THYROGLOBULIN AND THYROGLOBULIN ANTIBODY: GUIDELINES FOR USE IN THYROID CANCER MONITORING

Version:	2
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Name of originator/author:	Elizabeth Hall
Director responsible for implementation:	Edmund Lamb
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Version Control

Version	Date	Author	Status	Comment
1	6-8-2020	E Hall	Final	
2	6-12-21	E Hall	Final	TgAb cut-off increased to 5 kU/L Gel tubes (yellow top) can be used for analysis

Consultation Schedule

Name & Job Title of Individual / Meeting name	Date consulted
Thyroid TSSG	12-11-2019
Mr Alistair Balfour, Ear Nose and Throat Consultant	30-6-2020

Ratification Schedule

Name of Meeting / Committee	Date approved / authorised
Clinical Biochemistry Senior Staff Meeting	23-7-2020

Contents

1. Introduction, Background and Purpose

This policy gives guidance on requesting thyroglobulin (Tg) and thyroglobulin antibodies (TgAb) for the monitoring of thyroid cancer patients. It also gives guidance on the interpretation of Tg results in the presence of TgAb using the assays provided by East Kent Hospitals University NHS Foundation Trust (EKHUFT) and comparison of results with previous methods.

Tg is a large glycoprotein synthesised by thyroid follicular cells. It acts as a scaffold protein for the synthesis of thyroid hormones, triiodothyronine (T3) and thyroxine (T4), and also as the storage form of T3 and T4. When thyroid hormone secretion is stimulated by thyroid stimulating hormone (TSH) the Tg is endocytosed and digested to release the thyroid hormones.
Serum Tg is a specific marker for thyroid tissue and the circulating concentration is roughly proportional to thyroid gland mass. Its usefulness as a tumour marker for differentiated papillary or follicular thyroid carcinoma is greatest after total thyroid ablation (surgery and radioiodine treatment) and when patients are on suppressive doses of L-thyroxine.
Tg measurement is affected by the presence of endogenous TgAb in patient samples. The effect of this interference is dependent on the type of Tg assay used. Previously the different Trusts in Kent and Medway have sent samples for Tg and TgAb to several different laboratories, using assays with varying detection limits and subject to differing effects from antibody interference. Measurement of Tg and TgAb has recently been introduced using Abbott Architect assays in EKHUFT to enable a unified approach to patient management for all Kent and Medway patients.

Assay limitations

Tg assays use antibodies to detect Tg in patient serum. There are several limitations to these assays that should be considered when interpreting results. Some tumours may lose the ability to synthesise or secrete Tg. All assays were developed using a Tg reference preparation derived from normal thyroid tissue; this may not be representative of the Tg expressed by every cancer type. Endogenous antibodies to the reagent antibodies or to thyroglobulin may interfere in Tg measurement.
Endogenous TgAb interfere by reducing the binding of the reagent antibodies to the Tg in the patient sample.
The EKHUFT Abbott Tg assay is an immunometric assay (IMA); if present, TgAb may give falsely low Tg results.
Previously samples were analysed at Birmingham using a radioimmunoassay (RIA). In this assay, if present TgAb may give falsely high Tg results.
Patients who have received mouse monoclonal antibodies as diagnostic or therapeutic agents may develop endogenous human anti-mouse antibodies (HAMA). The presence of HAMA in a sample may cause falsely high or falsely low Tg or TgAb results.

2. Definitions

T4	thyroxine
T3	triiodothyronine
TSH	Thyroid stimulating hormone
Tg	Thyroglobulin
TgAb	Anti-thyroglobulin antibodies
HAMA	human anti-mouse antibodies
RIA	radioimmunoassay
IMA	immunometric assay

3. Scope

This policy outlines Tg and TgAb testing for patients within the Trust. All staff involved in the requesting of Tg and TgAb, whether clinical or laboratory, must adhere to this policy

4. Guidance

a. Guidelines for requesting thyroglobulin and thyroglobulin antibodies

As with any other laboratory investigation full and explicit clinical details should be provided. All requests will be reviewed before analysis and inappropriate requests will not be processed. TgAb should not be requested in the routine investigation and management of non-malignant thyroid disease.

Sample requirements

Blood may be taken into tubes with or without gel (yellow or red top). Serum must be separated within 8 hours. Separated serum may be stored at 4°C for 3 days and at -20°C for 30 days. At least 1.0 mL is required for measurement of Tg and TgAb at EKHUFT and to provide sufficient sample to send to Birmingham for dual reporting or confirmation of Tg results.

When to measure Tg and TgAb

Tg measurement is used as a tumour marker in the follow-up of patients who have been treated for thyroid cancer. Frequency of measurement will depend on the clinical situation. Annual Tg measurement is adequate for low risk patients with no evidence of biochemical or structural disease. Tg should not normally be measured more frequently than 3-monthly.

Assessment of Tg status should not be performed within 6 weeks of thyroid ablation (to clear Tg released during treatment).

TgAb will be measured with every Tg request.

b. Guidelines for interpretation of thyroglobulin and thyroglobulin antibody results

Interpretation of Tg results

Tg is useful as a tumour marker for differentiated thyroid cancer after thyroid ablation. Tg concentrations in individuals with an intact thyroid are usually in the range 3.7 – 64 µg/L using the Abbott assay. Detectable Tg in serum following total thyroidectomy and radioiodine ablation is highly suggestive of thyroid remnant, residual tumour or tumour recurrence. Rising Tg concentrations in patients on TSH-suppressing doses of L-thyroxine indicate tumour recurrence or progression. However the assay used in EKHUFT is a sensitive assay and there may be patients with very low detectable concentrations of Tg. The clinical significance of such low concentrations is unclear and it is recommended that a rising trend with serial measurements is used to indicate recurrence.

Trends in Tg concentration may have some value for monitoring low risk surveillance hemithyroidectomy patients.

Tg results are reported in µg/L. Results below the limit of quantitation of the Abbott assay are reported as <0.14 µg/L.

Stimulated Tg results

Dynamic Risk Stratification to assess the need for continued TSH suppression is determined 9–12 months following total thyroidectomy and radioiodine remnant ablation by performing a stimulated Tg test and neck ultrasound scan. Patients attend clinic C at Kent and Canterbury Hospital for pre-booked Thyrogen 900 mg IM injections on a Monday (day 1) and a Tuesday (day 2) and then have Tg, TgAb and TFT blood tests on the Friday of the same week (day 5).

Interpretation of TgAb results

TgAb is reported in kU/L to whole numbers. Some assays used in the past, or from other laboratories, may be reported with a reference range derived from a healthy population with intact thyroid glands. Such a population may have TgAb concentrations up to 4 kU/L in the Abbott assay. TgAb results from EKHUFT are reported with a decision limit at which potential TgAb interference in Tg measurement is unlikely. Negative TgAb results are reported as <5 kU/L. Results ≥5 kU/L are considered positive.

Serial measurements of TgAb have been recommended in the long-term monitoring of patients with differentiated thyroid cancer. Successful removal of the all thyroglobulin-producing tissue should lead to a decline in TgAb concentrations (median 3 years). A new occurrence of TgAb (using the same assay) is a risk factor for recurrent disease.

Interpretation of Tg results in the presence of TgAb

Endogenous antibodies to Tg may interfere in its measurement. If TgAb are present, the EKHUFT Tg level may be unreliable and give a false negative (low) result. Tg results in TgAb positive samples must be interpreted with caution. If TgAb is detectable the Tg result by any method is likely to be unreliable, especially if the Tg results obtained with different methods are discordant.

Any Tg results that do not fit with the clinical picture can be discussed with the duty biochemist. Such results could be due to other assay interferences such as HAMA.

Long term monitoring, comparison with previous methods and plans for double reporting

Detection of disease recurrence depends on changes in Tg or TgAb results with time as well as on absolute concentrations. Ideally patients are always monitored using the same analytical method to enable identification of trends.

Any sample with detectable TgAb will be sent to Birmingham for Tg measurement by RIA. Other samples may be sent to Birmingham after discussion with the Duty Biochemist for investigation of unexpected results.

5. Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy.

Consultation has been through e-mail and face-to-face communication between clinical biochemistry staff, K&M Thyroid TSSG, Mr Alistair Balfour. Records are kept on the S drive (S:\Path\SnrStaff\Comms with users\Clinical guidelines).

6. Review and Revision Arrangements

Two years from implementation date, by author.

7. Training

All staff involved in requesting, measuring or interpreting urinary albumin loss must adhere to this policy.

8. Document Control including Archiving Arrangements

Archive of this document will be through QPulse, and is responsibility of the owner defined on Q pulse.

9. Monitoring

Within the Trust, compliance with this policy must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional retrospective audit within Clinical Biochemistry.

10. References and Associated Documents

1. Peros P et al. Clin Endocrinol. 2014; 81 (s1): 1-122. British Thyroid Association guidelines for the management of thyroid cancer.

2. Pickett AJ, Jones M, Evans C. Ann Clin Biochem 2012; 49: 463-7. Causes of discordance between thyroglobulin antibody assays

3. Abbott insert for Architect Thyroglobulin assay. 2018

4. Abbott insert for Architect Thyroglobulin Antibody assay. 2015

5. Spencer C et al. Curr Opin Endocrinol Diabetes Obes 2014; 21: 394-404. How sensitive (second generation) thyroglobulin measurement is changing paradigms for monitoring patients with differentiated thyroid cancer, in the absence or presence of thyroglobulin antibodies.