

A DELAYED FATAL METASTATIC HÜRTHLE CELL CARCINOMA

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Summary: Hürthle (oxyphilic or oncocytic) cell carcinoma is a variant of follicular cell carcinoma of thyroid. Although this entity of thyroid cancer is well known, its occurrence in young patients has scarcely been reported. We report a case of a 26 year-old male patient, at the time of diagnosis, of Turkish origin, who developed a tracheal, pulmonary and mediastinal metastatic Hürthle cell carcinoma with bilateral cervical and mediastinal lymphadenopathies. This case illustrates an aggressive and metastatic cancer at the time of diagnosis and resistant to all treatment options including surgery, chemotherapy and radioactive iodine.

Key words: *Hürthle cell carcinoma; Oxyphilic cell tumor; Oncocytic cell tumor; Lymphadenopathy*

Introduction

Hürthle cells derive from thyroid follicular epithelium and consist of large polygonal cells with abundant granular cytoplasm due to numerous mitochondria and have a large prominent nucleus. Hürthle cell adenomas differ from its carcinomatous variant by the absence of capsular, vascular, lymphatic and visceral infiltrations, and has good prognosis. The carcinomatous forms are encapsulated collections of Hürthle cells and are a distinct type of thyroid tumors. They are generally considered to be an unusual variant of follicular neoplasm and are regarded as very aggressive in their biological behavior. We present a fatal case of a 26 year-old Turkish male patient who developed a pulmonary and tracheal metastatic Hürthle cell carcinoma with bilateral cervical and mediastinal lymphadenopathies.

Case Report

A 26 year-old Turkish male patient presented in 2004 to the ENT outpatient department (OPD) for an insidious and rapidly-growing thyroid nodule which appeared a year before. He reported a rapidly-growing mid left cervical node six months before he presented to the OPD. His past medical history was unremarkable except that he was a cigarette smoker. He had no medications and no known allergies. The patient had a cervical ultrasound which showed an enlarged right thyroid lobe of 34 cm³ containing two vascularised, isoechogenic macronodules measuring 2.7 x 2.4 cm and 1.6 x 1.1 cm respectively, along with enlarged cervical lymph nodes. The left thyroid lobe showed a nodule of 0.7 x 0.9 cm.

Fine needle aspiration cytology of the thyroid nodules suggested a carcinoma of either papillary or follicular origin. Hormonal evaluations showed a calcitonin level of 5 pg/ml (N: < 15), TSH 1.53 µU/ml (N: 0.3–4), fT₄ 1 ng/dl (N: 0.8–2), thyroglobulin 36.5 ng/ml (N: 0–25), anti-THG < 30 IU/ml (N: < 60), anti-TPO 35.6 IU/ml (N: 0–25). A thyroid scintigraphy demonstrated no iodine uptake. He underwent the following day a total thyroidectomy with bilateral cervical lymphadenectomy of regions II, III, IV, V and of the recurrent nerve. Frozen section analysis indicated a Hürthle cell carcinoma invading the capsule with nodal metastasis (Fig. 1a). TNM classification after definite histopathological analysis was pT3mN1bMx. He recovered without any complications and had a blood calcium level of 7.7 mg/dl on day 1 and 8.1 mg/dl (N: 9.1–10.2 mg/dl) on day 5. Thyroglobulin levels dropped to 5 ng/ml, TSH 226.12 µU/ml, fT₄ 0.2 ng/dl, fT₃ 0.2 pg/ml and anti-THG < 30 IU/ml. He had Elthyroxine 150 µg/day.

He underwent a thoraco-abdominal CT scan which showed bilateral infracentimetric pulmonary excavated lymph nodes, and neither hepatic infiltration nor other gastrointestinal visceral anomalies were present. A whole body ¹³¹I scintigraphy and a HDP-Tc^{99m} tomoscintigraphy showed no radioactive iodine concentration at the cervical and thoracic regions, and no skeletal metastasis, respectively. He underwent a thoracic biopsy of the excavated pulmonary lymph node with a sub-lobar pneumectomy which returned positive for a Hürthle cell carcinomatous invasion (Fig. 1b). The mediastinum was not investigated per-operatively because of high hemorrhagic risks and the size of the mediastinal masses in view that the patient bled profusely after

resection of the cervical masses which would have compromised immediate per-operative survival. A first-line chemotherapy regimen was initiated with 5-fluorouracil at 250 mg/m² with no improvement and thus discontinued. A second line chemotherapy of epirubicin with a total dose of 640 mg/m² failed and was discontinued. Vandetanib as a third-line chemotherapy agent at a daily dose of 300 mg for 3 months also proved to be unsuccessful and was discontinued.

Four years later, new cervical masses appeared with cutaneous fistulisation and profuse bleeding, mandating 3 surgical excisions with reconstruction via a *pectoralis major* flap. He further developed endotracheal granulomas due to the recurrence of the Hürthle cell carcinoma and a tra-

cheal prosthesis was inserted. The pulmonary metastasis flourished serendipitously. The tumor was sensitive to octreotide and as such he had octreotide for nearly a year.

One year following reconstructive surgery, massive infiltration of the cervical region occurred with vocal cord paralysis. A right posterior arytenoidectomy with CO₂ laser was carried out to relieve the patient. Hypocalcemia due to hypoparathyroidism secondary to loco-regional carcinomatous infiltration occurred. Mediastinal and cervical carcinomatosis invading the pulmonary parenchyma became predominant. This young patient died of a respiratory distress due to tumoral obstruction of the upper airway, pulmonary metastasis and bronchopneumonia with septicemia due to *Klebsiella pneumoniae*.

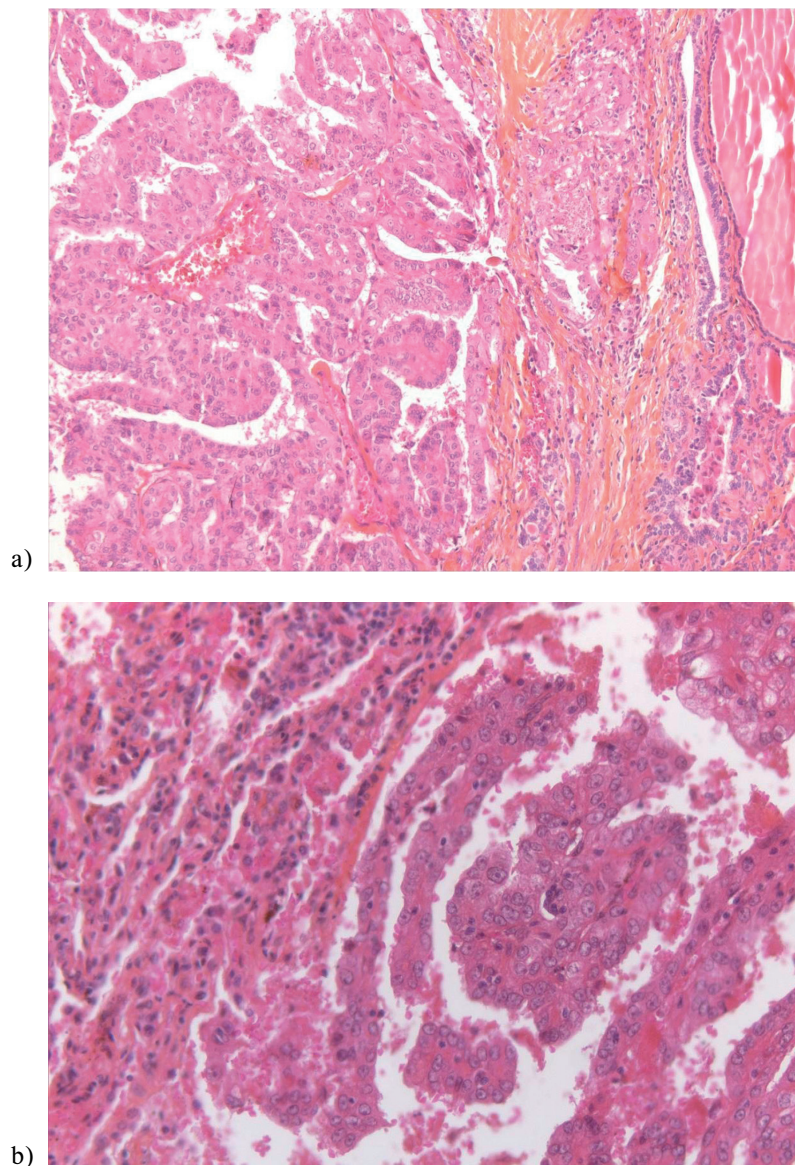


Fig. 1: (a) A Hematoxylin & Eosin (H&E) stain at x 200 of the Hürthle cell carcinoma having extended beyond the thyroid capsule. (b) An H&E stain (x 200) of lung infiltration by the Hürthle cell carcinoma.

Discussion

Hürthle cell carcinomas are rare, accounting for about 7 % of all well differentiated thyroid tumors (4). This carcinoma can be unique or multifocal, the latter having an estimated range of 16 to 70 % (4, 5). A diameter cutoff of 3.0 cm as a clinical factor for total thyroidectomy is not useful to predict malignancy, as in our case the carcinoma measured less than 3.0 cm in diameter (6). Moreover, many studies have suggested that an age > 45 years or elderly patients, are at greater risks for malignancy (2, 8) - in our case, the patient was 26 years old at the time of initial diagnosis.

Hürthle cell tumors secrete thyroglobulin which can be used to detect the recurrence of the disease. In our patient, thyroglobulin levels dropped immediately after surgery and over the years did not increase. Therefore thyroglobulin as a marker of recurrence was not of value in our patient. Our patient did not receive radiation therapy because the tumor failed to concentrate ¹³¹I during scintigraphy, despite chemotherapy being often ineffective, this was the only therapeutic option. This would have probably been more efficient to the disease free interval.

Analysis of ret/PTC oncogene, BRAF and deletions of 4977 base pairs region of mitochondrial DNA were not available in our institution, it is interesting to note that Cheung *et al.* found the expression of ret/PTC gene on chromosome 10 (1). The ret proto-oncogene found is not normally expressed in thyroid epithelial cells. Hürthle cell tumors express the ret/PTC oncogene irrespective of histologic structural organizations (4). This can be used as a biological marker to further strengthen histological findings (1,4). Moreover, follicular carcinoma display high prevalence of non silent mutation of complex I genes with common deletions of the 4977 base pairs region of mitochondrial DNA (mtDNA) (7).

Tumor size, extrathyroid extension and vascular invasions with nodal metastasis indicate poor prognosis. Recurrence is a predictor of tumor-related mortality (8). The presence of bronchial metastasis is a poor prognostic factor with a median survival of nine months after its detection, as observed in our case (3). Our patient had encapsulated

Hürthle cells infiltration in the lungs, lymph nodes and the trachea. External beam radiotherapy is an alternative for widely invasive carcinoma or locally advanced disease (8). However, our patient did not qualify for this treatment in view of a too large extension of the disease which would have resulted in a toxic dose of radiation for the neighboring pulmonary tissues. Total thyroidectomy is the mainstay treatment for Hürthle cell carcinoma. Cervical lymphadenectomy is mandated if pre-operative imaging studies identify suspect nodes.

Pisanu *et al* reported a recurrence rate for Hürthle cell carcinoma of 10.7 % while the mortality rate was 4 % at 5-year follow-up (5). Furthermore, after recurrence from a carcinoma, an average survival of 34 months has been reported while the mortality rate with distant metastasis at presentation oscillates at around 80 % at 5 years. In our case, the patient lived for 5.5 years with his metastases.

Conclusion

Hürthle cell carcinoma is a rare presentation of thyroid tumors. This case illustrates an aggressive and metastatic cancer at the time of diagnosis and resistant to all treatment options including surgery, chemotherapy and radioactive iodine. This young patient of 26 at the time of diagnosis survived 5.5 years before passing away.

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