Postoperative Pentagastrin-Stimulated Serum Calcitonin Concentrations in Patients with Medullary Thyroid Carcinoma: Reoperations in Patients with Concentrations Bordering the Detection Limit

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The case reports on two patients with medullary thyroid carcinoma show that even postoperatively stimulated serum calcitonin (CT) concentrations near the detection limit (using a polyclonal antibody against synthetic CT) can demonstrate persistent disease. Stimulated CT concentrations can be lowered to nondetectable levels by a second and third operation if a meticulous technique is used for dissection of the lymph compartments. The patient can then be assumed to be cured. Diagnostic accuracy at very low CT concentrations can be improved by selective venous catheterization with blood sampling for CT after stimulation. (Henry Ford Hosp Med J 1989:37:138-40)

The most important parameters in diagnosis and follow-up of patients with medullary thyroid carcinoma (MTC) are basal calcitonin (CT) and stimulated CT (CTstim) concentrations (1-7). Patients are assumed to be cured if their postoperative CTstim levels are in the normal range or even below the limit of detection (1,3,4,8,9). It seems possible, however, that a small tumor remnant does not have the potential to produce enough CT, even after stimulation with pentagastrin and calcium, to be an indicator for tumor persistence. The possibility of extrathyroidal CT production makes the interpretation of postoperative CTstim even more difficult (10,11).

We report two patients whose postoperative CTstim levels were found to be near the detection limit. During reoperations metastatic tumor tissue could be removed. These patients are cured in terms of our present follow-up investigations.

**Case Reports**

**Case 1**
A 24-year-old female member of a multiple endocrine neoplasia type 2A family had elevated CTstim levels repeatedly on routine screening. Physical examination was unrevealing. Total thyroidectomy and bilateral selective neck dissection were performed. Histologic examination of the specimens revealed multiple bilateral foci of MTC with C-cell hyperplasia. Lymph node metastases were not found. Follow-up examinations of the patient were done twice a year. During the first five years postoperatively, CTstim levels were near the detection limit. At 60 months, elevated CTstim levels were found. At nine years the CTstim concentrations were highly abnormal. Physical examination was unrevealing. Computed tomography and ultrasound investigations failed to show residual tumor. Selective venous catheterization with blood sampling revealed a CT concentration gradient in the area of the left proximal internal jugular vein. For this reason bilateral modified radical neck dissection according to the method by Tisell et al (12) was performed. Histologically, a metastatic lymph node measuring 8 mm in diameter was discovered in the lateral compartment at the proximal portion of the left internal jugular vein. After this operation the peripheral venous CTstim concentrations were below limits of detection (Fig 1). Selective venous blood sampling from the left internal jugular vein after pentagastrin stimulation gave identical results.

**Case 2**
This 44-year-old male patient had a cold nodule in the right thyroid lobe which was treated by unilateral subtotal resection. A MTC with a maximum diameter of 2.1 cm was found. In a second operation the remnant of the right lobe was removed, and contralateral subtotal resection was performed. Since the CTstim levels remained pathologically elevated after this procedure, a third operation with excision of the remnant of the left lobe and bilateral modified neck dissection was performed. The histologic examination revealed lymph node metastases in the right lateral compartment. After this third surgical intervention, peripheral CTstim was within the normal range. Selective venous blood sampling showed a minute gradient for CT (0.07 versus 0.05 ng/mL) in the proximal part of the right internal jugular vein. In a fourth operation a modified radical neck dissection according to the method by Tisell et al (12) was done on the right side. Histologic examination revealed four lymph node metastases (each measuring 1 mm in diameter) in the right central compartment and one lymph node metastasis (2 mm in diameter) in the right lateral compartment. After this fourth operation the CTstim levels proved to be below the limit of detection (Fig 2).

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Fig 1—Case 1: Pentagastrin-stimulated serum calcitonin (CT) concentrations during follow-up after the first operation. The closed circles represent CT values after pentagastrin and calcium gluconate stimulation, and the broken line represents the detection limit of the assay.

Fig 2—Case 2: Pentagastrin-stimulated serum calcitonin concentrations during follow-up after the first reoperation. The broken line represents the detection limit of the assay.

Radioimmunoassay and stimulation of CT secretion
Radioimmunoassay used a polyclonal antibody against synthetic CT with a normal range of < 0.1 to 0.3 ng/mL, intra- and interassay variation below 10% (13). For stimulation of CT secretion, pentagastrin (Gastrodiagnost, Fa. Merck Darmstadt, West Germany) 0.5 μg/kg body weight in 5 seconds intravenously (cases 1 and 2) and calcium gluconate 2 mg/kg body weight in 1 minute intravenously (case 1) were used (3,6).

Discussion
Postoperative CTstim is the crucial parameter for evaluating the success of surgery in MTC patients. When pentagastrin- and calcium gluconate-stimulated serum CT levels are repeatedly in the low normal range, then surgery is generally deemed curative (1,3,4,8,9). The case reports presented show that the remaining tumor volume may sometimes be so small that the amount of CT released is insufficient for the diagnosis of persistent disease. These results were obtained using a routine polyclonal antibody for the CT radioimmunoassay. This problem of insensitivity could be solved by performing a highly selective venous blood sampling and measuring the higher concentration in a tumor-draining vein. Experimental and clinical data have been reported concerning the preoperative and postoperative status of patients at risk for MTC (12,14-17). In case 1, we were able to demonstrate that the preoperatively observed CT concentration gradient disappeared after reoperation. Selective venous blood sampling with stimulation of CT secretion revealed postoperative concentrations below the limit of detection. The interpretation of postoperative CTstim is furthermore confused because, after identical stimuli, different concentration gradients can be observed in short-term intervals (2).

Whether the outcome of postoperative CTstim measurements provides a basis for assuming that a patient has been permanently cured remains to be established. A long-term follow-up is required for confirmation.

A prerequisite for postoperative CTstim normalization is the use of the method of Tisell et al (12) for central and lateral lymph compartment dissection. This is particularly important for patients in whom less aggressive procedures have failed (18-20). The follow-up data on our patients suggest that even minimal CTstim gradients show tumor persistence and that only CTstim levels below detection limits provide much confidence for cure.

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