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Invited critical review

Thyroglobulin in differentiated thyroid cancer

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ABSTRACT

Identification of differentiated thyroid cancer (DTC) is becoming increasingly common. Patients usually have an excellent prognosis. Most undergo total thyroidectomy, radioiodine ablation and treatment with suppressive doses of levothyroxine. Patients require long term follow-up which includes measurement of serum thyroglobulin (Tg). Interpretation of serum Tg requires knowledge of the concurrent thyroid stimulating hormone (TSH) concentration, as secretion is TSH dependant, and an awareness of the limitations of the methods used to measure it. These limitations include the heterogeneity of Tg in serum, the ability of assays to recognise forms of Tg secreted by a tumour, assay biases and not least the potential for interference in immunoassays for Tg from endogenous thyroglobulin antibodies (TgAbs) in patient serum. This review considers what the clinician wants to know and how Tg results can be interpreted in light of an awareness of assay limitations.

Contents

1. Introduction

The developed world is experiencing an epidemic rise in the incidence of thyroid cancer [1–3]. The vast majority are small papillary thyroid cancers diagnosed in women and are usually asymptomatic (incidental papillary thyroid microcarcinomas) [4,5]. Use of imaging of the neck by ultrasound, CT, MRI, PET CT, Doppler ultrasound of neck vessels and other modalities for other indications has been blamed [2,6,7], though there is probably a true rise in incidence independent of detection bias [1,8]. Patients with incidentally diagnosed papillary thyroid microcarcinomas as a rule have an excellent prognosis [9] and are at risk of being treated too aggressively.

2. What does the clinician want to know?

Clinician expectations from biochemical tests are sometimes unrealistic and misinformed. Serum thyroglobulin (Tg) is not a diagnostic test for thyroid cancer, but is recommended to monitor patients with DTC [10–14]. It is worth highlighting that thyroglobulin testing is only one

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(albeit probably most useful clinically) component of monitoring, which compliments other modalities comprising clinical assessment, ultrasound of the neck (the commonest site of recurrence), and in some cases iodine scan and other cross-sectional imaging (CT, MRI, PET).

Most patients with DTC undergo total thyroidectomy, radioiodine ablation and then are treated with suppressive doses of levothyroxine. For patients with differentiated thyroid cancer (DTC) who have been rendered athyreotic as a result of total thyroidectomy and radioiodine ablation, an undetectable serum thyroglobulin whilst on TSH suppressive therapy in the absence of TgAb interference, is highly reassuring and predictive of absence of disease [15,16]. This can be further improved by measuring serum Tg after TSH stimulation, with the negative predictive value of serum Tg < 0.5 μg/L being 98–99.5% [17–19]. Whilst a negative Tg result is helpful, detectable serum Tg is more difficult to interpret as the test cannot usually differentiate between thyroid remnant and thyroid cancer [20]. This scenario will be increasingly more prevalent in future as the trend in the UK and elsewhere is for less aggressive surgery, less use of radioiodine ablation and lower activities of radioiodine for low risk cases [21]. Trends in serum Tg concentrations over time are therefore important.

From the clinician's perspective the relevant questions are:

- Following total thyroidectomy and radioiodine, has the thyroid been ablated?
- Has the cancer recurred?
- What is the response to treatment of recurrent/metastatic cancer?
- What is the rate of progression of recurrent/metastatic cancer, when no specific treatment is used?

3. Serum thyroglobulin

Tg is a large glycoprotein involved in the production of thyroid hormones, which is synthesised in both normal thyroid tissue and DTC cells. It is released into the circulation as a by-product of normal thyroid hormone production and also secondary to any trauma to the thyroid. As Tg is synthesised and utilised entirely within the thyroid gland it is an ideal tumour marker (Struma ovarii is the only, rare, condition where this is not the case). However, differences in Tg mRNA splicing and differences in glycosylation, sialic acid content, sulfation and iodination of the protein [22,23] result in serum Tg being a very heterogeneous molecule.

The circulating concentration of Tg is dependent on the mass of thyroid tissue present. As Tg is produced as a by-product of thyroid hormone synthesis the concentration present in circulation is also dependent on the amount of stimulation to the TSH receptor. This can be via endogenous or recombinant TSH, human chorionic gonadotrophin (during pregnancy) or antibody stimulation of the TSH receptor. Since serum Tg concentration depends on the degree of TSH-R stimulation TSH should be measured at the same time as Tg to aid interpretation [10]. Tg can be measured when TSH is suppressed by levothyroxine therapy or, if greater diagnostic sensitivity is required, following TSH stimulation either by withdrawal of levothyroxine to achieve a serum TSH >30 mIU/L or following administration of recombinant TSH [10].

Whilst serum Tg measurement is universally recommended in the follow-up of all patients with DTC [10–14] there is less clarity on the timing of measurements [12]. The half-life of Tg post-surgery is 2–4 days, varying slightly depending on the post-translational modification of the molecule in the individual patient, and can be up to 3 months post-radioiodine treatment [references in [12]]. Current expert opinion is that Tg should not be measured until at least 6 weeks post-surgery and at 3–12 month intervals thereafter depending on clinical requirements [12]. A summary of the recommended use of serum Tg testing is shown in Fig. 1. Following initial successful treatment, however, serum Tg may continue to be detectable for well over a year [24], and this probably relates to the biological response of DTC cells to the treatment. Clinicians therefore need to pay attention to trends of serum Tg, sometimes over long periods of time. In contrast, serum Tg declines rapidly (within 4 weeks) in patients with metastatic disease after treatment with the protein kinase inhibitor Sorafenib [25], however the correlation between change in serum Tg and volume of disease in patients treated with tyrosine kinase inhibitors is poor [26] and clinicians should be cautious in interpreting serum Tg values in patients treated with tyrosine kinase inhibitors.

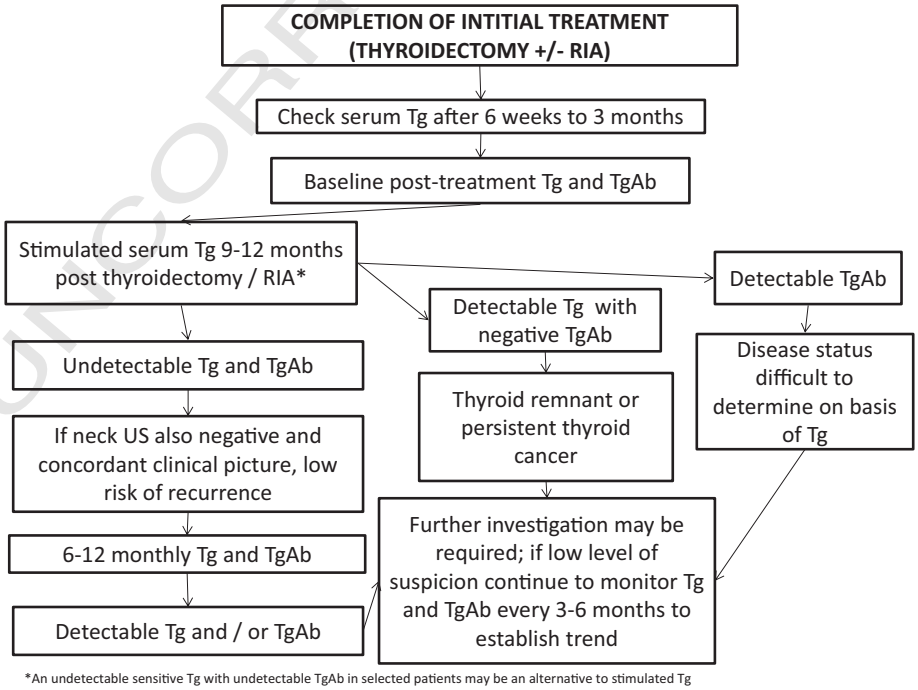

Fig. 1. Summary of Tg testing in DTC. Flow-chart summarising serum Tg testing for DTC monitoring, based on recommendations of the British Thyroid Association guidelines [10]. Interpretation of Tg results must always be made in the context of the clinical picture of the individual patient.

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