Rising serum antithyroglobulin antibody levels predict recurrence of differentiated thyroid carcinoma in thyroglobulin-negative patients

Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, Ryu JS, Gong G, Hong SJ, Shong YK. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2008;93:4683-9.

SUMMARY

BACKGROUND Serum antithyroglobulin antibodies (TgAbs) are found in 10 to 25% of patients with differentiated thyroid carcinoma (DTC), as compared with an incidence of approximately 10% in the general population. This poses a serious problem in the follow-up of patients with DTC, as circulating TgAb interferes with serum thyroglobulin (Tg) measurements performed by immunometric assays. Thyroid cancer management guidelines suggest that TgAb levels serve as a surrogate for serum Tg measurement during follow-up, providing TgAb is measured in the same laboratory. Kim et al. hypothesize that changes in serum TgAb might predict tumor outcome, which has been a point of contention in previous studies. The aim of this study was to determine whether a changing pattern of TgAb levels found soon after thyroidectomy could serve as a prognostic indicator.

METHODS This retrospective study was performed on 1499 consecutive patients treated for DTC in the authors' hospital from 1995 through 2003. All had total thyroidectomy followed by remnant ablation with 100 to 150 mCi (3.7 to 5.55 GBq) of ^{131}I about 6 weeks after surgery. Patients selected for study had no preoperative evidence of extracervical tumor, or ^{131}I uptake outside the thyroid bed on the posttreatment whole-body scan (RxWBS) or in the thyroid bed on the first diagnostic whole-body scan (DxWBS) during follow-up. Patients with extracervical metastases or poorly differentiated or anaplastic thyroid cancer were excluded from the study. Follow-up DxWBS was performed with 4 mCi (148 MBq) of ^{131}I after thyroid hormone withdrawal every 3 to 6 months along with serum Tg and TgAb measurements. When serum Tg was above 2 μg/L, other imaging studies were performed according to the clinical findings. Recurrence was defined as tumor reappearance after complete remnant ablation and undetectable serum Tg and TgAb. Persistent disease was defined as the identification of tumor confirmed by cytology or histopathology after complete ^{131}I ablation. Lymphocytic thyroiditis was diagnosed according to the classic histologic findings of Hashimoto's disease. Serum Tg measurements were performed by an immunometric assay with a functional sensitivity of 1 μg/L, and TgAb was performed by a radioligand assay in which a TgAb value greater than 100 U/ml was considered positive. Tumors were staged by the TNM (tumor–node–metastasis) classification system of the International Union Against Cancer and the American Joint Committee on Cancer, revised in 2002 (6th edition). The change in TgAb concentrations measured between the time of remnant ablation (TgAb1) and 6 to 12 months later (TgAb2) was evaluated as a possible prognostic indicator.

RESULTS A total of 824 patients were selected for study, 747 (91%) women and 77 (9%) men, all of whom had undetectable serum Tg values after thyroid hormone withdrawal and no visible uptake on the first DxWBS. Their mean (±SD) age was 46±11.6 years (range, 13.0 to 76.4). In all 88% had papillary thyroid cancer, 6% had follicular variant papillary thyroid cancer, and 7% had follicular thyroid cancer. Tumors were >4 cm in 7%, were multifocal in 35%, had extrathyroidal invasion in 53%, and had lymph-node metastases in 50%.

Twenty patients (24%) had recurrent or persistent tumor (1 man and 19 women). Their mean age was 51.5±12.8 years (range, 33.1 to 73.8). A mean interval of 50.4±21.7 months (range,

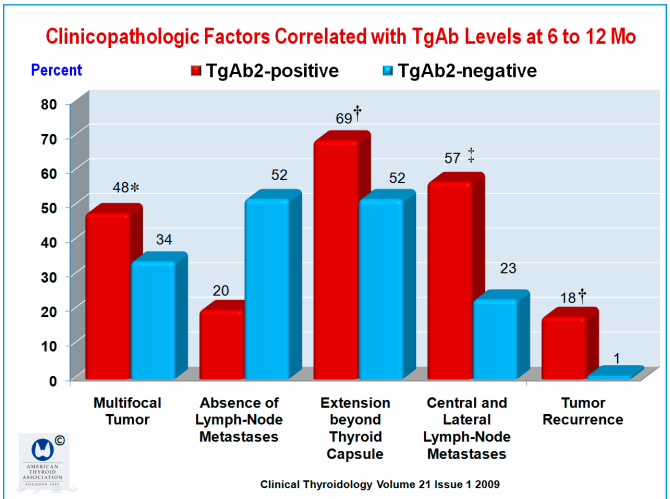

Figure 1. Clinical factors that correlate with TgAb levels at 6 to 12 months of follow-up *P = 0.04, †P< 0.001, ‡P = 0.01 comparing outcome in positive versus negative TgAb2. Not shown in the figure, 22 patients (39%) in the TgAb2-positive group and 150 (20%) in the TgAb2-negative group had lymphocytic thyroiditis (P<0.001). Figure is derived from data in Table 2 of Kim et al.

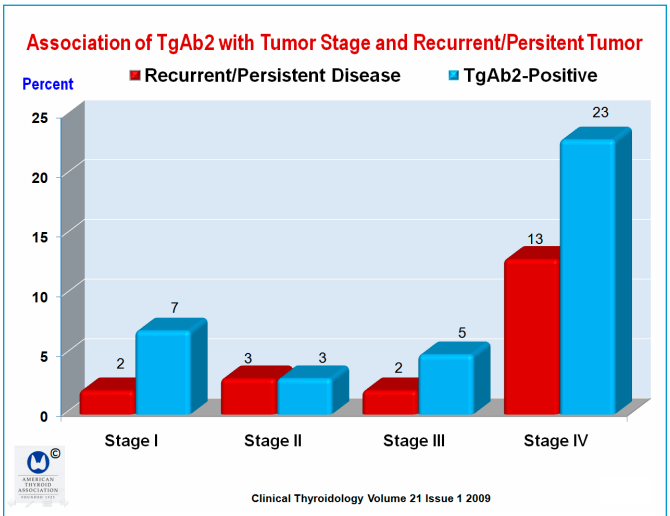

Figure 2. The association of TgAb2 with tumor stage and recurrent/persistent disease

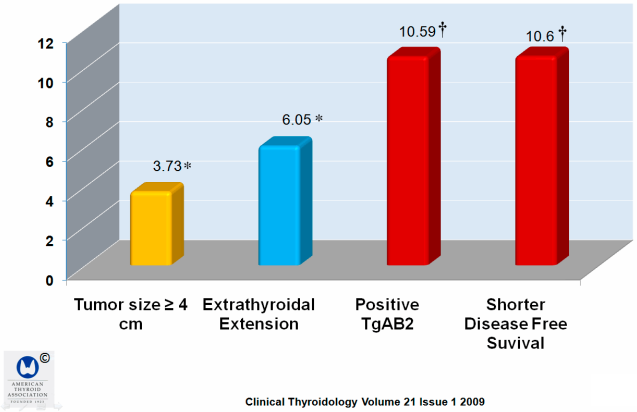

Figure 3. Clinicopathologic factors independently associated with persistent/recurrent tumor. *P<0.0.02, †P = 0.01. Figure is derived from multivariate analysis data in Table 3 of Kim et al.

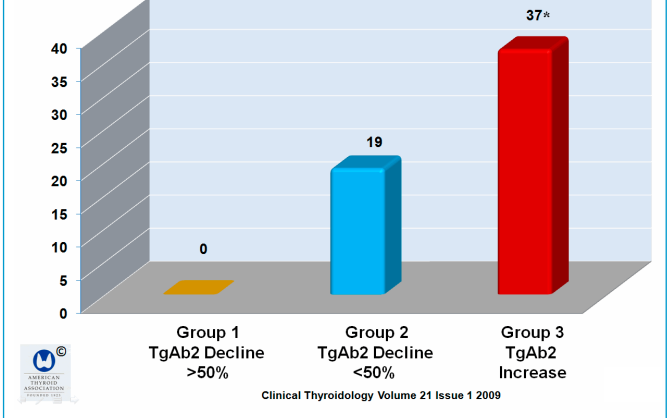

Figure 4. The association of recurrent/persistent disease with changing TgAb2 values *P = 0.016

16.2 to 118.5) transpired from the time of TgAb2 measurement and confirmation of recurrent or persistent disease. In all, 56 of the 824 patients (6.8%) had TgAb values >100 U/ml at the time of the first DxWBS (TgAb2). At 6 to 12 months there were no significant differences in age, gender, or tumor size in TgAb2-positive and TgAb-negative patients; however, compared with the TgAb2-negative patients, a greater number of TgAb2-positive patients had multifocal tumors (48 vs. 34%, P<0.04, Figure 1) and tumors with extension beyond the thyroid capsule (69 vs. 52%, P = 0.01) and central and lateral cervical lymph-node metastases (57% vs 23%, P<0.001) (Figure 1). Twenty-two patients (39%) in the TgAb2-positive group and 150 (20%) in the TgAb2-negative group had lymphocytic thyroiditis (P<0.001). There was an association between TgAb2-positivity and tumor stage (Figure 2).

TgAb2 was positive in 56 patients, 10 of whom (18%) had recurrence, while TgAb2 was negative in 768 patients, only 10 of whom (1%) had recurrence during 73.6 months of follow-up (P<0.001). Univariate analysis found that recurrent/persistent tumor was associated with tumor size (P = 0.02) and extrathyroidal extension (P<0.001) (Figure 3). Multivariate analysis found an independent association between recurrent/persistent disease and extrathyroidal extension of tumor (hazard ratio [HR], 6.05; 95% confidence interval [CI], 1.4 to 26.5; P<0.02) and larger tumor size (HR, 3.73; 95% CI, 1.2 to 11.2; P< 0.02) and that TgAb2 was independently associated with shorter disease-free survival (HR, 10.6; 95% CI, 4.4 to 25.7; P<0.001) (Figure 3).

The change between TgAb1 and TgAb2 levels was evaluated in TgAb2-positive patients divided into three groups. In 21 patients (group 1) the TgAb2 concentration decreased more than 50%, in 16 patients (group 2) it decreased less than 50%, and in 19 patients (group 3) it increased over the 6- to 12-month period. Among the three groups, there were no significant differences in the TgAb2 level, age, gender, tumor size, multifocality, lymph-node metastasis, or extrathyroidal extension. The recurrence rates in groups 1, 2, and 3 were 0, 19, and 37%, respectively (P = 0.06) (Figure 4).

CONCLUSION Changes in serum TgAb levels measured at 6 to 12 months after remnant ablation predict recurrence in patients with undetectable Tg values. Change in TgAb concentrations during the early postoperative period may be a prognostic indicator of recurrence.

COMMENTARY

This important study provides substantial information concerning the presence of TgAb in patients with DTC. For several decades it has been widely appreciated that immunometric Tg assays are prone to TgAb interference, commonly causing falsely low serum Tg measurements. Guidelines for the treatment of patients with DTC suggest that radioimmunoassays may be less prone to antibody interference, but they are not widely available and their role in the clinical care of patients is uncertain (1). Conflicting data concerning virtually every facet of TgAb surrounds this issue. For example, the prevalence of TgAb among patients with thyroid cancer ranges from 10 to nearly 30% in various publications (2,3), mainly because TgAb measurements are highly susceptible to differences among laboratories and TgAb methods. Serial TgAb studies must thus be performed in the same laboratory and assay. Even so, other issues plague the measurement of TgAb, including the timing and standardization of the test, without which results vary widely, similar to serum Tg measurements. What we have learned is that a spot serum Tg or TgAb is not nearly as accurate as performing serial tests in the same laboratory. Thus, different studies suggest that TgAb cannot reliably identify patients with persistent tumor.

For example, one study (3) found that the prevalence of TgAb at the initial examination was 29% (median, 130 U/ml); during follow-up the TgAb levels increased transiently in one-tenth of the patients, but thereafter the prevalence of TgAb decreased <10% after 3 years, leading the authors to conclude that the

development and course of TgAb cannot be predicted by initial or residual tumor volume and TgAb or Tg levels. Another study (4) of 1050 patients found circulating TgAbs in 102 patients (10%); these levels were elevated in 32 patients both before and after total thyroidectomy and ^{131}I ablation. As a result, no relationship could be found between preoperative serum TgAb levels and tumor stage at diagnosis or with outcome of the disease; yet during follow-up, TgAb serum levels decreased or disappeared in 21 patients who were considered tumor-free, while they remained unchanged or even increased among patients with proven metastases and others considered free of tumor. Among 102 TgAb-positive patients, serum TgAb levels measured after thyroid ablation were significantly higher in patients with metastases than in those considered tumor-free ($P<0.0001$). The problem is that the TgAb levels in this study were measured by different methods, and in some cases by the semiquantitative hemagglutination method, which is common in studies performed before the year 2000, underscoring how difficult it is to compare such studies (2,3,5)

A study performed in 2003 (6) by Chiovato et al. (6) investigated whether complete removal of thyroid antigens results in the abatement of humoral thyroid autoimmunity. A total of 182 patients with DTC who tested positive for serum TgAb and thyroid peroxidase antibodies (TPOAb) were treated with total thyroidectomy and ^{131}I to ablate residual or metastatic thyroid tissue. Mean (±SD) follow-up was 10.1 ± 4.1 years (range, 4 to 20). TPOAb, Tg, and TSH-receptor antibodies progressively disappeared after median of 6.3 years for thyroid peroxidase antibodies and 3.0 for TgAb. There was a statistically significant correlation between the disappearance of thyroid tissue and that of thyroid antibodies. The authors concluded that complete ablation of thyroid tissue with its antigenic components results in the disappearance of antibodies to all major thyroid antigens, thus supporting the concept that continued antibody production depends on the persistence of autoantigen in the body. Still, most studies have reported that TgAb levels did not show any association with a poor prognosis. In most cases, the studies were just after surgery or remnant ablation and did not exclude patients with metastatic disease (6-8).

Kim et al. present robust data that a change of serum TgAb levels detected between the time of remnant ablation and 6 to 12 months later is useful for predicting clinical recurrence in patients with undetectable serum Tg levels with positive TgAb concentrations, while decreasing TgAb levels suggest that the tumor is responding to therapy.

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