

## Calcitonin

Medullary thyroid carcinoma (MTC) is characterized by a high concentration of serum calcitonin. Routine measurement of serum calcitonin concentration has been advocated for detection of MTC among patients with nodular thyroid diseases. However, a minimal to moderate increase of serum calcitonin concentration has been frequently observed in diseases other than MTC.

Fine-needle aspiration cytology (FNAC) is not a reliable method for detection of MTC. Therefore, we evaluated the usefulness of routine measurement of serum calcitonin concentration in patients with nodular thyroid diseases, and studied the validity of pentagastrin stimulation test and FNAC in these patients.

Routine measurement of serum calcitonin concentrations in 1,448 patients (male, 285, female, 1,163) with nodular thyroid diseases was performed. The average age was 46 years (range, 14-86 years).

Initial examination included thyroid examination, thyroid scan or ultrasonography, measurements of serum free triiodothyronine (T<sub>3</sub>), free thyroxine (T<sub>4</sub>), thyrotrophin (TSH) levels, and antithyroid autoantibodies. FNAC was performed in all patients who had palpable or visible thyroid nodule by ultrasonography, and pentagastrin stimulation test was performed in 39 patients who consented. Serum calcitonin concentration was measured with a two-site immunoradiometric assay using commercial kits. The serum calcitonin concentration was also measured in 407 healthy subjects without thyroid or nonthyroid diseases.

**RESULTS:** Serum calcitonin concentration was 10 pg/mL or less in 403 normal subjects (99.0 percentile), and 11-13 pg/mL in the remaining 4 subjects. We found that 56 (3.87%) of 1,448 patients with nodular thyroid diseases had serum calcitonin level above 10 pg/mL. Ten patients (0.69%) with histologically confirmed MTC

were detected by the routine measurement of serum calcitonin. The prevalence of MTC was 5.2% in 194 patients with thyroid carcinoma. Five of 10 patients with MTC had basal serum calcitonin level more than 100 pg/mL. The remaining 5 patients had minimal or moderate elevation of basal serum calcitonin (range, 12-86 pg/mL).

Serum calcitonin concentration increased to more than 100 pg/mL by pentagastrin in all patients with MTC (2.4- to 37.7-fold increase). FNAC suggested MTC in only 2 patients (22.2%), and failed to diagnose MTC in 7 patients. FNAC was not performed in 1 patient with MTC, because he had no visible mass by ultrasonography.

**CONCLUSION:** These results suggested that routine measurement of serum calcitonin is useful in the early detection of MTC among patients with nodular thyroid diseases. Pentagastrin stimulation test may also be a reliable way for evaluating thyroid nodular patients with mild or moderate elevation of serum calcitonin concentrations. However, FNAC was not sensitive in detecting MTC. Routine measurement of serum calcitonin concentration in patients with nodular thyroid diseases is recommended.

Medullary tumors are the third most common of all thyroid cancers (about 5 to 8 percent). Unlike papillary and follicular thyroid cancers which arise from thyroid hormone producing cells, medullary cancer of the thyroid originates from the parafollicular cells (also called C cells) of the thyroid. These C cells make a different hormone called calcitonin (thus their name) which has nothing to do with the control of metabolism the way thyroid hormone does. The production of this hormone can be measured after an operation to determine if the cancer is still present, and if it is growing.

This cancer has a much lower cure rate than does the “well differentiated” thyroid cancers (papillary and follicular), but cure rates are higher than they are for anaplastic thyroid cancer. Overall 10 year survival rates are 90% when all the disease is confined to the thyroid

gland, 70% with spread to cervical lymph nodes, and 20 when spread to distant sites is present.

### *Characteristics of Medullary Thyroid Cancer*

- Occurs in 4 clinical settings, can be associated with other endocrine tumors
- Females more common than males (except for inherited cancers)
- Regional metastases (spread to neck lymph nodes) occur early in the disease.
- Spread to distant organs (metastasis) occurs late and can be to the liver, bone, brain, and adrenal medulla
- Not associated with radiation exposure
- Usually originates in the upper central lobe of the thyroid
- Poor prognostic factors include age >50, male, distant spread (metastases), and when seen in patients with other endocrine tumors due to MEN II-B syndrome.
- Residual disease (following surgery) or recurrence can be detected by measuring calcitonin (a hormone that should be measured every 4 months for the first few years and then every 6 months for ever).

### *Medullary Thyroid Cancer Occurs in Four Clinical Settings*

1. *Sporadic*- Accounts for 80% of all cases of medullary thyroid cancer. They are typically unilateral and there are no associated endocrinopathies (not associated with disease in other endocrine glands. Peak onset 40 - 60. Females outnumber males by 3:2 ratios. *One third will present with intractable diarrhea. Diarrhea is caused by increased gastrointestinal secretion and hypermotility due to the hormones secreted by the tumor (calcitonin, prostaglandins, serotonin, or VIP).*
2. *MEN II-A (Sipple Syndrome)*. Multiple Endocrine Neoplasia Syndromes (abbreviated as 'MEN' and pronounced 'M', 'E', 'N') are a group of endocrine disorders which occur together in

the same patient and typically are found in families because they are inherited. 'Syndromes' are medical conditions which occur in groups of *three*. Sipple syndrome has

1. Bilateral medullary carcinoma or C cell hyperplasia,
2. Pheochromocytoma
3. Hyperparathyroidism.

This syndrome is inherited and is due to a defect of a gene (DNA) which helps control the normal growth of endocrine tissues. This inherited syndrome is passed on to all children who get the gene (inherited in an autosomal dominant fashion), which theoretically, would be 50% of all offspring of a person with this defective gene. Because of this, males and females are affected equally. Peak incidence of medullary carcinoma in these patients is in the 30's.

3. *MEN II-B*. This syndrome also has

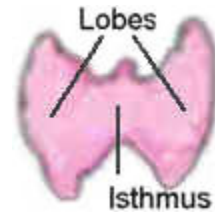
1. Medullary carcinoma
2. Pheochromocytoma, but only rarely will have hyperparathyroidism. Instead
3. These patients have an unusual appearance which is characterized by mucosal ganglioneuromas (tumors in the mouth) and a Marfanoid habitus.

Inheritance is autosomal dominant as in MEN II-a, or it can occur sporadically (without being inherited). MEN II-B patients usually get medullary carcinoma in their 30's, and males and females are equally effected. As with MEN II-A, pheochromocytomas must be detected prior to any operation. The idea here is to remove the pheochromocytoma first to remove the risk of severe hypertensive episodes while the thyroid or parathyroid is being operated on.

4. *Inherited medullary carcinoma without associated endocrinopathies.* This form of medullary carcinoma is the least aggressive. Like other types of thyroid cancers, the peak incidence is between the ages of 40 and 50.

### *Management of Medullary Thyroid Cancer*

*In contrast to papillary and follicular cancers, little controversy exists when discussing the management of medullary thyroid cancer.* After assessment and treatment of associated endocrine conditions (such as pheochromocytomas if present) by an endocrinologist, all patients should receive total thyroidectomy, a complete central neck dissection (removal of all lymph nodes and fatty tissues in the central area of the neck), and removal of all lymph nodes and surrounding fatty tissues within the side of the neck which harbored the tumor.



### *The Use of Radioactive Iodine Post-Operatively*

Although thyroid cells have the cellular mechanism to absorb iodine, medullary thyroid cancer does not arise from this type of thyroid cell. Therefore, radioactive iodine therapy is not useful for the treatment of medullary thyroid cancer. Similarly, if medullary cancer spreads to distant sites, it cannot be found by iodine scanning the way that distant spread from papillary or follicular cancer can.

In addition to the usual cancer follow up, patients should receive a yearly chest x-ray as well as calcitonin levels. Serum calcitonin is very useful in follow up of medullary thyroid cancer because no other cells of the body make this hormone. A high serum calcitonin level that had previously been low following total thyroidectomy is indicative of recurrence. Under the best circumstances, surgery will remove the entire thyroid and all lymph nodes in the neck which harbor metastatic spread. In this case, post operative calcitonin levels will go to zero. This is often not the case, and calcitonin levels remain elevated, but less than pre-operatively. These levels should still be

checked every 6 months, and when they begin to rise, a more diligent examination is in order to find the source.

### *Prognosis*

The prognosis of medullary thyroid carcinoma (MTC) is intermediate between differentiated and anaplastic thyroid carcinomas. In the absence of distant metastasis, the generally accepted first line treatment of MTC is total thyroidectomy and bilateral lymph node dissection.

When surgery has not fully normalized calcitonin, the natural history of MTC varies from rapid progression and survival for a few years, to very slow progression or stable disease extending over decades.

Until recently, therapeutic options for locally recurrent tumors were limited to repeated surgery and/or external beam radiotherapy, the impact of which on survival has been controversial.

Chemotherapy has a transient and limited efficacy in advanced stages of the disease. Radio immunotherapy, using anticarcinoembryonic antigen (anti-CEA) antibodies, and radio labeled octreotide have recently been studied as new therapeutic modalities, with encouraging results in early clinical trials. Tyrosine kinase inhibitors could also be effective in these tumors that express mutated forms of the RET oncogene. Synergistic effects have been demonstrated between radio immunotherapy and chemotherapy using taxanes or doxorubicin, and between unlabeled CEA antibodies and dacarbazine. These new therapeutic options confirm the need for an early distinction between high-risk patients who need to be treated and low-risk patients who warrant a 'watch and wait' behavior.

Among the various prognostic parameters that could identify high-, moderate-, and low-risk groups with the aim of defining optimal therapeutic strategies advanced age, advanced stage of the disease, and associated multiple endocrine neoplasia (MEN) 2B appear to be the best commonly accepted factors of poor prognosis. Individual

parameters have been associated within different staging systems, and Kebebew *et al.* concluded that the European Organization for Research and Treatment of Cancer (EORTC) prognostic scoring system, which takes into account age, gender, nature, and stage of the disease for all thyroid cancers, had the highest predictive value.

Serum kinetics of MTC markers, such as calcitonin and CEA, could be alternative predictors of survival, and Miyauchi *et al.* have proposed calcitonin doubling-times (CDT) as a prognostic factor.