

## **Anaplastic Carcinoma Following Well-Differentiated Thyroid Cancer: Etiological Considerations**

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Most cases of anaplastic thyroid carcinoma can be pathologically and often historically associated with the presence of low-grade (differentiated) cancer in the thyroid. That radiation therapy to the differentiated tumor plays an etiologic role in the transformation of a differentiated to an undifferentiated tumor has been suggested. If such therapy can be implicated, is there a difference in risk between external radiotherapy or radioactive iodine? Review of the literature discloses that more anaplastic carcinoma of the thyroid develop in patients without a history of prior radiation than in individuals who have received radiation. We report our recent experience with two patients who demonstrated the sequence of well-differentiated followed by anaplastic thyroid cancer subsequent to radiation and review the question.

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Anaplastic carcinoma of the thyroid represents one of the most aggressive of human epithelial neoplasms. A disease affecting predominantly older patients, the average survival rate is less than two years [1,2] and long-term survival is rare. Many of these tumors are associated pathologically with low-grade cancers in the same gland and the relationship between the two remains unclear. Williams[3] has suggested that radiation may play an etiologic role in the transformation of a well-differentiated thyroid cancer into an anaplastic one. Alternatively, certain neoplasms may be composed of more than one population of cells with variable degrees of susceptibility to therapeutic modalities. Hence, a selection process may occur, with less responsive cell clones surviving therapy.

We report the following two cases to refocus awareness on the problem of such a development in patients treated with radiation for well-differentiated thyroid carcinoma.

### **CASE REPORTS**

#### *Case I*

A 66-year-old, Caucasian male presented, in September 1975, with a chief complaint of a right neck mass. The mass had been noted for 13 years, with little change

in size, but with recent onset of associated pain. Physical examination revealed a large multinodular mass occupying the right lower neck and deviating the trachea and thyroid cartilage to the left. Needle biopsy of the neck mass showed papillary adenocarcinoma.

On September 17, 1975, the patient underwent subtotal thyroid resection and right radical neck dissection. The thyroid tumor consisted of a 3 × 2 cm cystic mass with gross extension beyond the thyroid into the soft tissue of the neck. Several grossly involved lymph nodes were also identified.

Microscopically, the thyroid tumor was a mixed papillary and follicular carcinoma (Fig. 1) which extended through the gland capsule and invaded muscle and perineural spaces. Focally solid areas and squamous metaplasia were seen. Twenty-seven cervical lymph nodes contained metastases.

The patient's postoperative course was unremarkable, and he received subsequent radiation therapy to the neck, to a total dose of 3,960 rads.

The patient was well until October 1980 when he developed slowly progressive neck pain and right lower extremity weakness. He was hospitalized in December 1980, at which time physical examination revealed a dense right hemiparesis and bilateral positive Babinski reflexes. No evidence of local recurrent disease was noted. A myelogram was performed which demonstrated extradural compression of the right side of the upper cervical cord. The patient underwent a decompressive laminectomy from C-2 to C-5, which revealed tumor in the subarachnoid space on the right side apparently invading the spinal cord. The recurrent tumor in the epidural space displayed a solid undifferentiated carcinoma pattern with nuclear and cellular pleomorphism. Spindle cell areas were noted also (Fig. 2). No evidence of differentiated papillary carcinoma was identified in these biopsy fragments. The patient was treated with an additional 3,060 rads. The patient experienced some return of his neurological function but within one month his condition worsened, and he expired on May 30, 1981.

### *Case II*

A 69-year-old Caucasian male presented, in February 1967, with a two-month history of a rapidly developing right anterior neck mass. Examination confirmed the presence of a supple, irregular, firm 3.0 × 3.0 cm nodular mass anterior to the right

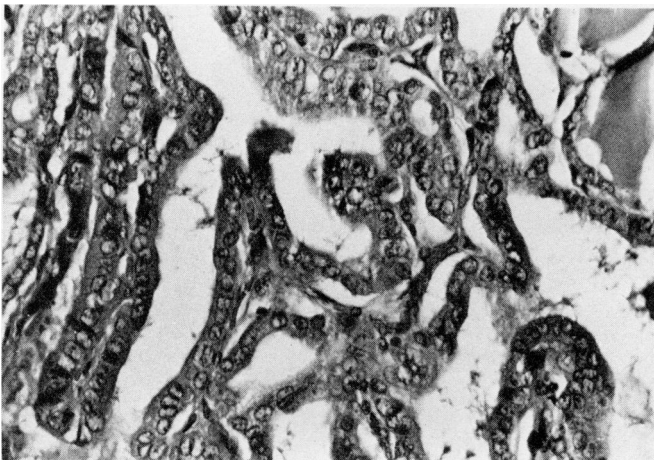


FIG. 1. Original mixed papillary and follicular carcinoma in case 1; clear nuclei and papillae are shown. (H&E, ×250)

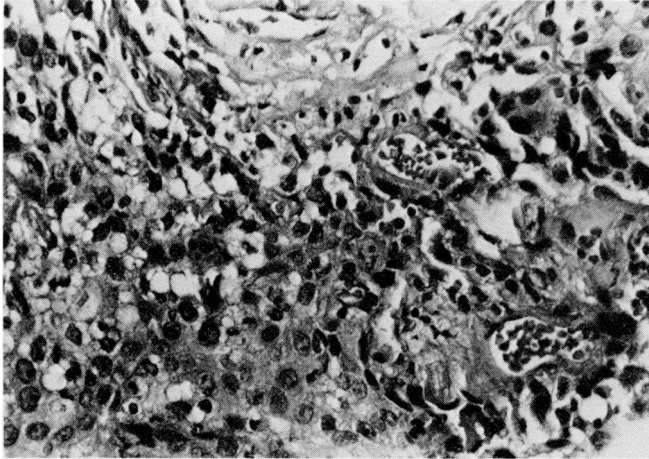


FIG. 2. Case 1: Epidural metastasis shows undifferentiated carcinoma only. (H&E,  $\times 300$ )

sternocleidomastoid muscle. On February 21, 1967, a total thyroidectomy and modified right radical neck dissection were performed. The thyroid tumor consisted of a grossly encapsulated but microscopically infiltrating differentiated carcinoma. It contained large zones of follicular differentiation but had clear nuclei of papillary cancer and psammoma bodies (Fig. 3). Small foci of more solid tumor were seen. One lymph node contained metastatic cancer. Thyroid scan revealed no uptake postoperatively. The patient was placed on 3 grains of thyroid extract per day which he continued to take until September 1978, when three right posterior cervical masses were noted. Excisional biopsy of one of these showed metastatic thyroid adenocarcinoma, predominantly solid in pattern. The patient refused additional therapy at that time and the residual cervical masses increased in size. An I-131 scan revealed increased uptake in the right posterior cervical area, the right supraclavicular area, sternal notch, the lower left cervical area, and the thyroid cartilage. On March 26, 1979, the patient received 140 millicuries of I-131.

The patient was seen at Yale-New Haven Hospital on March 19, 1980, complaining of pain from his right neck mass and weight loss. Physical examination at that time disclosed  $4.0 \times 2.5$  cm and  $2.5 \times 3.0$  cm right posterior cervical masses which

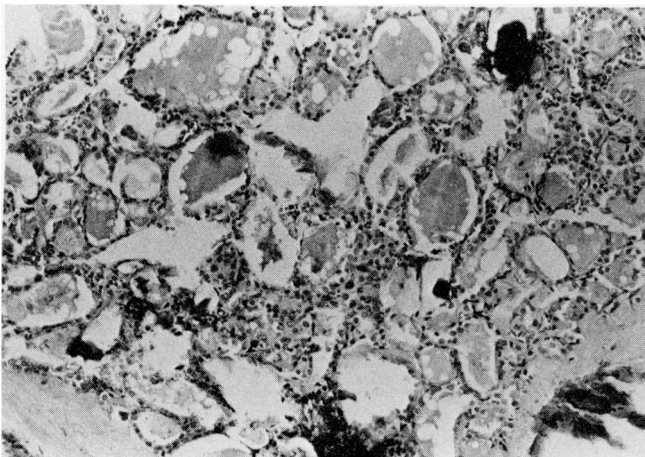


FIG. 3. Original thyroid cancer resected from case 2 in 1967 shows follicular pattern with clear nuclei and calcification. Occasional psammoma bodies were found. (H&E,  $\times 100$ )

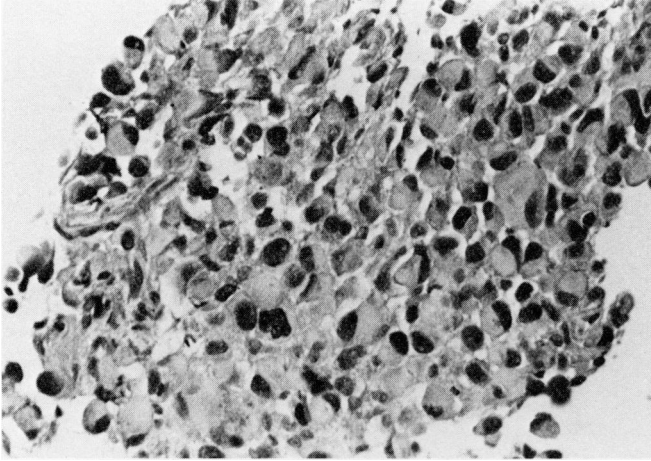


FIG. 4. Case 2: Recurrent neck mass in 1980 shows giant cell tumor predominantly. Needle biopsy. (H&E,  $\times 250$ )

were firm and fixed. In addition, a  $1.0 \times 1.0$  cm right supraclavicular node was appreciated. Intraoral examination disclosed a large mass in the right posterior pharynx. Needle biopsy showed undifferentiated carcinoma. The ultimate tumor in the neck showed both spindle and giant cells, with marked pleomorphism and extensive necrosis (Fig. 4). The patient's condition acutely deteriorated with diminution in vision and multiple cranial nerve palsies. The patient expired on April 9, 1980. At autopsy multiple brain and lung metastases were noted in addition to the massive recurrence in the neck. No differentiated carcinoma was found; the tumor in all areas was anaplastic with predominantly giant cell pattern (Fig. 5). No evidence for a second malignancy was identified.

#### DISCUSSION

These two cases represent examples of transformation of well-differentiated to anaplastic carcinoma in the thyroid. In each case, radiation had been given to the low-grade tumor. The possible etiological role of irradiation in this transformation is unclear, however. Anaplastic or undifferentiated carcinoma has classically been

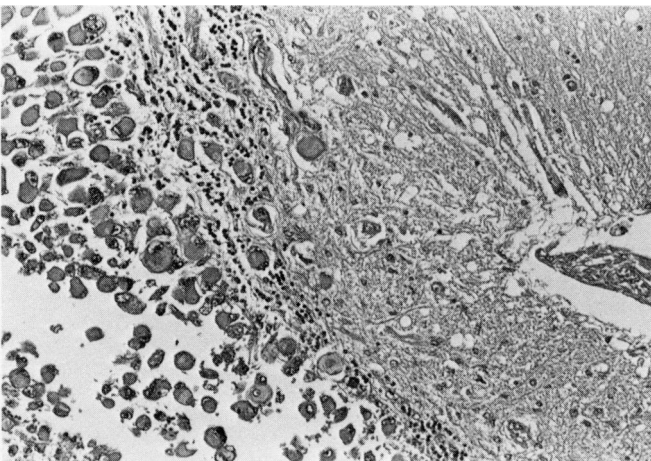


FIG. 5. Case 2: Cerebellar (*right*) metastasis of giant cell carcinoma (*left*) at autopsy. (H&E,  $\times 100$ )

divided into large cell (spindle and giant cell) and small cell types. This classification is, however, considered doubtful, since most small cell tumors represent either medullary thyroid cancer without amyloid or malignant lymphoma [4,5].

The large cell form is considered an epithelially derived neoplasm, usually from follicular epithelium, and comprises about 5 percent (range, 3–10 percent) of all thyroid malignancies [1,2,6,7]. Its exact incidence is unknown since diagnostic confusion has occurred in the past with large cell malignant lymphomas (immunoblastic sarcomas) arising in the thyroid [3,5].

Most studies of anaplastic carcinoma suggest an origin in an abnormal thyroid [1,2,6,8]. A history of “goiter” is elicited in over 75 percent of cases [2,8]. Many of the affected patients are elderly (over 50). Histologically, this goiter may represent adenomatous goiter, an adenoma, or a well-differentiated carcinoma. This striking association both by history and histology has led to the concept of transformation of a benign or low-grade malignant lesion to a high-grade one [1,2,6,7,8,9].

Evidence documenting this transformation sequence is impossible to obtain. Retrospective analyses of anaplastic carcinomas have shown associated benign or well-differentiated malignant tumors in about 80 percent of well-studied cases [7]. However, since the incidence of the highly aggressive lesions is low compared to the well-differentiated ones, other factors need to be assessed to define the influences required for “transformation” [10]. Age may be one such factor. Since anaplastic tumors occur more commonly in the elderly, there is a greater likelihood that the harbored papillary or follicular cancer could be exposed to a transforming agent such as virus or environmental pollutant [3]. The role of thyroid stimulating hormone (TSH) must be considered, since in certain areas of the world where iodine deficiency is prevalent anaplastic thyroid cancer is more common [3,5]; TSH might drive the thyroid to develop well-differentiated tumors which could transform by themselves or TSH could induce the lower grade lesions to be altered [11–15].

Radiation must be considered in the development of anaplastic thyroid cancer [3]. The possibility that thyroid radiation might produce hypofunction in the gland and stimulate pituitary TSH could be considered in some cases of transformation from low- to high-grade neoplasms. Individual case reports of anaplastic thyroid cancers following irradiation are recorded in the literature: some with external radiation [7,9,16–23], some with radioiodine [10,12,23–27], others with a combination of these [7,14,22,28–31] are rare instances following radon or radium used as the therapeutic agent [9,13,17].

In the present report, one patient had received radioiodine and the other external radiation to well-differentiated cancers before the transformations occurred.

The literature on this subject of radiation-associated transformation is extremely confused in several respects. First, the type of radiation involved, its method of delivery, and the dosages stated or calculated vary widely. Second, pathologic categorization of the initial tumors is incomplete or poorly documented. In some reports [9,27] reference is made to focal anaplastic areas in the original tumor, yet their pathologic definition or illustration is lacking. Are the authors referring to solid zones, squamous foci, or something else? Third, the patient population which received the various modalities of irradiation differs, making a comparison of absolute incidence difficult (Table 1). Finally, the pathologic classification of the “transformed” tumor is often unclear: some are diagnosed as “sarcoma,” some as carcinoma, and others as reticulum cell sarcoma [5,20].

A review of the world’s literature reveals anaplastic transformation after various modalities of irradiation, including I-131, teletherapy, and combination of both. It

TABLE 1  
Radiation Therapy Associated Transformation  
of Well-Differentiated Thyroid Cancer

Type of Radiation Treatment	No. of Patients	References
I-131	27	[10,12,23-27]
Teletherapy	18	[7,9,16-23,32,33]
Teletherapy and I-131	8	[7,14,22,28-31]
Radium implant	1	[13]
Radon seeds	1	[9]
Radium pack	1	[17]
Teletherapy and radon seeds	1	[9]
Type unknown	3	[18]

appears that I-131 treatment has been associated more frequently [10,12,23-27] with the transformation to higher grades of thyroid tumor than has external beam irradiation therapy [7,9,16-23,32,33] (Table 1). This may reflect the more extensive use of I-131 therapy in the management of well-differentiated thyroid cancers, the long survival times in most patients managed in this manner, or a more vigorous search for anaplastic transformation in this patient population, rather than any clear-cut dose relationship for induction of transformation. More often, however, anaplastic

TABLE 2  
Anaplastic Transformation in Well-Differentiated Thyroid Cancer

Authors	Reference	Patient Population	Anaplastic Transformation: No. of Pts. History of Prior Irradiation	
			YES	NO
Tollefsen et al.	[34]	Patients with spindle cell and/or giant cell carcinoma in addition to papillary Ca.	8	10
Wychulis et al.	[22]	Patients with mixed papillary and anaplastic carcinoma out of 162 patients with anaplastic cancers	3	13
Pochin	[27]	Patients (192) with mainly differentiated and inoperable thyroid cancers treated with I-131	8 <sup>a</sup>	—
Nishiyama et al.	[7]	Patients with anaplastic carcinoma found in conjunction with well-differentiated thyroid cancers out of 53 patients with anaplastic Ca.	2 <sup>b</sup>	39
Harada et al.	[18]	Patients with "accelerated growth pattern" of anaplastic thyroid cancer	4	10
Aldinger et al.	[26]	Patients with anaplastic carcinomas who had a prior history of differentiated thyroid cancer out of 84 patients with spindle and giant cell cancers of the thyroid	10 <sup>c</sup>	8

<sup>a</sup>Three had biopsies showing partially anaplastic carcinomas prior to I-131 treatment.

<sup>b</sup>A third patient developed anaplastic thyroid cancer three years after I-131 treatment for thyrotoxicosis.

<sup>c</sup>All had I-131 treatment.

tumors develop in patients who have not received any irradiation treatments for their well-differentiated thyroid carcinoma [34] (Table 2).

However, although most anaplastic tumors are derived in association with or from pre-existing differentiated cancers, only a small number of the latter progress. Indeed, the proportion is so small that the possibility of anaplastic transformation should not determine the treatment of low-grade cancer. Winship and Rosvoll reported three anaplastic transformations in 331 patients with papillary and follicular cancer following extensive beam irradiation [19]. Recently, no cases of transformation were reported in 352 patients treated at M.D. Anderson with I-131 for well-differentiated thyroid cancers [35]. Similarly, no cases of anaplastic transformation were mentioned by Tubiana in 359 patients with thyroid cancer treated with external radiation therapy or radioiodine [36].

If radiotherapy appears indicated for control of unresectable or locally recurrent differentiated thyroid tumors, it should be given. The rare event of transformation, an almost uniformly lethal circumstance, should not interfere with needed therapy [3,10].

Since dedifferentiation of low-grade thyroid cancers is considered a major mode of development of anaplastic carcinomas [37], it could be argued that our two patients represent cases of the natural history of transformation of papillary carcinomas; i.e., that the radiation was incidental. We recognize that the latency period in our Case 2 was relatively short for radiation *induction* of tumor; however, it is unclear what temporal relationships are acceptable for radiation-associated transformation of an already established malignant neoplasm. Careful attention to all possible etiological factors in the transformation of well-differentiated thyroid cancers into anaplastic carcinomas in future studies will be necessary to help define the role of radiation therapy in this process.

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