

Anaplastic Thyroid Carcinoma - Long Term Survival in a Man with Uncorrected Primary Hypothyroidism: A Case Report with Review of Literature

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Abstract

A 55-year-old male with a history of hypothyroidism treated with L-thyroxine (T_4), 120 mcg daily, was found to have large, fixed left neck mass. There was tracheal compression at the thoracic inlet on CT scan. Biopsy of the lesion revealed anaplastic thyroid carcinoma (ATC). The patient underwent emergent chemoradiation, at the end of which time his T_4 dose was reduced to induce a state of subclinical hypothyroidism. The tumor decreased in size, but re-enlarged after 4-5 months and the patient was treated with courses of an experimental drug, combretastatin, and of doxorubicin. Subsequently the patient underwent surgical removal of the residual left neck mass three years later and the excised mass revealed fibrosis and no residual carcinoma. His T_4 dose was increased to full replacement level and the patient remained disease-free for 7 years. ATC is an aggressive tumor with a median survival period of 3 months. Surgery, radiation and chemotherapy usually fail to achieve sustained survival. There is no evidence to suggest that TSH suppression prevents disease progression in patients with ATC. Well-standardized primary treatment and long-term management of differentiated thyroid carcinoma (DTC) include lowering or suppression of host thyrotropin (TSH) with exogenous L-thyroxine (T_4). T_4 has been shown to stimulate neo-angiogenesis and proliferation of a variety of human cancer cells *in vitro* and in certain experimental and retrospective clinical studies; thyroid hormone deprivation may slow tumor growth and apparently enhance response to certain chemotherapeutic agents. The ATC patient reported here exhibited an extraordinary response to conventional radiation therapy and chemotherapy while being maintained in a chemically hypothyroid state.

Keywords: Hypothyroidism; Survival; Anaplastic Thyroid Carcinoma

Abbreviations: ATC: Anaplastic Thyroid Carcinoma; CT: Computed Tomography; DTC: Differentiated thyroid carcinoma; ILK: Integrin-linked kinase; TSH: Thyroid Stimulating Hormone Thyrotropin

Introduction

Anaplastic thyroid carcinoma (ATC) is a very aggressive undifferentiated tumor. Most patients present with locally advanced, rapidly progressive disease and die with metastases within months of diagnosis [1]. While aggressive endogenous pituitary thyrotropin (TSH) suppression with L-thyroxine (T_4) may be part of the clinical management of differentiated thyroid cancers there is no evidence that anaplastic thyroid cancer is a TSH-dependent disease. There is evidence, however, that thyroid hormone, chiefly T_4 , at physiologic free levels, is a growth factor that induces proliferation of certain tumor cells and of blood vessel cells. Consistent with such observations, recent pre-clinical and clinical studies have provided evidence that a chemically hypothyroid state is associated with better outcome and response rate in certain neoplasms. In the patient reported here, we report an unusually long survival in a patient with ATC with T_4 deprivation.

Case Presentation

A 55-year-old male was seen in September of 1997 for symptoms of headache, fatigue and hoarseness of voice. He had 4-year history of hypothyroidism and was on replacement T_4 , the dose of which was increased two weeks prior to presentation from 100 mcg by mouth daily to 120 mcg, in response to an increase in serum TSH concentration to 16.39 (normal range, 0.32-5.00) μ IU/mL. On evaluation, he was found to have a

large fixed left neck mass. CT scan showed a $7.5 \times 5.0 \times 5.0$ cm mass at the level of the thoracic inlet extending to the thyroid gland and compressing the trachea to the right (Figure 1), biopsy of the mass revealed anaplastic thyroid carcinoma (Figure 2). Immediately initiated treatment consisted of radiation to the mass of a total dose of 5760 cGy in 36 fractions over 6 weeks (Figure 3), along with cis-platinum chemotherapy. At that point, T_4 was reduced to 5 mcg daily with the purpose of inducing a subclinical hypothyroid state. Over the ensuing 24 months, the patient's serum TSH level fluctuated between 23-58 μ IU/mL while he was taking 5 mcg T_4 daily. He did well physically, including walking about 3 miles a day. The tumor decreased in size, both clinically and on CT scan over several months, but then re-enlarged and the patient was treated with doxorubicin and an experimental agent, combretastatin, in February and June of 1998, respectively. In May of 2000, he underwent surgery for the residual left neck mass and pathology examination revealed fibrosis with no residual carcinoma (Figure 4). L-thyroxine was subsequently increased to 175 mcg in 2001 and was maintained at this level thereafter (Table 1). The patient remained disease-free for 10 years following the making of the diagnosis. He died of metastatic prostate cancer.

Discussion

ATC represents <2% of thyroid cancers, but is an aggressive cancer that accounts for 14-39% of deaths from thyroid carcinomas. The median



Figure 1: CT scan of the neck showing the mass at the level of the thoracic inlet extending to the thyroid and compressing the trachea to the right.

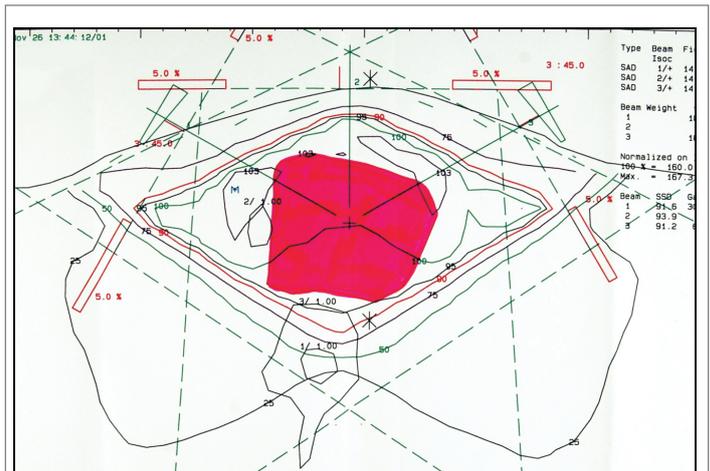


Figure 3: Radiation Plan: tumor volume and isodoses from the central axis

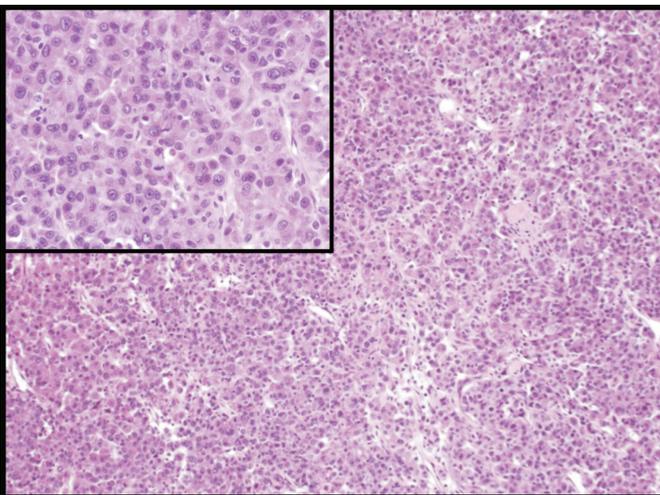


Figure 2: Anaplastic thyroid carcinoma (H&E, original magnification $\times 40$; insert $\times 400$).

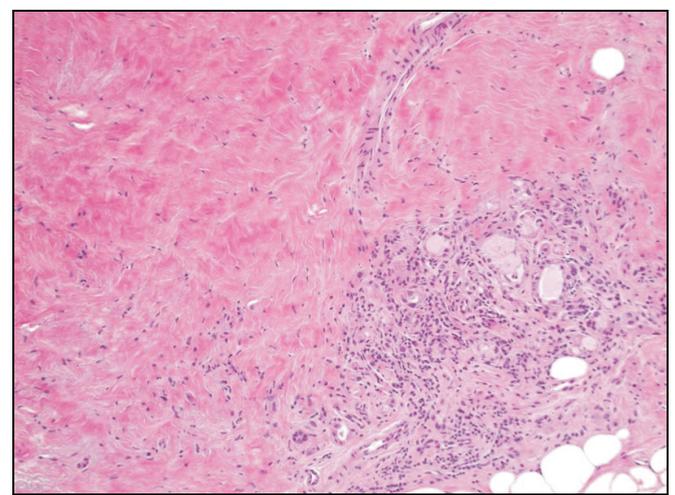


Figure 4: Fibrotic thyroid with chronic inflammation and scattered acini with Hürthle cell features (H&E, original magnification $\times 100$)

survival time is 3-7 months and prognosis is especially poor when the tumors are large, have distant metastasis, acute obstructive symptoms, and leukocytosis [1]. As per a recent report, the presence of a pre-existing tumor, epithelial growth, a squamous cell carcinoma component, no neutrophilic infiltration and lymphocytic infiltration are favorable prognostic factors in anaplastic thyroid carcinoma. In the operable patient, surgery is followed by radiation and chemotherapy [2]. For patients presenting with locally advanced tumor, combined therapy is used. Patients frequently at presentation have widespread local neck invasion and develop metastasis to lungs, pleura, bone and brain.

Drugs used in ATC

Doxorubicin has been used frequently for treatment, but responses are infrequent. Other drugs such as methotrexate, bleomycin and cisplatin have had disappointing outcomes and paclitaxel has been recommended recently. Manumycin is a new drug that is a farnesyl-protein transferase inhibitor and has been shown to inhibit the growth of anaplastic carcinoma in both an *in vivo* model and *in vitro*; it has synergistic activity when combined with paclitaxel. Targeted molecular therapy has been investigated in the treatment of ATC and this includes an integrin linked

kinase (ILK) inhibitor, since ILK is over expressed in ATC. Currently, the recommended treatment of this aggressive tumor is multi-modality therapy that combines surgery (total thyroidectomy), chemotherapy and radiation. From a prognostic point of view, the patient of less than 60 years of age who has an intrathyroidal tumor has the longest survival. Surgical resection with external beam radiotherapy for ATC is associated with lower cause-specific mortality [1].

Thyroid hormone: effect on cell surface receptors and growth factors

In dividing endothelial cells, tumor cells, osteoclasts and certain other cells, the plasma membrane bears in large quantities a structural protein, integrin $\alpha v \beta 3$, whose extracellular domain contains a specific receptor for thyroid hormone. T_4 appears to be the primary ligand for the hormone receptor on the integrin—that is, the receptor has a higher affinity for T_4 than 3, 5, 3'-tri-iodo-L-thyronine (T_3), the principal ligand of nuclear thyroid hormone receptor proteins—and, when activated, induces a mitogen-activated protein kinase (MAPK) cascade that culminates in expression of a number of genes critical to angiogenesis and to tumor cell proliferation and survival pathways [3,4].

Date	TSH (0.32-5.0 µIU/mL)	FT4 (0.71-1.85 ng/dL)	T3 (60-200 ng/dL)	T4 (4.5-11 mg/dL)
9/30/1997	6.180			
12/9/1997	16.39	0.85		
12/15/1997	16.39	0.85		
6/29/1998	57.26	0.67		
5/14/2000	22.86	0.85		
3/19/2001	6.57			9.2
9/24/2001	0.33	1.66	126	11.3

Table 1: Thyroid function tests of the patient

Serial number	Study title	Cancer type	Observation/ conclusion	Reference
1	Propylthiouracil-induced chemical hypothyroidism with high-dose tamoxifen prolongs survival in recurrent high grade glioma: a phase I/II study	High grade glioma	significantly longer survival when chemical hypothyroidism was induced with propylthiouracil	9
2	Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma.	Breast cancer	Primary hypothyroidism was associated with a reduced risk for primary breast cancer and a more indolent invasive disease	10
3	Spontaneous remission of metastatic lung cancer following myxedema coma--an apoptosis-related phenomenon?	Lung cancer	Myxedema coma with resultant severe deficiency of T3 caused possible apoptosis of metastatic non-small cell lung cancer	11
4	Medically induced euthyroid hypothyroxinemia may extend survival in compassionate need cancer patients: an observational study.	Glioblastoma multiforme	The survival time of majority of patients exceeded the 20% expected 1-year survival for hypothyroxinemic, end-stage cancer group with a significant difference between actual and expected survival	12

Table 2: Clinical studies and reports

This mechanism has been described in a large number of solid tumor cell lines and in myeloma cells [5,6]. Via the receptor on integrin $\alpha\beta 3$, thyroid hormone also modulates activities of the insulin-like growth factor receptor (IGFR) and epidermal growth factor receptor (EGFR) pathways. This effect is noteworthy because these growth factors may be overexpressed in various tumor cell types and are associated with activation of mitogenesis, cell proliferation and resistance to apoptosis. Thyroid hormone is anti-apoptotic in nonmalignant cells and in cancer cells. The action is desirable in non-cancer cells such as neurons and myocardiocytes, but is undesirable in tumor cells where it is a defense mechanism. The hormone may limit chemotherapy-induced apoptosis by shortening intracellular residence time of anticancer drugs that are pro-apoptotic contributing to chemotherapy resistance [7]. In ATC cells, overexpression of EGFR has been reported. Schiff et al. [8] described the effect of gefitinib on blocking EGFR in ATC cells, inducing apoptosis *in vitro* and anti-tumor activity in a mouse tumor model. Lower levels of growth factors have been observed in hypothyroid individuals. At a subcellular level, thyroid hormone modulates mitochondrial ATP synthesis, bcl-2 expression and supports maintenance of the mitochondrial membrane potential; leakage or collapse of this membrane potential is associated with apoptosis. Thyroid hormone may also induce angiogenesis and cell migration.

Thyroid hormone actions on solid tumor cells

The effect of thyroid hormone deprivation on different tumor cell types has been investigated. Thyroid hormone effects on such cells include nongenomic actions of T_4 on mitogenesis and tumor proliferation via the $\alpha\beta 3$ -integrin interaction, as well as anti-apoptotic actions.

Preclinical and experimental data

Pre-clinical data suggest that tumor allo- and xenografts in rodents and *in vitro* in cell culture systems may undergo accelerated growth/

proliferation following an increase in ambient T_4 in physiological free hormone concentrations or T3 at supraphysiological levels. *In vitro* proliferation of various model tumor types including breast carcinoma, glioma and differentiated thyroid cancer cell lines has been induced by increasing concentrations of thyroid hormone.

In-vivo experimental tumor model systems in rodents have demonstrated significant growth modulation by thyroid deprivation. An increased complete response to chemotherapy and propylthiouracil induced hypothyroidism in mice bearing a mouse mammary carcinoma has been reported. Low thyroid hormone levels improve survival in murine model for ocular melanoma [9].

Clinical studies and reports of hypothyroidism and cancer (Table 2)

In a clinical study of recurrent high-grade gliomas, patient survival was significantly longer in patients who had propylthiouracil-induced chemical hypothyroidism [10].

Cristofanilli et al. [11] reported a reduced risk of primary breast carcinoma in women with primary hypothyroidism, as well as an eight-year delay in age at diagnosis and a less aggressive disease [9]. A similar association has been observed between development of hypothyroidism and improved survival in patients with head and neck cancer.

Anecdotally, spontaneous remission of non-small lung cancer has been reported following recovery from myxedema coma [12]. Accelerated progression of metastatic breast cancer has been reported following increase in dose of T_4 supplementation.

ATC and thyroid hormone deprivation: a basis for therapy?

The decision for inducing biochemical hypothyroidism may be more challenging in our patient with ATC, since TSH suppression is standard in thyroid cancer.

TSH suppression has been proven effective in DTC after initial surgery to decrease morbidity and mortality, but this is not the case in ATC. In our patient, however, the tumor had appeared and enlarged extremely rapidly within two weeks of an increase in dosage of T_4 replacement in response to a rise in his TSH; this suggests a cause-effect relationship. The patient was therefore advised that lowering his dose of T_4 might be therapeutic. A growing body of data supports the lowering of thyroid hormone levels and maintenance of chemical hypothyroidism in individuals with solid tumors. There is also a lack of evidence for the utility of TSH modulation in ATC. As noted above, thyroid hormone is anti-apoptotic in nonmalignant cells and cancer cells and this serves to engage the hormone in cancer cell defense. The hormone may limit chemotherapy-induced apoptosis by shortening intracellular residence time of anticancer drugs that are pro-apoptotic contributing to chemotherapy resistance [7]. The hormone may limit chemotherapy-induced apoptosis by shortening intracellular residence time of anticancer drugs that are pro-apoptotic contributing to chemotherapy resistance [7]. We suggest that the novel approach in this patient warrants further investigation and validation. We postulate that our patient's durable survival is related to reduction in L-thyroxine supplementation and long term maintenance of chemical hypothyroidism in combination with standard chemo and radiation therapy. Medically induced euthyroid hypothyroxinemia has been shown to extend survival in patients with advanced cancers to whom other avenues of treatment are closed, e.g., in 23 end-stage solid tumor patients in whom hypothyroxinemia was induced to prolong life [13]. There have been recent interesting advances showing that tetraiodothyroacetic acid (tetrac), a T_4 analog, blocks binding of T_4 and T_3 by $\alpha\beta_3$ and inhibits angiogenic activity of thyroid hormone [14]. Tetraiodothyroacetic acid (tetrac) and nanoparticulate tetrac arrest growth of renal cell carcinoma xenografts [15], medullary carcinoma of the thyroid [16] and a variety of other grafts.

In conclusion, our patient presented initially with a locally advanced anaplastic thyroid tumor for which he received chemotherapy and radiotherapy. In spite of his extremely poor prognosis he stayed disease-free 7 years following the diagnosis; previous reports state survival of 6 years and 10 years being highest documented. Throughout the survival period, he was chemically hypothyroid. His disease remained under control and he never developed metastases. No additional tissue pathology diagnosis was obtained prior to receiving chemotherapy with an experimental drug combrestatin. We suggest that this unusual outcome of ATC is in part attributable to T_4 deprivation complementing multimodality therapy. Further research is warranted to establish the role of subclinical hypothyroidism in the management of anaplastic thyroid cancer.

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Conflict of Interest

None

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