SUDDEN HEMORRHAGE IN METASTATIC THYROID CARCINOMA OF THE BRAIN DURING TREATMENT WITH IODINE-131

Donald L. Holmquest and Peter Lake

Texas A&M University, College Station, Texas, and The Eisenhower Medical Center, Palm Desert, California

A patient with papillary–follicular carcinoma of the thyroid, with metastases to the lungs, skeleton, and brain, was treated 5 weeks after thyroidectomy with 135 mCi of ^{131}I. Although preliminary studies with 1 mCi had not shown any iodine uptake by the brain metastasis, this lesion showed intense concentration at the time of the larger therapeutic dose. Four days later, acute hemorrhage of the tumor occurred, requiring surgical removal. Although ^{131}I therapy would seem an unlikely cause of acute necrosis and hemorrhage in these lesions, the association of therapeutic radioiodine and hemorrhage is interesting. Since recent reports suggest that brain metastasis may be somewhat more common than previously suspected, we suggest that brain imaging be included in the workup prior to radioiodine therapy of patients with advanced metastatic disease or neurologic symptoms.

Papillary, follicular, and mixed papillary–follicular carcinomas of the thyroid are well-differentiated tumors that are generally regarded as only mildly malignant. There is a high rate of cure with localized disease, and even multiple metastases are compatible with many years of survival (*1,2*). Death, when it does occur, is often related to complications produced by a recent or long-standing metastasis. This report describes the complication of sudden hemorrhage which occurred in a previously stable brain metastasis during the course of treatment with radioiodine.

A characteristic clinical feature of well-differentiated carcinoma of the thyroid is its preferential spread to certain specific sites. In the majority of cases metastases are limited to regional lymph nodes; secondary sites include the lungs and skeleton with infrequent involvement of distant lymph nodes, the liver, and the brain (*3*). Recognition of favored sites for metastasis is important in the workup because ^{131}I therapy may be helpful if definite metastatic disease capable of concentrating iodine is detected.

Millicurie quantities of ^{131}I facilitate the search for functioning metastatic disease. However, since the extended time required for diligent search may restrict scanning to the more likely sites, metastatic tumor may only be detected if it is present in the expected places. Recent reports have again stressed the value of routine imaging of the lungs (*4*) and liver (*5*) for patients who may undergo treatment and who may need to be followed during an extended course of their disease. Our experience with a patient whose widespread metastases included a cerebral lesion suggests that a foreknowledge of such lesions obtained from brain imaging with ^{99m}Tc-pertechnetate may contribute materially to the management of the patient. Sudden hemorrhage in a brain tumor is not an unusual occurrence; however, the close temporal relationship to treatment in this case raises the possibility, though seemingly remote, that this complication may be related to some aspect of the therapeutic regimen.

CASE REPORT

The patient was a 56-year-old man who presented with a 2-year history of episodic left upper quadrant and flank pain, confusion, and numbness and spasm of his left arm and hand. He was occasionally found at his work unconscious; however, he specifically denied any worsening of his central nervous system or abdominal symptoms in recent months. His principal complaint was his inability to gain relief from the periodic left upper quadrant pain.

Received May 30, 1975; revision accepted Oct. 7, 1975.

For reprints contact: Donald L. Holmquest, Associate Dean of Medicine, Texas A&M University, College Station, Tex. 77843.

A chest x-ray showed a large retrosternal mass and a widespread distribution of micronodular densities throughout both lungs. A thyroid scan showed replacement of the lower half of the left lobe with a nonfunctioning mass that appeared to extend inferiorly beneath the sternum. A lung scan showed no detectable iodine concentration.

At surgery, a large substernal tumor was removed and a total thyroidectomy was performed. Pathologic examination showed principally papillary carcinoma with a few scattered follicular elements. Five days after surgery the patient was discharged without thyroid medication but with instructions to return in 6 weeks for a ^{131}I scan of the neck and chest.

Approximately 2 weeks after surgery the patient developed total aphasia lasting approximately 1 hr, followed by his recurring complaint of left upper quadrant and flank pain. Because of the resemblance of his symptoms to "abdominal epilepsy," a brain scan was performed. The perfusion images showed a small highly vascular lesion over the right convexity. Static images showed a 3–4-cm spherical mass in the right parietal region. A bone scan with ^{99m}Tc-diphosphonate (sodium ethane-1-hydroxy-1, 1-diphosphonate) showed probable bone metastases in the T-10 vertebra, right sacroiliac joint, and right heel.

Twenty-four hours after administration of 1 mCi of ^{131}I, a scan of the neck and chest showed concentrating tissue in the neck but none in the lungs. A careful survey of the brain in the region of the parietal shadow failed to show increased radioactivity. A similar survey of the skeleton in the region of proven metastases also failed to show significantly increased radioactivity.

Approximately 5 weeks after surgery, the patient again returned to the hospital, complaining of his abdominal symptoms. Since his serum thyroxine measured less than 1 mg%, he was isolated and treated with 135 mCi of ^{131}I orally as sodium iodide. No exogenous thyroid-stimulating hormone was given. No preliminary survey of the neck, chest, and other metastatic sites with a millicurie dose of ^{131}I was performed since only 2 weeks had elapsed since the previous study. Three days after iodine administration, a whole-body scan was performed. In addition to large amounts of radioactivity in the residual thyroid tissue in the neck and in several metastatic sites, a discrete focus of iodine concentration was visible in the right parietal region. A scan of the brain showed intense localization of radioiodine in the previously proven right parietal tumor mass (Fig. 1). No detectable activity was present in the lungs or in the metastasis in the right heel.

Early in the fourth day after treatment, the patient experienced unusual left-sided seizures associated with clonic flexion of the arm and fingers and stiffness in the upper and lower extremities. The seizures continued intermittently for 1 hr, after which the patient was briefly uncommunicative with a postictal appearance. Throughout the day there was considerable weakness of the entire left side with a poverty of spontaneous motion. Because of deterioration of the patient's alertness and motor strength the following day, a cerebral angiogram was performed. A highly vascular mass, 3–4 cm in diameter, was visible in the right posterior parietal region with compression of a large amount of surrounding tissue.

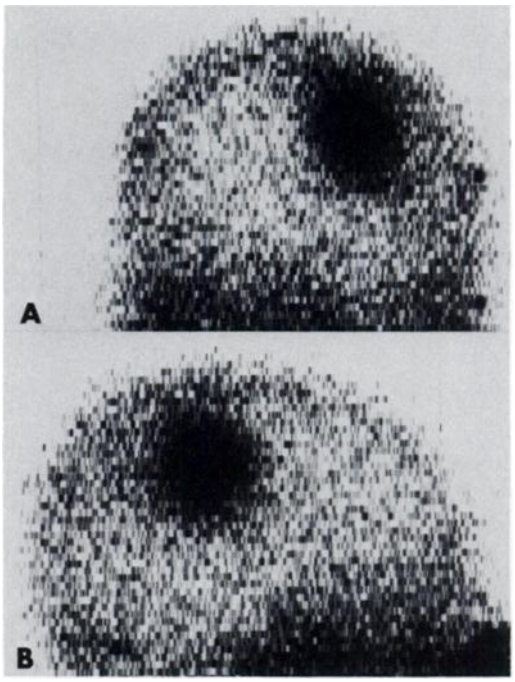

FIG. 1. Brain distribution of ^{131}I. (A) Posterior view; (B) right lateral view. Intense concentration of radioactivity is present in right parietal tumor mass.

The next day, 6 days after radioiodine therapy, the patient continued to show depression of his sensorium and total paralysis of his left side. A craniotomy was performed, and a bulging hemorrhagic tumor was removed. Pathologic examination of the tissues revealed a well-differentiated tumor of a purely follicular type with considerable central necrosis. Assay of several samples of the less necrotic tissue in a dose calibrator showed an average uptake of 1.2 μCi of ^{131}I per gram of tissue. The tumor mass measured approximately 40 gm.

The patient had an uneventful postoperative course with gradual improvement of his neurologic deficits under physical and occupational therapy. Since the tumor had been on his nondominant side, the neurologic deficits consisted primarily of a disturbance

of body image and a poverty of spontaneous motor activity on the left. Four months after surgery, the patient resumed many of his previous activities and was free of his former abdominal symptoms. A bone scan performed 14 months after the original showed no radionuclide localization in the metastasis in the right heel and questionably abnormal areas of concentration in the midlumbar spine, distal right femur, and proximal left tibia. A brain scan showed the effects of the previous craniotomy but no evidence of tumor recurrence. Today the patient remains free of symptomatic disease except for his remaining neurologic deficits.

DISCUSSION

The temporal association of acute hemorrhage in this tumor mass with its intense ^{131}I localization is striking, and it is tempting to suggest a causal relationship. Perhaps a highly vascular tumor residing in delicate brain tissue is very susceptible to radiation. Perhaps the biologic turnover of iodine in the tumor was sufficiently rapid that the measured content of radioactivity 6 days after administration represented only a small fraction of a much larger and perhaps significant concentration earlier. Perhaps a high level of circulating thyroid-stimulating hormone caused rapid growth that could both have aggravated central nervous system symptoms and increased susceptibility to ionizing radiation.

On the other hand, the presence of 1 or even 100 μCi of ^{131}I per gram of tumor does not seem sufficient to evoke hemorrhage when 60–80 μCi per gram of thyroid tissue are commonly produced in the treatment of Graves' disease. Furthermore, no hemorrhages from other metastatic sites after comparable ^{131}I doses have been reported to our knowledge. The fact that the patient's symptoms intensified after thyroidectomy suggests that induction of the hypothyroid state alone could have contributed to the hemorrhage by stimulating sudden growth in a previously quiescent tumor.

This case raises a number of interesting questions for those who treat thyroid carcinoma with radioactive iodine. Are we missing an occasional cerebral metastasis because we simply are not looking for it? How often does a thyroid cerebral metastasis compromise the survival of the patient? In a patient with a cerebral metastasis, is therapeutic ^{131}I potentially dangerous? Should postsurgical hypothyroidism be avoided?

Because of the potentially adverse effects of a cerebral metastasis, it is perhaps appropriate that we be more sensitive to signs of central nervous system involvement in patients with disseminated thyroid carcinoma. Perhaps we should also listen with more interest to those neurosurgeons who advocate the surgical removal of solitary cerebral metastases.

REFERENCES

1. SHELLEY WB, BEERMAN H, ENTERLINE HT: Metastatic thyroid carcinoma. *JAMA* 226: 173–174, 1973

2. WOOLNER LB: Thyroid carcinoma: Pathological classification with data on prognosis. *Semin Nucl Med* 1: 481–502, 1971

3. THOMAS CG: Thyroid cancer: Clinical aspects. In *The Thyroid*, Werner SC, Ingbar SH, eds, New York, Harper & Row, 1971, pp 442–452

4. BONTE FJ, MCCONNEL RW: Pulmonary metastases from differentiated thyroid carcinoma demonstrated only by nuclear imaging. *Radiology* 107: 585–590, 1973

5. WOOLFENDEN JM, WAXMAN AD, WOLFSTEIN RS, et al: Scintigraphic evaluation of liver metastases from thyroid carcinoma. *J Nucl Med* 16: 669–671, 1975