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A Thyroid Antibody Primer in Five Quick Cases

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Hypothyroidism and hyperthyroidism are common and often the result of thyroid autoimmunity. The widespread availability ofserum thyroid antibody laboratory testing may prompt questions from patients and clinicians.

What do thyroid antibodies really tell us? Here's an overview of the most ordered serum thyroid antibodies as interpreted incommon clinical scenarios.

Case #1: Thyroid Antibodies in Hashimoto's Thyroiditis

A healthy 24-year-old woman is incidentally found to have elevated serum thyroid peroxidase antibody (TPOAb) andthyroglobulin antibody (TgAb) titers in the setting of a normal thyroid-stimulating hormone (TSH) of 3.5 mIU/mL and freethyroxine (T4) of 0.9 ng/dL. She is asymptomatic. Her mother has type 1 diabetes and Hashimoto's thyroiditis. She asks, "Whatdo my positive thyroid antibodies mean?"

Referrals for patients like this are common for endocrinologists. Serum TPOAb and TgAb positivity are associated withHashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis. These antibodies can affect thyroid hormonesynthesis to cause thyroid dysfunction (usually hypothyroidism). While TPOAb might directly attack the thyroid gland, TPOAblevels may also reflect a chronic immune response involving both T- and B-cell–mediated immunity (Khoury and colleagues;Ramos-Leví and Marazuela). About 90% of patients with HT will have positive TPOAb titers, whereas only 50% will have apositive TgAb level.

We informed our patient that she has increased risk of developing thyroid dysfunction over time, on the order of 1%-2% per year(Tunbridge and colleagues; Vanderpump and colleagues; Huber and colleagues) because of chronic thyroid inflammation andimmune cell infiltration. We advised her to have her serum TSH and free T4 measured at least annually, and educated her abouthypothyroid symptoms. Although it is not pertinent to her now, we also discussed that having elevated TPOAb and TgAb levelsincreases her risk of developing thyroid dysfunction during pregnancy, or if she were placed on amiodarone for arrhythmias,lithium for psychiatric disorders, and tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors (ICIs) for cancer.

Case #2: Thyroid Antibodies in Thyroid Cancer Surveillance

A 37-year-old man with a history of papillary thyroid cancer and a total thyroidectomy is seen for thyroid cancer surveillance. Heis active in his care and wants to learn more about how his cancer will be monitored over time.

With open access to patient data within the electronic medical records, we have noticed more patients wanting to learn abouttheir thyroid cancer and what to expect regarding its surveillance. As endocrinologists, we are fortunate to have serumthyroglobulin (Tg) as a reliable tumor marker in differentiated thyroid cancer. Tg levels can be monitored after totalthyroidectomy, whether or not radioactive iodine ablation is given, but are generally not helpful in persons who have undergoneonly a hemithyroidectomy (Park and colleagues; Ritter and colleagues). Increasing Tg levels suggest persistent or recurrentthyroid cancer which may prompt further imaging or treatment. When TgAb levels are also present, however, Tg levels may notbe reliable. It's important to always order both TgAb and Tg levels, even if the TgAb is initially negative, because some patientsmay generate TgAb over time.

Most labs use an immunometric assay (IMA) to measure serum Tg levels in TgAb-negative patients. IMA is automated,inexpensive, has rapid turnaround times, and has good accuracy. However, about 10%-20% of patients will have positive TgAblevels that can interfere with the IMA assay; in such cases, artificially low Tg levels may be seen, resulting in erroneousreassurance. In patients with positive TgAb levels by IMA, measuring them by radioimmunoassay is preferred. Newer assayssuch as mass spectroscopy also showed initial promise in patients with positive TgAb levels but can still yield false-negative Tgvalues (Netzel and colleagues; Spencer and colleagues).

Case #3: Thyroid Antibodies in Graves' Disease

A healthy 52-year-old woman has had persistent palpitations recently. Serum TSH is < 0.02 mIU/mL (reference, 0.3-4.7mIU/mL), free T4 is 5.70 ng/dL (reference, 0.8-1.7 ng/dL), and free triiodothyronine (T3) is 1920 pg/dL (reference, 222-383pg/nL). She has fine bilateral hand tremors and sinus tachycardia. How do we work up this new diagnosis of thyrotoxicosis?12/30/21, 12:46 PM https://www.medscape.com/viewarticle/962626_print https://www.medscape.com/viewarticle/962626_print 2/2

This is one of the most common consults we receive. Thyroid antibodies may be helpful in teasing apart the differentialdiagnosis of thyrotoxicosis.

TSH receptor antibodies (TRAb) target the TSH receptor and may have an inhibitory, neutral, or stimulating effect. Thethyrotropin binding inhibitory immunoglobulin (TBII) test measures antibodies that inhibit TSH binding to its receptor. StimulatingTRAbs, known as thyroid-stimulating immunoglobulins (TSIs), are associated with Graves' disease; they stimulate the TSHreceptor, leading to increased production and release of thyroid hormone. Though the names may vary in commercial labs,positive TBII, TRAb, or TSI titers can all be used to diagnose Graves' disease. These antibodies are cost-efficient, have fastturnaround times, and are more

convenient compared with radioactive iodine uptake scans. Because TRAbs also bind to orbitalfibroblasts and muscle cells, they may cause proptosis and ocular muscle hypertrophy, known as thyroid eye disease. Thethyroid antibody levels can monitor the risk for and treatment response to thyroid eye disease, which does not always mirror thebiochemical severity of hyperthyroidism.

Our patient was started on a short course of propranolol to manage the hyperthyroidism. A couple days later, her TSI titer resultwas 10 times greater than the upper limit of normal, confirming Graves' disease. After starting methimazole, we can track herserum TSI levels to predict chances of future remission.

Case #4: Thyroid Antibodies in the Use of TKI and ICI

We received a message from a patient's oncologist who had started the patient on pembrolizumab, an anti–programmed celldeath protein (PD-1) ICI, for metastatic melanoma. Screening thyroid labs done with her fourth cycle of therapy showed a TSHof < 0.02 mIU/mL and a free T4 of 3.40 ng/dL, suggestive of ICI-induced thyroiditis.

With the emergence of TKIs and ICIs in cancer treatments, we are seeing a rise in associated thyroiditis. ICI thyroiditis occurs in10%-25% of patients, who usually are asymptomatic and show decreased radioactive iodine uptake consistent with destructivethyroiditis (Iyer and colleagues; Muir and colleagues; Peiró and colleagues). Serum TgAb and TPOAb are frequently absent andnot needed for diagnosis (Iyer and colleagues; de Moel and colleagues; Mazarico and colleagues).

ICI thyroiditis is destructive; it is not driven by TSIs, and while TRAb is sometimes detected, these lab results are consideredsecondary to the robust immune response rather than contributory to the underlying pathogenesis.

TKI-associated hypothyroidism occurs in up to 40% of patients and is associated with a gradual development of permanenthypothyroidism (Lechner and colleagues; Torino and colleagues). Thyroid antibodies are frequently absent. Of interest, bothTKI- and ICI-associated thyroid dysfunction have been associated with an improved response to cancer therapy; they are not areason to stop or interrupt cancer treatment (Peiró and colleagues; de Moel and colleagues; Ma and colleagues).

Case #5: Thyroid Antibodies in Pregnancy

A 31-year-old woman with a history of miscarriage and Hashimoto's thyroiditis (positive TPOAb) has just confirmed a 7-weekpregnancy. How should this patient be monitored or treated?

Thyroid hormone is needed for normal fetal development (Leung and colleagues; Smallridge and colleagues). The risks ofadverse pregnancy outcomes, including miscarriage, are increased in women with positive TPOAb levels and higher TSHconcentrations. The American Thyroid Association recommends starting levothyroxine for TPOAb-positive women with TSH

>2.5 mIU/mL and considering levothyroxine in TPOAb-negative women with TSH levels between the upper limit of the referencerange and 10 mIU/mL. After starting levothyroxine, the thyroid labs should be checked every 1-2 months during the course ofpregnancy.

It's important to also remember that in pregnant women with current or previous Graves' disease, serum TRAb measurementscan provide useful prognostic information about the fetus, because TSH receptor–stimulating antibodies can cross the placentato increase the risk for fetal hyperthyroidism. Serum TSI titers may still be positive to pose this risk, even if the mother is nolonger hyperthyroid or has an intact thyroid gland.

Final Thoughts

Thyroid autoantibodies are an important tool in the diagnosis and management of thyroid disease (including Hashimoto'sthyroiditis and Graves' disease), in the surveillance of thyroid cancer, and in the optimization of thyroid hormone status inpregnancy. As these tests are readily available in most labs, we hope that this summary is helpful toward their interpretation andin the management of these common thyroid conditions.

Credits:Lead Image: Dreamstime

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