Thyroid Cancer—iatrogenic and Otherwise

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The concept of thyroid cancer as a single disease entity should be abandoned. In fact, there are three distinct clinical and histological patterns, which can be identified as: (1) the commonly occurring differentiated cancer; (2) anaplastic cancer; and (3) medullary cancer. Depending on the tumor type, survival varies from years and even decades, to only a few months after diagnosis. A clear understanding of the type of cancer involved is essential to render an appropriate prognosis.

Differentiated Thyroid Carcinoma

Thyroid cancer has many fascinating features, not the least of which is its unwitting induction by physicians. It is, perhaps, the most notorious tumor developing as a complication of treatment for another medical condition. The differentiated variety of thyroid cancer can be produced by exposure to moderate doses of ionizing radiation. It should be emphasized that this tumor is induced by a moderate dose of radiation, thus limiting the population at risk. For the most part, these high-risk patients received moderate doses of external beam radiation for benign conditions in the head and neck area, such as tonsillitis or enlargement of the thymus. Many patients are just now completing the latent interval usually required for the tumor to become clinically apparent. However, the incidence of thyroid cancer in patients receiving relatively large doses of radiation, as with radioactive iodine for hyperthyroidism, is not increased. The large dose is sufficient to prevent cell division and, therefore, tumor development. Furthermore, it should be stressed that moderate doses of radiation increase the incidence of both benign and malignant tumors. Literature on radiation-induced thyroid cancer has sometimes created the impression that all such tumors are malignant.

Differentiated thyroid carcinoma is comprised of four histological types: pure follicular; pure papillary; mixed papillary and follicular; and Hurthle cell. In general, the clinical course for these types is indistinguishable, except for pure follicular and Hurthle cell carcinomas, which more frequently involve bone. A significant number of these patients present with pathological fractures as the initial manifestation of disease. The four histological types are characterized by indolent biological behavior. Survival is usually measured in decades after diagnosis; even when distant metastases have developed, it may be measured in years. Because differentiated thyroid cancer is most common, many physicians regard thyroid cancer as an essentially “benign” process. The indolent biological behavior also explains the observed discrepancy between the number of surgically diagnosed differentiated thyroid cancers and the low incidence of death from the disease: all thyroid cancer results in only
about 0.1 percent of cancer deaths.

Factors that account for the characteristically favorable course in most patients are not clear. It has been observed, however, that those who have more aggressive disease are usually over 40 years old at the time of initial diagnosis, and have local invasion or metastases outside the neck.

The only significant feature in the history of patients with differentiated thyroid cancer is previous exposure to radiation before puberty. The vast majority of these tumors produce no symptoms, and are most frequently discovered accidentally by the patient while rubbing the neck, applying makeup or shaving, or the tumefaction is noticed by a neighbor or friend.

There are no definitive findings on physical examination that distinguish malignant from benign nodules. However, since the differentiated variety usually metastasizes first to regional lymph nodes, the most positive physical sign of a malignant nodule is probably the combined discovery of a thyroid nodule and one or more enlarged lymph nodes in the anterior cervical chain on the ipsilateral side.

Unfortunately, there are also no laboratory tests that definitively identify this type of thyroid cancer. Imaging the thyroid gland after administration of a radionuclide such as $^{131}$I or $^{99m}$Tc frequently shows diminished concentration of the isotope in the tumor area. However, the overlap between malignant and benign thyroid diseases is great, preventing positive differentiation of these two types of conditions.

Surgery is the treatment of choice for primary disease. Controversy remains over the extent of the procedure when the disease is apparently confined to a single lobe and there is no evidence of regional lymph node spread. Some authorities advocate lobectomy of the involved lobe along with an isthmectomy, and others, total thyroidectomy in all patients. The latter recommendation is based on the high incidence of microscopic intraglandular dissemination of the disease. The use of a classic radical neck dissection on the involved side, regardless of whether there is clinical evidence of involvement of the lymph nodes on that side, has generally been abandoned. Objective evidence comparing the superiority of the two approaches is not available due to the lack of significant numbers of patients in comparable groups, followed for a sufficiently long interval. The major objection to total thyroidectomy in all patients is the relatively high incidence of hypoparathyroidism that accompanies the procedure.

The preferred treatment for recurrent and/or metastatic disease is also surgical, if possible. Because of their characteristically slow growth, surgical removal of solitary remote lesions is advocated. For disease that cannot be surgically removed, radioactive iodine and external beam radiotherapy are recommended. Favorable results with the cytotoxic antibiotic, adriamycin, have recently been reported for the treatment of patients with disseminated differentiated thyroid carcinoma.\(^1\)
Anaplastic Thyroid Carcinoma

The survival pendulum swings completely to the opposite side in this category of thyroid cancer. Here, survival is measured in months, instead of years and decades, as with the differentiated cancers. The median survival from diagnosis to death in the Anderson series is three months, making it one of the most virulent tumors known to man.

Microscopically, this tumor is characterized by a mixture of spindle and giant cells, usually with a predominance of the former. When only these morphological features appear on the slide, it is impossible to identify the thyroid as the origin of the tumor. We believe an anaplastic tumor develops from a pre-existing differentiated thyroid cancer and, in almost all instances, the differentiated component exists somewhere in the tumor specimen. Because anaplastic tumors are characteristically large and bulky, identification of both components is sometimes overlooked. This has practical consequences, since the proper prognosis cannot be given the patient nor, in some cases, can proper treatment be rendered. For example, if only the anaplastic portion of the tumor is identified and the tumor is indeed not a primary thyroid tumor, an unrealistically bad prognosis may be rendered and totally inappropriate treatment given. If, on the other hand, only the differentiated component is identified, the surgeon may inform the patient that the outlook is bright, whereas in reality he will most likely die in a few months. Whenever the anaplastic component is present, the tumor almost invariably behaves aggressively. It is, therefore, important for the pathologist to study many sections from various portions of any large, bulky, rapidly growing tumor of the thyroid. A needle biopsy tissue specimen is almost always inadequate for this purpose.

Evidence that anaplastic carcinoma develops from the differentiated variety is supported by three observations: (1) In all cases in which we have had adequate histological material for study, the two histological components have been found in intimate association in the same tumor specimen. (2) Anaplastic carcinoma has occurred in a high percentage of patients previously diagnosed and treated for differentiated thyroid carcinoma, or in patients with long-standing undiagnosed goiter that suddenly began to grow rapidly. (3) At the interface between the differentiated and anaplastic component there are morphological features suggesting transformation from one type to the other.

Treatment for anaplastic carcinoma has, in general, been uniformly poor. We have had encouraging results in patients whose disease is confined to the neck with a treatment program consisting of: operative removal of all tumor, or as much as possible; radiation to the neck, both supraclavicular areas and upper mediastinum as soon as wound healing permits; and actinomycin D beginning after one-half of the radiation dose has been administered. The dose of radiation is 6,000 rads. The dose of actinomycin D varies between 1 mg. and 5 mg., depending on the tolerance of the patient. The latter is given as a 0.5 mg. "push" twice weekly. Because of its known "recall" effect, repeated courses of the drug are administered at two to three month intervals after initial therapy until no "recall" effect can be elicited. Since anaplastic thyroid cancer is very rapidly growing, it is difficult to find patients eligible for this treatment program. A number of patients have been referred to us after the development of recurrence in the neck or distant metastases, for which no treatment is known to be effective. In many of these patients, the anaplastic component of the tumor was not identified in the pathological specimen at the time of initial treatment. Our results suggest that survival could have been improved had the
anaplastic component been recognized and the above treatment program been applied.

Medullary Carcinoma of the Thyroid (MCT)

This tumor has been the subject of prodigious investigation in the past 10 years, and the results are most fascinating. Technically, medullary carcinoma is not a thyroid tumor, if one defines thyroid tumors as derived from thyroid follicular epithelium. This tumor is derived from a second epithelial cell system, which migrated from the neural crest into the thyroid gland during embryogenesis.

Hazard and colleagues first recognized medullary carcinoma of the thyroid as a distinct clinicopathological entity, based on the characteristic histological picture of sheets of polyhedral cells traversed by connective tissue septa containing amyloid, early lymph node involvement and an intermediate grade of malignancy. Since this report, investigation has revealed that the tumor has the following characteristics:

- Occurs in both a sporadic and familial form.
- Is associated with pheochromocytoma, parathyroid adenomata and/or hyperplasia, as well as mucosal neuromata.
- Produces a variety of proteins: (1) serum calcium lowering hormone, calcitonin; (2) histaminase; (3) “ectopic” hormone (ACTH, serotonin, possibly MSH); (4) perhaps a humoral gastrointestinal tract stimulant that produces diarrhea.
- Is frequently associated with desmoplastic reactions, peptic ulceration, visceral diverticulum and Marfanoid habitus.

The literature suggests that the familial variety of the tumor predominates. But, although the total number of familial cases may exceed the sporadic, the incidence of the sporadic variety exceeds that of the familial. The mode of inheritance is autosomal dominant. (See the Editor’s Interview on “Familial Susceptibility to Cancer,” page 143 of this issue.) The genetic determination of medullary carcinoma of the thyroid (MCT) seems to convey special properties to the tumor per se, and indeed probably accounts for its association with other tumors. All of our patients with familial MCT and all reported in the literature have had bilateral involvement of the gland. This has practical significance: a total thyroideectomy should be done in all patients with medullary carcinoma to determine how vigorously a family study should be pursued. In the absence of a familial history, unilateral involvement of the gland is good presumptive evidence that the tumor is of the sporadic variety, and an exhaustive family study is therefore unjustified.

In the Anderson series, only the familial variety of MCT has been associated with other tumors. The pheochromocytoma is bilateral in a very high percentage of patients, although it may not develop in both adrenal glands simultaneously. Pheochromocytomas in locations other than the adrenal medulla have been reported, but the vast majority are located in the adrenal. In patients having both MCT and a pheochromocytoma simultaneously, the pheochromocytoma should be removed first for obvious reasons. In most instances the pheochromocytoma is asymptomatic. The association of parathyroid adenomata with MCT seems to be less than with the pheochromocytoma, however, microscopic hyperplasia has been reported as a frequent finding. Mucosal neuromata may occur on the eyelids, lips, tongue, buccal mucosa and in the myenteric and submucosal plexus of the intestinal tract, causing both megacolon and severe diarrhea.

One of the most spectacular advances in early tumor diagnosis has been the discovery that both the sporadic and familial varieties of medullary carcinoma
of the thyroid produce calcitonin, and the development of a sensitive radioimmunoassay, which makes detection in the serum practical. Although the low incidence of the tumor does not justify mass screening, the introduction of this technique has provided members of a high-risk family the possibility of early diagnosis never before available. In most instances, the basal level of the hormone is elevated. However, the tumor can be stimulated to produce excesses of the hormone either by calcium or pentagastrin infusion. The latter usually produces a greater rise in the level and is a much quicker procedure. The tumor cell of origin of medullary carcinoma of the thyroid has subsequently been termed "C-cell," since it produces calcitonin.

Approximately 30 percent of patients with MCT have severe, unexplained diarrhea. The diarrhea may precede the diagnosis and is, therefore, the only specific symptom indicating that the thyroid nodule is malignant and not benign.

Medullary carcinoma of the thyroid has been associated with the production of "cousin" hormones, ACTH, serotonin and possibly melanocyte stimulating hormone (MSH). This may represent a further dedifferentiation in the tumors producing such substances, and suggests that they will behave in a more aggressive manner.

The observed desmoplastic reactions, peptic ulcerations, visceral diverticulum and Marfanoid habitus have unknown significance, but have accounted for some significant clinical manifestations.

Other Tumors
A variety of other tumors may initially manifest themselves in the thyroid gland. Among those reported are squamous cell carcinomas, lymphomas (all types), fibrosarcomas, hemangiosarcomas, osteogenic sarcomas and chondrosarcomas. Lymphoma should be treated as a systemic condition from the onset and appropriate studies conducted to stage the disease for proper therapy. One type of tumor reported by some investigators is the so called "small-cell carcinoma." In our opinion this tumor is in reality a lymphoma and should be treated as such. We believe the diagnosis of "small-cell carcinoma" is potentially dangerous, since it may prevent or delay proper treatment.

References
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4. Hill, C.S., Jr. et al.: Medullary (solid) carcinoma of the thyroid gland: an analysis of the M.D. Anderson Hospital experience with patients with the tumor, its special features, and its histogenesis. Medicine (Baltimore) 52:141-171, 1973.

Why did you study medicine?
There are many reasons, all meritorious, but it was a deep yearning for independence that brought many of us into the study of medicine. It is a sad but true fact that the much-sought-for free independent status is no longer completely available to the average physician, particularly not to young graduates, unless they are willing to create the machinery for their continuing emancipation. That is my message and my plea.—Alfred A. Angrist: New Challenges for the Medical Graduate. New York State J. Med. 71:1112, 1971.