Spontaneous Remission of Metastatic Lung Cancer Following Myxedema Coma—an Apoptosis-Related Phenomenon?

Lung cancer is not a hormonally sensitive disease in the classic sense, and spontaneous remissions are rare, with only two unequivocal cases reported (1). We report here a case of metastatic non-small-cell lung cancer that resolved spontaneously following resuscitation from myxedema coma.

A 69-year-old man had undergone a left upper lobectomy for an anaplastic carcinoma (T1 N0 M0) (2). One year after surgery, this patient presented with severe lower back pain and, on investigation, was found to have multifocal osseous metastatic lesions and a left hilar mass approximately 4 cm x 4 cm.

Following palliative radiation therapy to the spine (2000 cGy in five fractions from a 60Co source), the patient began chemotherapy (1200 mg cyclophosphamide intravenously every twice weekly for 3 weeks). The disease remained clinically stable, but the patient began to receive amiodarone, which contains 37.3% iodine by weight, induces thyroid function abnormalities in 5% of patients (3).

The patient continued on chemotherapy intermittently; he had marked palliation of bone pain but no objective change in bone disease or in the size of the hilar mass for almost 18 months, when he was hospitalized because he lost consciousness. Thyroid function test results were grossly abnormal: thyroxine (T4) 0.5 µg/100 mL (reference range, 5.0-10.5 µg/100 mL), thyrotropin (thyroid-stimulating hormone [TSH]) greater than 40 mUI/mL (range, 0.4-5.5 mUI/mL), and free-thyroxine index 0.3 µg/100 mL (range, 6.4-10.7 µg/100 mL). A diagnosis of myxedema coma was made, and the patient recovered completely with administration of L-thyroxine, hydrocortisone, and supportive therapy. Subsequently, the patient elected to receive no further chemotherapy and did not attend oncology clinic on a regular basis; no further staging studies were obtained, although serial chest radiographs that were ordered by the patient’s internist showed no evidence of the hilar mass.

The patient lived for 4 years after the myxedema coma event. He died of a myocardial infarction. No autopsy was performed. During this 4-year period, he received daily maintenance of L-thyroxine (as well as digoxin and diuretics), and no disease recurrence or progression was documented.

To our knowledge, such an outcome has not previously been reported in association with severe thyroid hormone deficiency. We therefore propose that this patient entered clinical remission coincident with, or possibly precipitated by, this life-threatening metabolic state.

In defense of our hypothesis, it should be noted that there have been clinical reports of increased life span and enhanced response rates in hypothyroid patients with metastatic breast cancer (4,5), renal cell cancer, or malignant melanoma after various hormonal, cytotoxic, and cytokine therapies (6-8). Experimentally, the induction of a hypothyroid state in mice bearing either rodent tumors or xenografted human tumors has been shown to markedly reduce neoplastic growth rates (9-14).

With regard to a possible mechanism, it has been shown that triiodothyronine (T3) is a potent stimulator of production of growth factors such as epidermal growth factor (EGF) (15,16), nerve growth factor (17), insulin-like growth factor (18), and EGF-receptor levels (19) via a rapid induction of increased mRNA levels for these proteins. These effects of T3 on gene expression, growth factors, and growth-factor receptors could therefore clearly alter autocrine pathways within the tumor or paracrine pathways between the host and the neoplasm (20). In this regard, apoptosis [a growth regulatory mechanism of normal cell proliferation (21)] also occurs after cytotoxic insult to the cell (22) and has been observed shortly after exposure to agents such as etoposide, cisplatin, and fluorouracil in model tumor systems. Such acute induction of cell loss via apoptosis may account for the very rapid responses observed clinically in lymphomas and in other highly chemosensitive or radiosensitive solid tumors, such as seminoma of the testis or Wilms’ tumor. Similarly, apoptosis is important in androgen-dependent prostate cancer after testosterone is withdrawn (23). Expression of the product of the Bcl-2 gene (also known as the BCL2 gene) is associated with inhibition of apoptosis (24); this protein is located within the inner mitochondrial membrane and is analytically inseparable from succinate dehydrogenase (25). Because both mitochondrial biogenesis (26) and the activity of succinate dehydrogenase (27) are modulated by T3, severe deficiency of T3 (e.g., myxedema coma) might then be sufficient to induce apoptosis in a particular neoplasm, such as the metastatic non-small-cell lung cancer in this case report.

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Notes

"In autocrine function, cells producing growth factor are the target cells for the growth factor. In paracrine function, cells other than those producing growth factor are the target cells."

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Cancer Breakthroughs Require Mavericks

As a patent attorney, I have been impressed by the courage of National Cancer Institute researchers in seeking new approaches to cancer treatment. Inventive breakthroughs frequently occur when one abandons the obvious and conventional approach and strikes out in a new direction. I am thus particularly impressed by the courage of National Cancer Institute researchers in seeking new approaches to cancer treatment.

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