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Diagnostic value of currently available tumor markers in thyroid cancers

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In the follow-up management of cancer patients, tumor markers are a powerful and essential tool for both early detection of tumor progress, i.e. relapse or metastases, and monitoring therapy response. In thyroid cancer well-established tumor markers are available for the most common tumor types such as papillary and follicular carcinomas of the thyroid epithelium and for medullary thyroid carcinoma, which arises from the parafollicular C-cells of the thyroid gland. The tumor markers thyroglobulin, calcitonin, and carcinoembryonic antigen and their employment in routine clinical work-up in patients with thyroid cancer are presented. Furthermore, tissue polypeptide antigen and neuron-specific enolase as potential tumor markers in selected cases of thyroid cancer are discussed.

Key words: thyroid neoplasms – diagnosis; tumor markers, biological; thyroglobulin – calcitonin – carcinoembryonic antigen – tissue polypeptide antigen – neuron-specific enolase

Introduction

Carcinomas are the most common tumor type of thyroid malignancies. They may be classified into two varieties depending on whether the tumor arises in thyroid follicular epithelium or from the parafollicular C-cells. The general histologic types of the former one are the well-differentiated papillary and follicular carcinoma including the oxyphilic cell subtype, and, least common, the histologically undifferentiated anaplastic carcinoma. The tumor type arising from the C-cells is the so-called medullary thyroid carcinoma (MTC), which occurs familial at least in 10%. It usually appears as a component of multiple endocrine neoplasia (MEN) tpye IIa or IIb. The thyroid may also be the site of other rare tumors such as squamous cell carcinomas, various kinds of sarcomas and lymphoproliferative diseases, and metastases from primary tumors elsewhere.

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Tumor markers in thyroid cancer

The term tumor marker in connection with thyroid cancer implicates a somewhat different and unique quality showing that the most important markers – i.e. thyroglobulin and calcitonin – are not specific antigens of tumor tissue but common specific components of normal thyroid tissue. Their use is based on a unique option in thyroid cancer treatment, namely on the possibility of completely removing any thyroid tissue by combined surgical and radioiodine therapy. Thus, the appearance of any thyroid-specific substrate in the patients plasma after total thyroid ablation is highly indicative of recurrence and/or metastases.

Next to the mostly used tumor markers thyroglobulin and calcitonin applied in the sense mentioned above, "classical" tumor markers such as carcinoembryonic antigen, tissue polypeptide antigen, and neuron-specific enolase, which are mainly used

in others than tumors of the thyroid gland, may be useful for follow-up examinations in selected cases. In the following short review, the tumor markers and their indications in thyroid cancers are described.

Thyroglobulin (TG)

TG is an iodinated glycoprotein peculiar to the thyroid, which is essential for synthesis and storage of thyroid hormones.[1] Under physiological conditions usually small amounts of TG can be found in the blood with normal serum levels of less than 50 ng/ml. Since TG is exclusively produced by thyroid epithelium cells, serum concentrations should be less than 2 ng/ml in athyrotic state. For follow-up examinations the total absence of thyroid tissue is required as achieved by thyroidectomy and subsequent ablative radioiodine therapy.[2] Since TG release is stimulated by TSH, TG measurements should be performed under TSH elevation, i.e. 2–4 weeks after stopping exogenous thyroxin hormone substitution.[3] Under TSH supression there may be low TG serum concentrations and, thus, false negative results in 10–20% of the patients with even extended thyroid cancer including metastases or local recurrences.

Since false negative results may also be caused by plasma antibodies directed against TG, the determination of TG antibody concentrations and recovery measurements after adding a defined amount of TG are essential for reliable TG measurements.[4] Taking these prerequisites into account, any post-therapeutic TG elevation indicates either remnant thyroid tissue requiring further ablative treatment or it is indicative of metastases or local recurrences. TG plasma concentrations correlate well with tumor mass thereby indicating successful therapy. Thus, TG is a useful tumor marker for both therapy monitoring and follow-up examinations in patients with differentiated thyroid carcinoma, i.e. follicular, papillary, and oxyphilic cell carcinomas.[3] Since TG is usually produced only by differentiated thyroid carcinomas, TG is neither of use in nearly all cases of anaplastic carcinomas nor in MTC.

Tissue Polypeptide Antigen (TPA)

TPA is a cytokeratin-related non-specific proliferation marker for nearly all kinds of carcinomas. Its sensitivity for thyroid cancer including papillary, follicular, and medullary thyroid carcinoma, however, is only about 40–60% showing a good correlation to tumor progression or therapeutic response with a high positive predictive value of 90%.[4] In combination with more specific tumor markers such as TG or calcitonin both the sensitivity and the specificity for thyroid cancer can be increased. Additionally, TPA may be used as a substitute for standard thyroid tumor markers in patients with non-reliable tumor marker values, e.g. in patients with high levels of anti-thyroglobulin antibodies.

Calcitonin (CT)

CT, a peptide hormon for regulating calcium metabolism, is produced in the C-cells of the thyroid gland, and, to some extent, in the central nervous system. CT release is stimulated by increasing calcium levels as well as by pentagastrin and other hormones of the gastrointestinal tract. In thyroid cancer CT is a highly specific and sensitive tumor marker for diagnosis and follow-up of MTC. In patients with clinically manifested MTC the serum levels of CT are elevated in about 90% of the cases so it can be used for differential diagnosis in suspected thyroid cancer.[4] Furthermore, CT measurement in side-specific jugular venous blood sampling may be helpful for the localization of occult MTC.[3,4] After tumor removement normal serum concentrations indicate successful therapy. However, for follow-up examinations as well as for screening tests in patients with suspected MEN IIa/IIb or their relatives a pentagastrin stimulation test is mandatory for efficient diagnosis.[4] After intravenous injection of 0.5 μg pentagastrin per kg body weight only normal serum levels with no significant increase up to 5 min p.i. as compared to basic CT levels sufficiently exclude MTC or any relapse while a more than 2-fold increase of CT is evident for MTC.

Carcinoembryonic Antigen (CEA)

CEA is an unspecific tumor marker with a good sensitivity for colorectal cancer, breast cancer, and MTC. Since up to 10% of extended MTC have no increase of CT serum concentrations even after stimulation with pentagastrin a combination of CT and CEA is recommended for the follow-up of pa-

tients with MTC. The diagnostic sensitivity of CEA ranges from 10 to 80 % for MTC depending on the stage of disease. However, there is only a weak correlation of CEA serum concentration and tumor relapse with a positive predictive value of 70 %.[4] Therefore, CEA provides essential information only in those subjects with no CT release and, thus, false negative CT tests. Furthermore, CEA may serve as a tumor marker in anaplastic thyroid carcinomas in which TG serum levels are in the normal range in most cases. However, increased CEA serum concentrations are often found in extended disease only.

Neuron-specific Enolase (NSE)

Another marker for neuro-endocrine tumors including MTC is NSE. While this enzyme of the glycolysis, the γ-enolase of neuro-endocrine cells, is highly sensitive for small cell lung cancer and neuroblastomas, only a sensitivity of about 15% is reported for MTC. Furthermore, the positive predictive value for a relapse in NSE positive patients with MTC averages only 70% and there is no strong correlation of NSE serum levels and tumor spread as compared to CT.[4] NSE therefore, may be of clinical use only in those patients with non-reliable CT values and it cannot be recommended for routine clinical follow-up examinations.

Conclusion

In agreement with the recommendations of the German Society of Endocrinology the following regimen of routine tumor marker measurements in patients with cancers of the thyroid gland is suggested:[3]

Thyroglobulin: for the follow-up in patients with papillary, follicular, or oxyphilic carcinoma

Calcitonin: for diagnosis and follow-up in patients with medullary thyroid carcinoma as well as for screening of the relatives of patients with multiple endocrine neoplasia type II

CEA: for the follow-up in patients with medullary thyroid carcinoma

In contrast, there is no general recommendation for the use of TPA and NSE. These tumor markers, however, may be useful for the follow-up in selected patients with thyroid cancer.

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