RISK OF PERSISTENT DIFFERENTIATED THYROID CANCER DESPITE NEGATIVE THYROGLOBLIN AND THYROGLOBULIN ANTIBODIES PERFORMED ON SOME COMMERCIAL TESTS

Spencer C, Petrovic I, Fatemi S. **Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer.** J Clin Endocrinol Metab. February 16, 2011 [Epub ahead of print] doi:10.1210/jc.2010-2762.

SUMMARY

BACKGROUND

Serum thyroglobulin (Tg) is used as a postoperative tumor marker for persistence and recurrence of differentiated thyroid cancer (1,2). It is recommended that Tg autoantibodies (TgAb) be measured concurrently, because an elevated level interferes with the Tg immunometric assays (IMAs), resulting in a false negative result. In addition, Tg antibody levels may be used quantitatively as a surrogate marker for thyroid cancer in patients with positive levels (3).

RESULTS

This study examined four commercial TgAb assays ability measure serum TgAb while comparing the serum's activity interference with the Tg IMA that causes abnormally low Tg (IMA) to Tg radioimmunoassay (RIA) ratios. The TgAb assays were all standardized against the World Health Organization (WHO) reference serum 65/93. Serum samples from patients with TgAb-negative and TgAb-positive differentiated thyroid cancer had serum Tg measured by both IMA and RIA and TgAb measured by a reference method and three additional methods. Group A was composed of 143 of 785 consecutive specimens that were unequivocally TgAb-positive specimens using the Kronus thyroglobulin assay. But the false negative misclassification using the manufacturer's recommend reference range was found frequently using the Roche Elecsys 2010 (44.1%), Beckman Coulter Access (35%), and Siemens Immulite (62.2%) assays. The high frequency of apparent false negative TgAb misclassification using the manufacture's reference range prompted further investigation using Group B with unequivocally positive Tg RIA level. When the analytic cutoff (lowest level that can be measured with an assay) is used rather than the lower limits of the recommended reference range, all the false negative results were eliminated for the Kronus and the Roche assays. But the Beckman Coulter and the Siemens assays continued to have a high number of false negative misclassifications, at 21.9% and 34.3%, respectively.

CONCLUSIONS

The authors demonstrate that the Tg IMA and Tg RIA values were concordant when TgAb was absent. TgAb interference was present when the Tg IMA to Tg RIA ratio was below 75%. When manufacturer-recommended cutoffs were used, many specimens displaying functional Tg interference were classified as TgAb-negative. False negative misclassification was eliminated for two of four methods by using the analytical sensitivity (AS) as the detection limit for TgAb. misclassifications. AS limits failed to detect interfering TgAb in 20% to 30% of case in other two of four assays. TgAb relationships between values for different specimens were too variable to establish between-method conversion factors.

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COMMENTARY

Serum Tg measurement during levothyroxine suppression or after TSH stimulation with neck ultrasound has been the main method of detecting differentiated thyroid cancer persistence or recurrence. This is an important report that shows that four commercial TgAb assays often do not detect TgAb levels that are capable of interfering with the Tg IMA. Clinically, this is critical, as patients with persistent disease can be misclassified as NED (no evidence of disease). Two of the four TgAb assays could predict interference of the Tg IMA when the analytical sensitivity was used instead of the recommended reference range. But two of the four assays missed interfering TgAb in 20% to 30% of cases even when the AS was used. Personally, I have had 2 patients in the past 6 months who presented with neck nodes that were abnormal on sonography and had recurrent papillary thyroid carcinoma and negative Tg IMA and TgAb by one of the methods described above. Biopsy of the abnormal node and Tg IMA of the node aspirate were both positive for recurrent tumor in my patients. This reminds us that Tg alone may not be sufficient in all patients to reflect tumor status. It is also important to know which assay your laboratory is using to measure TgAb. The results should be reported using the analytic limit rather than the manufacturer's reference range when a serum Tg is simultaneously requested. The dilemma for many of us is when our lab is using one of the two assays that cannot detect interfering antibodies, even when the analytic cutoff is used. I am requesting that our laboratory change the TgAb assays to one of the two that can predict interference of the Tg IMA when the analytic cutoff is used.

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