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Management of Aggressive Metastatic Papillary Thyroid Cancer Involves Multiple Treatment Methods

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CASE PRESENTATION

The patient is a 37-year-old man who found a painless lump in his neck in March 2010. An ultrasound revealed a 4-cm right-sided thyroid nodule with microcalcifications; fine-needle aspiration results were suspicious for papillary thyroid cancer (PTC). He underwent thyroidectomy in April and was found to have a multifocal, bilateral, midline PTC with a dominant right-sided nodule measuring 5.8 cm. There was lymphovascular invasion, extrathyroidal extension of the tumor and extension of the tumor into the soft tissue through the lymph nodes. The tumor involved five of six left jugular lymph nodes, with extranodal extension. Metastatic carcinoma involved six of seven regional pretracheal lymph nodes. The pathological diagnosis was pT3b, pN1b, pMX. Postoperatively, a serum thyroglobulin (Tg) was >3000 ng/ml. The patient was begun on levothyroxine for TSH suppression. Postoperatively, he had a CT scan of the neck and chest with the inadvertent administration of contrast material, which demonstrated bilateral diffuse metastatic disease throughout both lung fields as well as mediastinal and supraclavicular lymphadenopathy consistent with metastatic disease.

He presented to our institution for a second opinion regarding ongoing management of his thyroid cancer. He had palpable lymphadenopathy and an ultrasound performed in the office revealed diffuse malignant lymphadenopathy involving levels II, III, and IV in the right jugular chain and levels II to IV in the left jugular chain. Because he had been given iodine contrast for the CT scan, radioactive iodine (RAI) treatment was postponed. Bilateral central and lateral neck dissections were recommended, and these were performed at another institution. A total of 22 of 54 lymph nodes were found to have metastatic PTC. Five months later, he received 155 mCi of 131I. An RAI whole-body scan (WBS) performed 9 days later showed diffuse uptake in the pulmonary parenchyma as well as in both sides of the neck, anterior mediastinum, and right supraclavicular area. In March 2011, the Tg was 134 ng/ml, TgAb <0.4 U/ml, and TSH 0.11 mIU/L.

The patient returned to our institution the following year. To further assess the extent of disease involvement, he underwent a high-resolution neck ultrasound and repeat thyroglobulin testing. The ultrasound of the neck showed a mass overlying the trachea measuring 2 cm and biopsy confirmed metastatic PTC. There were two small (<1 cm) lymph nodes in the right lateral neck. His Tg level was 88 ng/ml, TgAb <0.4 U/ml, and TSH <0.01 mU/L.

The patient's clinical data was reviewed by our multidisciplinary institutional Thyroid Cancer Tumor Board, which is composed of endocrinologists, surgeons, nuclear medicine specialists, oncologists, radiation oncologists, and pathologists. On the basis of their consensual recommendation, the patient underwent resection of the mass overlying the trachea, which showed a metastatic lesion measuring 2.5 cm by 1.0 cm by 1 cm consisting of one lymph node and soft tissue. The surgery was followed by a second dose of RAI (209 mCi) after recombinant human TSH stimulation. The 7-day post-RAI WBS demonstrated uptake in the right thyroid bed and diffuse uptake in the lungs. An FDG–PET scan showed moderate

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activity in the right paratracheal region measuring 4 mm, corresponding to a 1.5-cm lymph node on simultaneous CT scanning. Because of persistent macroscopic metastatic disease in the neck, some of which had dedifferentiated based on PET positivity, external-beam radiation therapy (EBRT) was recommended. He received 5940 cGy to his thyroid using intensity-modulated radiation therapy (IMRT).

One year later, his Tg was 126 ng/ml and TgAb <0.4 U/ml. FDG–PET imaging showed decreased metabolic activity at the site of the prior abnormality in the right neck corresponding to a decrease in size of the lymph node on CT scanning. Lung imaging showed relatively stable micronodules in both lungs, with the largest nodule decreased in size from 7 mm to 3 mm. A 123I scan showed persistent uptake in the lungs, and he was treated with another dose of 250 mCi of RAI, which resulted in a cumulative dose of 614 mCi of 131I. The lungs and two areas in the right neck took up iodine on the 7-day posttreatment WBS.

ANALYSIS AND COMMENTARY

This young man initially presented with biologically aggressive but histologically differentiated thyroid cancer metastatic to central compartment and lateral neck lymph nodes, cervical soft tissue, and lungs. He had persistent disease in his neck despite extensive resection of lymph-node metastases and one treatment with RAI. Although the Tg level decreased with postoperative thyroid hormone suppression, its elevated level was consistent with distant metastatic disease. The primary goals for ongoing treatment were to decrease morbidity from potential invasive metastatic disease to the major vessels in the neck and trachea and to improve overall survival despite pulmonary metastatic disease.

The majority of patients under 45 years of age who have differentiated thyroid cancer confined to the thyroid with lymph-node involvement have an excellent prognosis. The presence of distant metastases to the lungs at the time of initial diagnosis is not common and is reported to be between 3% and 15%. While there are many different staging systems, the American Thyroid Association guidelines recommend use of the UICC/AJCC TNM staging system for differentiated thyroid carcinoma (1,2). Patients younger than 45 years who have distant metastasis are classified as stage II with a 100% 5-year disease-specific survival (DSS), while those patients over age 45 with distant metastases are stage IV, which confers a 51% 5-year DSS. Good prognostic factors in patients with pulmonary metastases include young age (<45 years), micronodular pulmonary metastases, complete local control, and RAI-sensitive disease. Clinicopathological features that confer a poor prognosis include age over 70 years, distant metastases not confined to the lungs, macronodular lung metastases (>2 cm), lymph-node metastases >3 cm, follicular histology, and a poorly differentiated component in the primary thyroid neoplasm. Multiple institutional reviews report the 10-year DSS to be significantly better for younger patients with pulmonary metastases versus older patients, ranging from 94% to 100% and 36% to 46%, respectively (3-8).

A recent retrospective review from the Memorial Sloan-Kettering Cancer Center identified 52 patients of 1810 (2.9%) treated from 1985 to 2006 with distant metastases at the time of initial diagnosis with a male:female predominance of 3:2. Similar to our patient, the majority of their subjects with pulmonary metastases had pT3 or higher disease (77%) and lymph-node involvement, primarily in the lateral compartment (75%). Treatment included total thyroidectomy with lymph-node resection followed by RAI. The 5-year overall and disease-specific survival of the whole cohort (including pulmonary and extrapulmonary metastases) were 65% and 62%, respectively.

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Of the patients under age 45 years with pulmonary metastases, none died from thyroid cancer after a median follow-up of 80 months (range, 18 to 188), for a 100% 5-year DSS, whereas patients over age 45 years had a 56% 5-year DSS. As expected, patients with iodine-avid pulmonary metastases had a better 5-year DSS as compared with those with non–iodine-avid metastases (85% and 62%, respectively). Higher numbers of patients under age 45 had iodine-avid pulmonary metastases as compared with those over age 45 (P = 0.049) (9).

EBRT is used to improve local control and prevent relapse, especially in patients with gross extrathyroidal extension, or local failure despite adequate surgery and appropriate RAI. It is also considered in patients with poorly differentiated or insular thyroid carcinoma with minimal extrathyroidal extension or even in those with no extrathyroidal extension and close margins, where no further surgery is possible. EBRT has significant morbidity and is usually reserved for patients at high risk for tumor recurrence and those with gross residual disease. Acute (0 to 6 months) EBRT side effects include esophagitis, dysphagia, erythema, and a need for tracheostomy, while late complications (6 months to 2 years) include xerostomia, esophageal stenosis, tracheal constriction, carotid stenosis, and brachial plexopathy. IMRT offers dose intensification while reducing side effects of treatment by avoiding or reducing exposure to normal tissue and critical structures such as the esophagus (10,11). Because of a lack of prospective, randomized clinical trials, the benefit of EBRT, particularly in patients under 45 years of age, is uncertain. Nevertheless, as was done in our patient, EBRT should be considered in those with significant local progression after RAI therapy.

Our patient is nearing the maximum dose of RAI beyond which the risk for leukemia and other secondary malignancies increases, such that the risks may outweigh the benefits. Other options, such as targeted therapy using tyrosine kinase inhibitors (TKIs), must be considered. Clinical trials using TKIs for thyroid carcinoma have shown stabilization of disease in 50% to 70% of patients, but the response tends to be limited to 2 to 3 years, after which disease progresses (12-14). Because of this short-lived response, it is often difficult to decide when to initiate TKI therapy. We would consider a TKI in our patient when the doubling time of the lung nodules is less than 1 year.

Conclusions

While the majority of patients with differentiated thyroid cancer may be cured, the biologic behavior of the cancer varies substantially. We present an uncommon case of a young man with aggressive PTC with extensive lymph-node involvement and lung metastases. Despite advanced disease, he has a fairly good prognosis since he is young and the tumor is iodine-avid.

References

1. Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A III, eds. AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
2. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
3. Casara D, Rubello D, Saladini G, Masarotto G, Favero A, Girelli ME, Busnardo B. Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. J Nucl Med 1993;34:1626-31.

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4. Haq M, Harmer C. Differentiated thyroid carcinoma with distant metastases at presentation: prognostic factors and outcome. Clin Endocrinol (Oxf) 2005;63:87-93.

5. Sugitani I, Fujimoto Y, Yamamoto N. Papillary thyroid carcinoma with distant metastases: survival predictors and the importance of local control. Surgery 2008;143:35-42.

6. Lee J, Soh EY. Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis: clinical outcomes and prognostic factors. Ann Surg 2010;251:114-9.

7. Shaha AR, Shah JP, Loree TR. Differentiated thyroid cancer presenting initially with distant metastasis. Am J Surg 1997;174:474-6.

8. Showalter TN, Siegel BA, Moley JF, Baranski TJ, Grigsby PW. Prognostic factors in patients with well-differentiated thyroid cancer presenting with pulmonary metastasis. Cancer Biother Radiopharm 2008;23:655-9.

9. Nixon IJ, Whitcher MM, Palmer FL, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. Thyroid 2012;22:884-9. Epub July 24, 2012.

10. Brierley J, Sherman E. The role of external beam radiation and targeted therapy in thyroid cancer. Semin Radiat Oncol 2012;22:254-62.

11. Tuttle RM, Rondeau G, Lee, NY. A risk-adapted approach to the use of radioactive iodine and external beam radiation in the treatment of well-differentiated thyroid cancer. Cancer Control 2011;18:89-95.

12. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol 2008;26:4714-9. Epub June 9, 2008.

13. Kloos RT, Ringel MD, Knopp MV, et al. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 2009;27:1675-84. Epub March 2, 2009.

14. Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. N Engl J Med 2008;359:31-42.