodulating drugs.

In summary, this case illustrates that patients with thyroid nodule can be overtreated multiple times due to the insufficient understanding of the nuances of histological diagnosis and of the comprehensive interpretation of positive laboratory test results. Treatment of thyroid nodules should be individualized. The new nomenclature of NIFTP (replacing EFVPTC) and awareness that TgAb levels can be altered by immunomodulating drugs should help reduce overtreatment of thyroid nodules.

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Run Yu

*Division of Endocrinology, UCLA David Geffen School of Medicine, Los Angeles, CA 90095, United States*
*E-mail address:* runyu@mednet.ucla.edu



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