Malignant Transformation of a Hürthle Cell Tumor: Case Report and Survey of the Literature

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Hürthle cell carcinoma is a relatively uncommon type of well-differentiated thyroid carcinoma. Its diagnosis has been controversial due to the difficulty in separating Hürthle cell adenoma from Hürthle cell carcinoma, thus the term Hürthle cell tumor is often used to describe both lesions. The present case of anaplastic giant-cell carcinoma in an 81-yr-old woman arose in a Hürthle cell tumor. This case illustrates the propensity of Hürthle cell tumor to undergo "malignant transformation" and argues for a more aggressive approach to such tumors.

J Nucl Med 1991; 32:1266–1269

The work-up of a solitary "cold" thyroid nodule as observed on radionuclide scan and ultrasound generally progresses to fine needle aspiration (FNA) or needle biopsy (*1–3*). The rate of malignancy commonly quoted is 15%–20%, with some studies ranging as high as 38% (*3*). Morbidity and mortality will vary with histologic type, lesion size, local invasion, distant metastases, history of irradiation, patient age, and gender (*1,2,4,5*). Approximately 86% of malignancies found in cold thyroid nodules are slow-growing, well-differentiated adenocarcinomas with a relatively low morbidity and mortality, and include papillary, follicular, and mixed papillary/follicular carcinomas (*2,3,6*). Many consider Hürthle cell carcinoma (HCC) as an additional category of well-differentiated thyroid carcinoma rather than a subcategory of follicular carcinoma (*7–11*). Another significant category is anaplastic or undifferentiated carcinoma (*1,3,5,12,13*), which is one of the most lethal of all the known carcinomas (*14, 15*). The remainder of thyroid malignancies are comprised of medullary carcinomas (3%) as well as sarcomas, lymphomas, and metastases (1%–3%) (*3,16*).

In this report, we describe a case of an elderly female who presented with an extensive thyroid mass that was followed clinically for at least 18 mo. Following surgical resection, the mass was found to be an anaplastic giant-cell carcinoma, arising in a Hürthle cell tumor. We reviewed the available literature regarding anaplastic thyroid carcinomas and the controversial Hürthle cell tumors.

Received Jul. 5, 1990; revision accepted Dec. 5, 1990.

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CASE REPORT

An 81-yr-old white female was in good health until about 2 mo prior to admission when she experienced fatigue, a 5-pound weight loss, and a decreased appetite, without hoarseness, dysphagia, or dyspnea. Work-up revealed anemia of chronic disease and a lower neck and upper mediastinal mass with partial tracheal compression. On chest radiographs, the mass had not changed significantly for at least 18 mo and was felt to be consistent with a substernal goiter.

Further diagnostic study of the thyroid proceeded. The serum T4 was 9.2 μg/dl (normal 5.5–11.5) and the RT3U was 30.5% (normal 25%–36%). Microsomal and thyroid antibodies were absent. FNA with a 22-gauge needle was performed in two locations of the right lobe mass and obtained no malignant cells with only colloid and inflammatory cells. The radioiodine uptake, with 5 μCi (185 MBq) of ^{131}I, was 13.4% at 24 hr (normal 10%–36%) and the thyroid scan, with 200 μCi (7.4 MBq) of ^{123}I, revealed a large hypofunctional nodule in the right lower pole of the thyroid (Fig. 1). Computerized tomography revealed an inhomogeneous mass extending from the midportion of the right neck into the superior mediastinum at the level of the aortic arch, narrowing the trachea and causing shift and compression of adjacent structures but without local invasion. Ultrasound examination, with a 7-MHz real-time scanner, showed an inhomogeneous, lobulated, solid mass measuring 9.3 × 5.3 cm, without cystic areas, originating in the right lobe of the thyroid and extending caudally. One month later at elective surgery a necrotic tumor mass was found in the neck extending into the mediastinum and involving the innominate artery. A right thyroidectomy, isthmusectomy, and partial removal of a mediastinal tumor mass was performed. The patient refused further treatment and died 3 mo later in a nursing home of causes related to the tumor.

Pathology

Grossly, the enlarged right lobe of the thyroid measured 10 × 6 × 6 cm and weighed 171 g. The cut surface of the upper one-half of the tumor was red-tan, encapsulated and lobulated, while

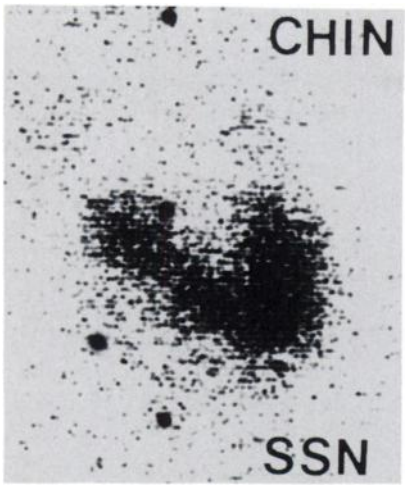

FIGURE 1. Thyroid scan with 200 μCi (7.4 MBq) ^{123}I revealed a large hypofunctional nodule in the right lower thyroid pole. (SSN16-suprasternal notch).

the lower one-half was fleshy and grey-white with areas of obvious necrosis and hemorrhage (Fig. 2).

Microscopically, sections of the upper portion of the tumor revealed polygonal neoplastic cells with homogeneous, granular, eosinophilic cytoplasm with mostly central round vesicular nuclei. In some areas, these cells were arranged in cords and sheets surrounding small follicle-like structures containing colloid. Electronmicrographs demonstrated that the cytoplasm of these cells was filled with mitochondria (*17*). This histologic picture is typical of Hürthle cell tumor (*17*).

Microscopic sections of the necrotic lower pole demonstrated tumor cells haphazardly arranged in solid sheets that were highly undifferentiated showing indistinct cytoplasmic borders, hyperchromatic nuclei, and many tumor giant cells with large irregular nuclei or multinucleation. Areas of extensive vascular invasion

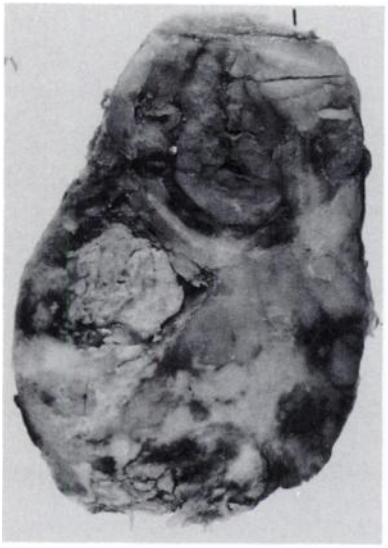

FIGURE 2. Gross surgical specimen of the right thyroid lobe measuring 10 × 6 × 6 cm and weighing 171 g. The homogenous upper portion is Hürthle cell tumor and the lower portion is anaplastic giant-cell carcinoma.

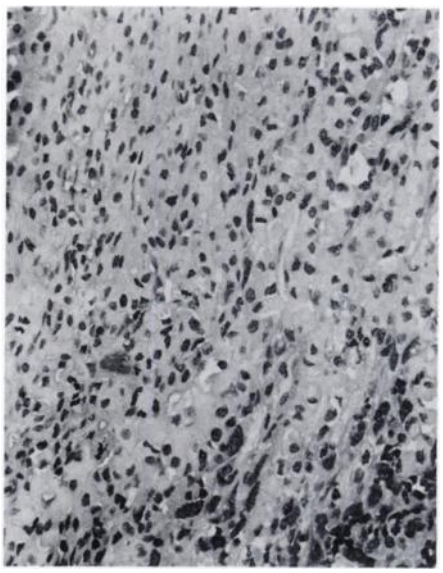

FIGURE 3. Region of Hürthle cell tumor with transition to spindle-cell and then to giant-cell anaplastic carcinoma. (H&E × 400).

were noted and there were numerous mitotic figures. The features were those of a giant cell variant of anaplastic carcinoma. Several of the sections demonstrated an apparent transformation of Hürthle cells to anaplastic tumor cells (Fig. 3).

A separately submitted portion of tissue, measuring 3.2 × 5.1 cm and labeled "mediastinal lymph node," contained pure giant cell anaplastic carcinoma. No additional lymph nodes were obtained.

DISCUSSION

Anaplastic carcinoma of the thyroid, seen in two histologic forms–giant cell and spindle cell (*13–15*)—represents 5%–13.6% of all malignant solitary "cold" thyroid nodules (*1,3,5,12,18*) and is more prevalent in older age groups (*5,12,15,19,20*). Many investigators have proposed that anaplastic thyroid carcinomas may originate in longstanding, well-differentiated thyroid carcinomas since there is a high coincidental existence of anaplastic carcinomas and well-differentiated carcinomas, with many of the former found to be arising in the latter (*12,14,15,21*). Although this feature, termed "malignant transformation," would appear to be a likely origin for anaplastic carcinoma, it is very difficult to prove. The clinical course of anaplastic thyroid carcinoma is rather dismal, with only a 2.5-mo mean survival (*14,15*) and an 8% 2-yr survival (*16*). Treatment options are limited as the disease is usually widespread and beyond cure at the time of clinical presentation (*14,19,21*).

HCC represents from 1.2% to 10% of all primary thyroid malignancies (*4,7,11,18,22,23*). Much of the debate in the literature regarding HCCs, also known as oxyphil tumors, oncocytomas, or Askenazy cell tumors (*7,17,24,*), arises from the lack of good long-term data (*7,25*). This

may have been contributed to by early investigators classifying this tumor as a variant of follicular cell carcinoma (*17,20*) rather than as a distinct pathologic entity (*1,4,7,9, 22,23,25–27*). HCC clearly differs from follicular cell carcinoma as it infrequently concentrates radioiodine (*4,7–11,27,28*), does spread to lymph nodes (*7,9–11,23, 27,29*), metastasizes to lungs (*28*), and has a higher morbidity and mortality (*4,9,27*), although this becomes less prominent in older age groups (*30*).

A current controversy stems from the view that all Hürthle cell tumors are malignant or potentially malignant. This view seems to be based, at least in part, on a study that demonstrated that 14 out of 26 cases diagnosed as Hürthle cell adenoma (HCA) were later found to be malignant and, moreover, those with lesions greater than 2 cm who were treated with total thyroidectomy, versus a more conservative procedure, had a significantly lower recurrence rate (21% versus 59%) of malignant disease (*9, 25*). This view has recently been refined somewhat in acknowledgment that the referral pattern of the patient population studied very likely biased the data toward more severe disease (*27*). Furthermore, early HCA and HCC are histologically similar and require the presence of local invasion or metastases to distinguish them, which would also tend to bias many HCC series with more advanced cases. Some investigators believe that Hürthle cell neoplasms cannot be reliably separated into benign and malignant types and therefore prefer the designation Hürthle cell tumor to HCA or HCC. Most investigators do agree that malignant lesions demonstrate vascular or capsular invasion, regional lymphatic spread, or distant metastases (*7,9,10,17,23–25,31–34*). Due to the relative rarity of the tumor, it also can be argued that in a clinical setting where the pathologist has limited experience with such lesions, the chances of misdiagnosis may be significant. In general, proponents for aggressive treatment contend that Hürthle cell lesions (>2 cm) excluding reactive Hürthle cell change in goiter and in chronic thyroiditis should be treated with total thyroidectomy (*9,25,26*). In contrast, other investigators believe that the majority of Hürthle cell neoplasms can be separated histologically into benign and malignant types using the criteria previously mentioned and recommend lobectomy (or lumpectomy) for HCA and total thyroidectomy for HCC (*10,22,23,31–37*). The wisdom of this approach is borne out in a review of multiple published series in which only 6 of 642 patients (0.9%) diagnosed with HCAs were misdiagnosed and later found to have HCCs (*34*), although one should note that these series were obtained at medical centers with pathologists experienced in interpreting such lesions.

HCC may have a greater propensity for malignant transformation to anaplastic carcinoma than other well-differentiated thyroid carcinomas. Aldinger et al. (*21*) found that 5 of 18 cases (27%) of malignant transformation occurred in HCC, a frequency much higher than would be expected based on the incidence of HCC among other well-differentiated thyroid carcinomas (10% or less) (*4*). Also, HCCs have a greater morbidity and mortality compared to the other well-differentiated thyroid carcinomas, although this is still relatively low (*4*).

Our patient had an anaplastic giant-cell carcinoma that had arisen in a Hürthle cell tumor. Rosen et al. (*24*) described a similar case of a 65-yr-old female patient with a HCA, for which she refused surgery, and 3 yr later died from an anaplastic carcinoma. The possibility that an untreated or incompletely excised Hürthle cell lesion, or for that matter any other well-differentiated thyroid lesion, may give rise to an anaplastic carcinoma is a sobering thought. Lumpectomy or lobectomy of a lesion that is less than 2 cm in a patient without a contralateral nodule or a history of head and neck irradiation and is clearly a HCA that has been thoroughly sampled histologically is the most rational approach supported by the data currently available. Those with clearly malignant lesions should undergo total thyroidectomy or near-total thyroidectomy with ablation. It is those patients with lesions histologically difficult to categorize as clearly benign or malignant or those patients with factors predisposing them toward malignancy (such as a history of irradiation, a previous thyroid malignancy, in a male less than 20 yr of age, or in anyone over 60 yr of age, with a contralateral nodule or having a lesion size greater than 2 cm) that should not be given the benefit of the doubt and should also undergo total thyroidectomy or near-total thyroidectomy with ablation. Perhaps in the future thyroglobulin markers or DNA analysis may play a definitive role in making the distinction between benign and malignant Hürthle cell lesions (*9,17,32,38*).

ACKNOWLEDGMENT

This work was supported in part by a grant from the Department of Veterans Affairs.

REFERENCES

1. Rossi RL, Nieroda C, Cady B, Wool MS. Malignancies of the thyroid gland—the Lahey clinic experience. *Surg Clin N Am* 1985;65:211–230.
2. DeGroot LJ, Sridama V. Thyroid neoplasia. In: DeGroot LJ, ed. *Endocrinology*. Philadelphia: WB Saunders; 1989:758–776.
3. Molitch ME, Beck JR, Dreisman M, Gottlieb JE, Pauker SG. The cold thyroid nodule: an analysis of diagnostic and therapeutic options. *Endocr Rev* 1984;5:185–199.
4. Samaan NA, Maheshwari YK, Nader S, et al. Impact of therapy for differentiated carcinoma of the thyroid: an analysis of 706 cases. *J Clin Endocrinol Metab* 1983;56:1131–1138.
5. Jarvi K, Mokka R, Vorne M. Problems of cancer diagnosis in thyroid nodules. *Acta Chir Scand* 1988;154:93–96.
6. Ridgeway EC. Clinical evaluation and solitary thyroid nodules. In: Ingbar SH, Braverman LE, eds. *Werner's the thyroid*. Philadelphia: JP Lippincott Co; 1986:1377–1383.
7. Har-El G, Hadar T, Levy R, Sidi J. Hrthle cell carcinoma of the thyroid gland—a tumor of moderate malignancy. *Cancer* 1986;57:1613–1617.
8. Krishnamurthy GT, Blahd WH. Radioiodine I-131 therapy in the management of thyroid cancer—a prospective story. *Cancer* 1977;40:195–202.
9. Gundry SR, Burney RE, Thompson NW, Lloyd R. Total thyroidectomy for Hürthle cell neoplasm of the thyroid. *Arch Surg* 1983;118:529–532.
10. Arganini M, Behar R, Wu TC, et al. Hürthle cell tumors: a twenty-five-year experience. *Surgery* 1986;100:1108–1114.
11. Frazell EL, Duffy Br Jr. Hürthle cell cancer of the thyroid—a review of 40

cases. *Cancer* 1951;4:952–956.
12. Harada T, Ito K, Katsutaro S, Hosoda Y, Yakamura K. Fatal thyroid carcinoma. *Cancer* 1977;39:2588–2596.
13. Woolner LB. Thyroid carcinoma: pathologic classification with data on prognosis. *Semin Nucl Med* 1971;4:481–502.
14. Ibanez ML, Russel WO, Albores-Saavedra J, Lampertico P, White EC, Clark RL. Thyroid carcinoma–biologic behavior and mortality. *Cancer* 1966;19:1039–1052.
15. Nishiyama RH, Dunn EL, Thompson NW. Anaplastic spindle-cell and giant-cell tumors of the thyroid gland. *Cancer* 1972;30:113–127.
16. Van Herle AJ, Rich P, Ljung BE, Ashcraft MW, Solomon DH, Keeler EB. UCLA conference. *The Thyroid Nodule* 1982;96:221–232.
17. Flint A, Lloyd RV. Hürthle cell neoplasm of the thyroid gland. *Pathol Annual* 1990;25:37–52.
18. Brooks JR, Starnes HF, Brooks DC, Pelkey JN. Surgical therapy for thyroid carcinoma: a review of 1249 solitary thyroid nodules. *Surgery* 1988;104:940–946.
19. Jereb B, Sternsward J, Lowhagen T. Anaplastic giant-cell carcinoma of the thyroid. *Cancer* 1975;35:1293–1295.
20. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR Jr. Classification and prognosis of thyroid carcinoma—a study of 885 cases observed in a 30-year period. *Am J Surg* 1961;102:354–387.
21. Aldinger K, Samaan NA, Ibanez M, Hill CS, Jr. Anaplastic carcinoma of the thyroid. *Cancer* 1978;41:2267–2275.
22. Watson RG, Brennan MD, Goelpner JR Jr, Van Heerden JA, McCohaney WM, Taylor WF. Invasive Hürthle cell carcinoma of the thyroid: natural history and management. *Mayo Clin Proc* 1984;59:851–855.
23. Tollefsen HR, Shah JP, Huvos AG. Hürthle cell carcinoma of the thyroid. *Am J Surg* 1975;130:390–394.
24. Rosen IB, Luk S, Katz I. Hürthle cell tumor behavior: dilemma and resolution. *Surgery* 1985;98:777–783.
25. Thompson NW, Dunn EL, Batsakis JG, Nishiyama RH. Hürthle cell lesions of the thyroid gland. *Surg Gynecol Obstet* 1974;139:555–560.
26. Miller RH, Estrada R, Sneed WF, Mace ML. Hürthle cell tumors of the thyroid gland. *Laryngoscope* 1983;93:884–886.
27. McLeod MK, Thompson NW. Hürthle cell neoplasms of the thyroid. *Otolar Clin NA* 1990;23:441–452.
28. Samaan NA, Schultz PN, Haynie TP, Ordonez NG. Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. *J Clin Endocrinol Metab* 1985;60:376–380.
29. Gonzalea-Campora R, Herrero-Zapatero A, Lerma E, Sanchez F, Galera H. Hürthle cell and mitochondrial-rich tumors: a clinopathological study. *Cancer* 1986;57:1154–1163.
30. Ruegemer J, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. *J Clin Endocrinol Metab* 1988;67:501–508.
31. Bondeson L, Bondeson A, Ljungberg O, Tibblin S. Oxyphil tumors of the thyroid—follow-up of 42 surgical cases. *Ann Surg* 1981;194:677–680.
32. Gosain AK, Clark OH. Hürthle cell neoplasmsm—malignant potential. *Arch Surg* 1984;119:515–519.
33. Heppe H, Armin A, Calandra DB, Lawrence AM, Paloyan E. Hürthle cell tumors of the thyroid gland. *Surgery* 1985;98:1162–1165.
34. Grant CS, Barr D, Goellner JR, Hay ID. Benign Hürthle cell tumors of the thyroid: a diagnosis to be trusted? *World J Surg* 1988;12:488–495.
35. Marzano LA, Finelli L, Marranzini A, et al. Hürthle cell neoplasm. *Int Surg* 1989;74:97–98.
36. Khan MS, Al-Manee MS, Huzaimeh IA, Ahmad MS. Hürthle cell lesions in thyroid neopalsms. *Int Surg* 1989;74:261–266.
37. Caplan RH, Abellera RM, Kisken WA. Hürthle cell tumors of the thyroid gland: a clinopathologic review and long-term follow-up. *JAMA* 1984;251:3114–3117.
38. Joensu H, Klemi P, Eerola E. DNA Aneuploidy in follicular adenomas of the thyroid gland. *Am J Path* 1986;124:373–376.