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The malignant C-cell releases several markers of potential clinical significance into the circulation. To determine the usefulness of these markers for management of medullary thyroid carcinoma (MTC), it is necessary to compare the usefulness of these markers with calcitonin (CT), the classical tumor marker for MTC. Measurement of serum concentrations of the peptide PDN-21 (katacalcin), a carboxyterminal cleavage product of procalcitonin, showed a high correlation with serum CT levels ($r = 0.99$, $P < 0.01$, $n = 65$ patients with MTC). The presence of equimolar concentrations of CT and PDN-21 (CT/PDN-21 molar ratio = 0.95 ± 0.33) indicates the peptide is cosecreted with CT. Stimulation of CT release by intravenous pentagastrin was associated with a parallel increase of PDN-21, providing further evidence of cosecretion of these two peptides. Finally, measurement of either PDN-21 or CT in selective venous catheterization specimens was useful for localization of MTC. Chromogranin A (CgA) levels were also measured in patients with MTC. Circulating levels were elevated in most patients with advanced disease. There was a moderate correlation between CgA and CT serum levels ($r = 0.87$, $P < 0.01$, $n = 61$ patients with MTC). Pentagastrin did not stimulate CgA, and the long half-life of CgA in the circulation did not make it possible to use this peptide for tumor localization by selective venous catheterization. We conclude that measurement of PDN-21 provides an independent assay system for diagnosis, localization, and postoperative management of MTC, whereas CgA measurement is not useful in early diagnosis of MTC and is of limited value for localization or management of progressive disease. (Henry Ford Hosp Med J 1992;40:296-8)

Malignant C-cells are able to release several biologically active substances into the circulation (Table 1). During the last 20 years, several of these secretory products have been tested as markers for medullary thyroid carcinoma (MTC), but only a few have achieved clinical importance. Calcitonin (CT), the main peptide derived from the CT gene, is released from normal and malignant C-cells and its usefulness as a serum marker of MTC is well established. Another peptide derived from the CT precursor peptide is a 21-amino acid C-terminal flanking peptide, PDN-21 or katacalcin (1). It has already been tested as a marker for MTC, but it is less often used for the diagnosis of MTC than CT (2-6).

Chromogranin A (CgA), a 431-amino acid protein involved in intracellular packaging and processing of peptide hormones and neuropeptides, is a prototype of the "neuroendocrine" marker family (7). It is found in many neuroendocrine tissues, and circulating levels can be elevated in patients with tumors of these tissues such as pheochromocytoma, parathyroid adenoma, insulinoma, and carcinoid (8). As the determination of CT is still the "gold standard" for investigation of MTC patients, it is important to compare new markers to measurement of serum CT in a variety of clinical situations to determine the usefulness of the marker. In this study we evaluated the usefulness of plasma CgA and serum PDN-21 with serum CT in patients with MTC to determine the relative usefulness of these markers.

Patients and Methods

Plasma from 61 patients (29 women and 32 men) with histologically proven MTC at different stages of the disease with either the sporadic (n = 46) or the familial (n = 15) variety of the disease was measured in a radioimmunoassay (RIA) for CgA or CT. PDN-21 and CT were compared in 65 patients with proven MTC. The response to pentagastrin (0.5 μg/kg body weight, intravenously) was tested in nine patients with MTC. In one patient with MTC who had a postoperative elevation of CT levels, selective venous catheterization with blood sampling for determination of CT, PDN-21, and CgA was done. Plasma CT levels were determined by an in-house RIA (9). The normal range for this assay is < 0.05 to 0.2 ng/mL. PDN-21 plasma levels were determined by RIA using a goat antiserum (G 47-8/89), ^{125}I Tyr^0-PDN-21 as a tracer, and synthetic PDN-21 as standard (6). The reference range for this assay is < 10 to 40 pg/mL. CgA in plasma was measured by RIA (10) with slight modification (11); this assay has a detection limit of 7 ng/mL and an upper limit of the reference range of 50 ng/mL.

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Table 1
Substances Produced or Released by Medullary Thyroid Carcinoma

Peptides derived from the calcitonin gene:
Calcitonin (CT)
PDN-21 (katacalcin)
PAS-57
Calcitonin gene-related peptide (CGRP)
Neuroendocrine markers:
Chromogranin A (CgA)
Neuron-specific enolase (NSE)
Synaptophysin
7B2
HISL-19
Peptide hormones and releasing factors:
Somatostatin (SRIF)
Gastrin-releasing peptide (GRP)
Adrenocorticotropic hormone (ACTH)
Parathyroid hormone-related protein (PTHrP)
Others:
Carcinoembryonic antigen (CEA)
Histaminase
L-Dopadecarboxylase
Helodermin
Prostaglandin
Tissue polypeptide antigen (TPA)

Results

Linear regression analysis of the basal levels of PDN-21 and CT in 65 patients with MTC gave a slope of $r = 0.99$ ($P < 0.01$); the average ratio of CT/PDN-21 was 0.96 ± 0.33 (mean ± SD). The average molar ratio of CT/PDN-21 for pentagastrin tests was 1.45 for basal values and became nearly equimolar during pentagastrin stimulation (Fig 1). In serum samples collected during selective venous catheterizations, the concentrations of PDN-21 as well as CT were highest at the site of the suspected MTC tissue (Fig 2). The exact localization was subsequently confirmed by operation. Basal levels of CgA and CT in 61 patients with MTC correlated significantly ($r = 0.87$, $P < 0.01$), but CgA was elevated into the abnormal range in only 23% of cases, mainly in progressive disease (CT > 10 ng/mL, CgA elevated in 83.3%) (Table 2). In response to pentagastrin, no change in CgA levels was observed (Fig 1). In selective venous catheterization blood sampling studies, no gradient was observed for CgA (Fig 2).

Discussion

These studies demonstrate clearly that PDN-21 and CT are comparable for diagnosis of MTC. This is true for basal measurements and pentagastrin-stimulated values, a point which has been demonstrated previously for only small numbers of patients (2,4,5). These results also indicate that PDN-21 and CT are secreted in equimolar amounts in patients with MTC. This was confirmed by measurement in both peripheral venous samples and in samples obtained during selective venous catheterization, the latter a more direct indication of secretion by the tumor. It is our belief that PDN-21 is as good a tumor marker for MTC as CT, although for historical reasons CT is most commonly used for diagnostic purposes. However, PDN-21 may be helpful for clarification of the diagnosis of MTC in patients with borderline pentagastrin test results.

The usefulness of CgA determination in the plasma of MTC patients is limited as only patients with advanced disease have elevated CgA levels. Measurement of CgA was not useful for detection of early cases of MTC because basal levels are in the

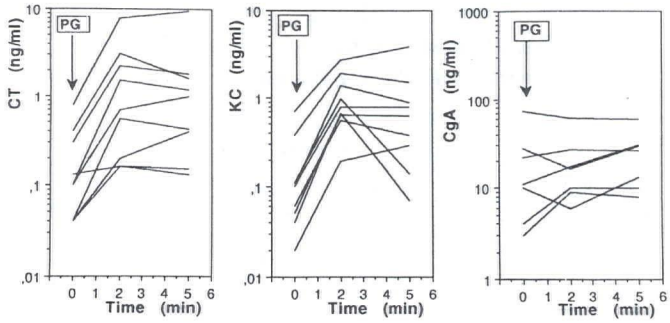

Fig 1—Plasma levels of calcitonin (left panel, n = 9), PDN-21 (middle panel, n = 9), and CgA (right panel, n = 7) before and after stimulation with pentagastrin (0.5 μg/kg body weight intravenously) in patients with MTC. (CT values below 0.04 ng/mL were considered to be below the limit of detection of the assay.)

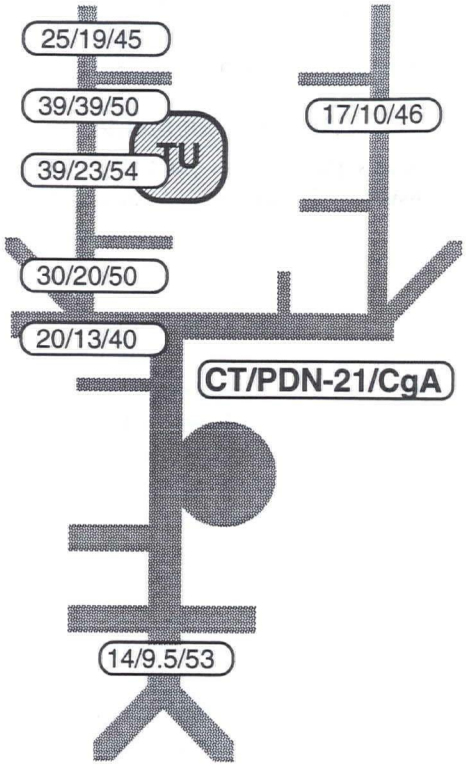

Fig 2—Concentrations of CT (left), PDN-21 (middle), and CgA (right) (in ng/mL) in serum samples obtained by selective venous catheterization from a patient with MTC (the values shown are in ng/mL of serum). MTC tissue at the right side of the neck was confirmed by operation.

Table 2
Elevated Chromogranin A Levels in 61 Patients with Medullary Thyroid Carcinoma

CT (ng/mL)	Chromogranin A Mean (ng/mL)	Chromogranin A Percent Elevated	n
< 0.2	16.0	7.1%	14
0.2–10	12.0	15.4%	41
> 10	806	83.3%	6

normal range and do not increase after pentagastrin stimulation. In addition, several sources of CgA may exist in MEN 2 including the adrenal, parathyroid, or the CT-producing cells. We conclude that measurement of CT remains the "gold standard" as a tumor marker for diagnosis of MTC. PDN-21 is cosecreted with CT and may be used as a second independent marker to clarify the diagnosis in borderline cases. CgA is useful as a marker only in patients with progressive sporadic MTC.

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References

1. Hillyard CJ, Myers C, Abeyaskekera G, Stevenson JC, Craig RK, MacIntyre I. Katacalcin: A new plasma calcium-lowering hormone. Lancet 1983; 1:846-8.

2. Raue F, Boden M, Girgis S, Rix E, Ziegler R. Katacalcin—a new tumor marker in C-cell carcinoma of the thyroid. Klin Wochenschr 1987;65:82-6.

3. Hurley DL, Katz HH, Tiegs RD, Calvo MS, Barta JR, Heath H III. Cosecretion of calcitonin gene products: Studies with a C_{18} cartridge extraction method for human plasma PDN-21 (katacalcin). J Clin Endocrinol Metab 1988;66:640-4.

4. Ittner J, Dambacher MA, Born W, et al. Diagnostic evaluation of measurements of carboxyl-terminal flanking peptide (PDN-21) of the human calcitonin gene in human serum. J Clin Endocrinol Metab 1985;61:1133-7.

5. Takami H, Shikata JI, Horie H, Sekine K, Ito K. PDN-21: Possible tumor marker for medullary thyroid carcinoma. J Surg Oncol 1990;44:205-7.

6. Blind E, Raue F, Klaiber T, et al. Evaluation of sensitive PDN-21 (katacalcin) determination as tumor marker in medullary thyroid carcinoma. J Endocrinol Invest 1992;15:93-8.

7. Huttner WB, Gerdes HH, Rosa P. The granin (chromogranin/secretogranin) family. Trends Biochem Sci 1991;16:27-30.

8. O'Connor DT, Deftos LJ. Secretion of chromogranin A by peptide-producing endocrine neoplasms. N Engl J Med 1986;314:1145-51.

9. Raue F, Minne HW, Ziegler R. Calcitonin. In: Pesce A, Kaplan LA, eds. Methods in clinical chemistry. St. Louis: Mosby, 1987:696-701.

10. O'Connor DT, Pandian MR, Carlton E, Cervenka JH, Hsiao RJ. Rapid radioimmunoassay of circulating chromogranin A: In vitro stability, exploration of the neuroendocrine character of neoplasia, and assessment of the effects of organ failure. Clin Chem 1989;35:1631-7.

11. Blind E, Schmidt-Gayk H, Sinn HP, O'Connor DT, Raue F. Chromogranin A as tumor marker in medullary thyroid carcinoma. Thyroid 1992; 2:5-10.