

METASTATIC HÜRTHLE CELL CARCINOMA PRESENTING WITH LOW FREE THYROXINE, SEVERE HYPERCALCEMIA AND SPURIOUS GROWTH HORMONE PRODUCTION

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ABSTRACT

Objective: Hürthle cell tumors constitute about 5% of thyroid neoplasms. They have malignant potential, behaving very aggressively compared to other differentiated thyroid cancers. The objective of this case report is to describe a case of a Hürthle cell carcinoma with a single large metastasis in the liver presenting almost 17 years after hemithyroidectomy. We highlight the difficulties in making a histologic diagnosis and the unpredictable nature of this cancer.

Methods: The patient history and biochemistry were detailed. Thyroid function tests analyzed on multiple platforms (single-photon emission computed tomography, dynamic magnetic resonance imaging, technetium-99m bone scan, and radioactive iodine) were used to aid biochemical and radiologic diagnosis.

Results: The patient's thyroid function test showed persistently low free thyroxine concentrations with normal thyroid stimulating hormone and free triiodothyronine, suggesting rapid deiodination in the context of a large liver

lesion. Radiologic and morphologic appearances of the liver lesion led to an initial misdiagnosis of primary hepatocellular carcinoma, revised to metastatic Hürthle cell carcinoma after positive immunochemistry. Nonparathyroid hormone-related intractable hypercalcemia of malignancy with an unusual pattern of elevated 1,25-dihydroxyvitamin D and raised fibroblast growth factor 23 concentrations culminated in his demise.

Conclusions: In Hürthle cell carcinomas treated with partial thyroidectomy, subsequent abnormal thyroid functions tests may herald a more sinister underlying diagnosis. The management of Hürthle cell carcinoma relies heavily on the initial histology results. Histologic diagnosis should be sought earlier in abnormal and suspicious distant masses. Malignant hypercalcemia poses a great challenge in delayed presentations and can prove resistant to conventional treatments. (AACE Clinical Case Rep. 2019;5:e204-e209)

Abbreviations:

CT = computed tomography; FGF23 = fibroblast growth factor 23; FT3 = free triiodothyronine; FT4 = free thyroxine; IGF-1 = insulin-like growth factor 1; MRI = magnetic resonance imaging; PTH = parathyroid hormone; PTHrP = parathyroid hormone-related peptide; TSH = thyroid stimulating hormone

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CASE REPORT

A 69-year-old man was referred to the endocrine department with progressive lowering of his free thyroxine (FT4) concentration over the preceding 9 years. He had undergone a partial thyroidectomy 17 years prior for a neck lump, that at the time, had a histologic classification as a fully encapsulated Hürthle cell thyroid tumor. His medical history consisted of Barrett esophagus, hypertension,

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osteoarthritis, a dilated aortic root, bladder and bowel irritability, and a superficial facial basal cell carcinoma. Six years prior to presentation to the endocrine department, as part of his investigations for a dilated aortic root, he had a computed tomography (CT) aortogram, which showed a 9.4 cm by 7.3 cm liver mass. A magnetic resonance imaging (MRI) scan of the liver concluded that the mass was a “benign focal nodular hyperplasia” based on its morphologic appearance.

At his presentation to the endocrine clinic he was taking lansoprazole, solifenacin, perindopril, bisoprolol, and mebeverine. Physical examination revealed marfanoid features with arachnodactyly, a positive Walker’s sign, and a high arched palate, with no specific features of acromegaly. The rest of the physical examination was normal, with no goiter or features of hormonal deficiency or excess.

His biochemistry is shown in Tables 1, 2 and 3. His thyroid profile showed a persistently low FT4 at 6 pmol/L (normal, 8 to 21 pmol/L), with normal thyroid stimulating hormone (TSH) at 1.71 mU/L (normal, 0.35 to 3.5 mU/L), and normal free triiodothyronine (FT3) at 5.9 pmol/L (normal, 3.8 to 6 pmol/L). The low FT4 was confirmed using multiple assays from different regional laboratories, including Abbot, the ADVIA Centaur CP immunoassay system, and dissociation-enhanced lanthanide fluorescence immunoassay. Total thyroxine was also low at 10.5 nmol/L on mass spectrometry, pointing towards a diagnosis of secondary hypothyroidism. Although the patient was clinically eupituitary he had an elevated adrenocorticotrophic hormone at 72 ng/L (normal, <47 ng/L), and insulin-like growth factor 1 (IGF-1) of 29.0 nmol/L (normal, 5.8 to 25.0 nmol/L), raising the possibility of pituitary disease. Further dynamic tests carried out were a 75 g oral glucose load which failed to suppress growth hormone (GH) concentrations below 0.92 µg/L (normal, <0.4 µg/L), and a short tetracosactide test that was normal, with a peak cortisol of 676 nmol/L at 60 minutes (normal, >450 nmol/L). An MRI scan of his pituitary gland showed no abnormality. There was no evidence of skeletal metastasis on technetium-99m bone scan. A repeat CT scan of his liver showed that the lesion had increased in size to 20 cm in maximal diameter. Dynamic MRI scan of the liver

with contrast showed central calcification with washout in the equilibrium phase followed by reduced contrast uptake in the hepatocyte phase, highly suggestive of primary hepatocellular carcinoma.

A liver biopsy was undertaken and reported as hepatocellular carcinoma on its morphologic basis despite negative immunochemistry for hepatocytes, synaptophysin, alpha fetoprotein, and chromogranin A. However, informing the histopathologist about the history of a Hürthle cell tumor prompted a re-examination of the tissue block with immunochemistry for thyroglobulin and thyroid transcription factor 1, which showed strong expression of these markers. As shown in Table 3, the serum thyroglobulin was also elevated to >38000 ng/ml (normal, <55 ng/ml). The diagnosis was subsequently revised to a metastatic Hürthle cell carcinoma. The initially resected thyroid gland from 17 years prior was re-examined and reported as showing a 42 mm right thyroid adenoma with some evidence of capsular invasion consistent with a minimally invasive thyroid cancer.

After discussions amongst the multidisciplinary team of endocrinologists, hepatologists, oncologists, and surgeons, the liver mass was deemed too large for primary resection or embolization. Therefore, completion thyroidectomy was carried out and postoperative radioactive iodine-131 was administered. However, there was no uptake of radioactive iodine on the single-photon emission CT suggesting that the mass had dedifferentiated. Whole body planar imaging showed no evidence of other metastases. Histology of the remnant thyroid showed there was no evidence of neoplasia.

Over the next 2 weeks, the patient developed intractable hypercalcemia with adjusted calcium measuring up to 4.2 mmol/L (normal, 2.1 to 2.6 mmol/L), with a suppressed parathyroid hormone (PTH) at 1.1 pmol/L (normal, 1.6 to 6.9 pmol/L) and undetectable parathyroid hormone-related peptide (PTHrP) at <1 pmol/L (normal, <1.8 pmol/L). His 1,25-dihydroxyvitamin D was elevated at 258 pmol/L (normal, 55 to 138 pmol/L) and fibroblast growth factor 23 (FGF23) was significantly elevated at 8890 RU/mL (normal, <100 RU/mL). This severe hypercalcemia failed to respond to conventional treatment with intravenous

Table 1
Thyroid Function Tests

Date	09/06/2006	08/07/2009	31/05/2011	24/12/2012	11/02/2013	28/11/2016	12/12/2016	03/01/2017	11/05/2017
Thyroid stimulating hormone (normal, 0.35-3.5 mIU/L)	1.58	1.23	0.93	1.71	1.4	2.13	1.82 ^a	1.22	0.59
Free thyroxine (normal, 8-21 pmol/L)	10	11	7	6	6	<5	<5 ^a	<5	6
Free tri-iodothyronine (normal, 3.8-6.0 pmol/L)								5.9	6.7

^aTests that prompted urgent referral to the endocrinologists.

Table 2 Subsequent Hormonal Profile	
Adrenocorticotrophic hormone (normal, <42 ng/L)	72
Follicle stimulating hormone (normal, <8 IU/L)	6.3
Luteinizing hormone (normal, 3-8 IU/L)	7.2
Prolactin (normal, 53-360 mIU/L)	135
Random growth hormone (μ g/L)	3.13
Testosterone (normal, 9.9-27.8 nmol/L)	22.5
Total thyroxine (normal, 69-141 nmol/L)	12.3
Thyroid stimulating hormone (normal, 0.4-4.0 mU/L)	1.41
Free thyroxine (normal, 9-20 pmol/L)	2.7 ^a
Calculated free thyroxine (pmol/L)	1.5 ^a
Free tri-iodothyronine (normal, 3.5-6.5 pmol/L)	5.93 ^a
Thyroid binding globulin (normal, 14-31 μ g/mL)	16.6 ^a
Total thyroxine (normal, 69-141 nmol/L)	12.4 ^a
Total thyroxine (mass spec)	10.5 ^a
Short (250 μg) tetracosactide test (cortisol nmol/L)	
Time 0	331
Time 30 minutes (>450 nmol/L)	552
Time 60 minutes	676
^a These results were from samples sent to different regional laboratories using multiple assays including Abbot, the ADVIA Centaur CP immunoassay system, dissociation-enhanced lanthanide fluorescence immunoassay, and mass spectrometry.	

fluids, oral glucocorticoids, bisphosphonates, cinacalcet, calcitonin, or denosumab. Renal failure ensued as a consequence of his persistent hypercalcemia and the patient became increasingly confused and frail. An octreotide scan was planned but the patient was not fit enough to undergo the test, and was palliated and died of progressive disease. The family declined a postmortem examination.

DISCUSSION

We present a case of a fatal metastatic Hürthle cell carcinoma with highly unusual biochemistry of persistently low FT4, elevated IGF-1, and severe hypercalcemia, presenting 17 years after initial diagnosis.

Hürthle cells, also known as oncocytes or oxyphilic cells, can be found in benign and malignant thyroid carcinomas. They are large polygonal cells with an eosinophilic-rich granular cytoplasm and abundant mitochondria derived from thyroid follicular epithelium. The oncocytic transformation of follicular cells can be caused by chronic inflammation (thyroiditis), hyperthyroidism (Graves disease) or a hyperplastic multinodular goiter (1). Hürthle cells exhibit alterations in mitochondrial deoxyribonucleic acid (DNA) genes and nuclear DNA genes coding for proteins involved in oxidative phosphorylation. However, the exact mechanism of tumorigenesis still remains unclear (2). Histologic evidence of capsular or vascular invasion

and distant metastasis reliably distinguishes benign from malignant disease (3,4). Factors predisposing to reduced survival rates in Hürthle cell carcinomas are advanced age, male gender, and nodule size (5).

The World Health Organization classifies Hürthle cell carcinomas as an oxyphilic variant of follicular carcinomas (3), but some authors consider them as a separate clinical entity based on genomic studies (6). Female to male preponderance is 2:1, with a mean age of diagnosis being 50 years (3). Distant metastases are seen in up to a third of cases (5), with bone and lungs being the most frequent sites (7). As with other thyroid carcinomas, the neoplastic prediction is dependent on the accuracy of the initial histologic diagnosis in terms of capsular/lymphovascular invasion. Because of these difficulties, one critical pathologic appraisal resulted in diagnostic revision of 28% of their cases with Hürthle cell carcinomas (8). As with our case, patients who have undergone a partial hemithyroidectomy or lobectomy may present with distant metastatic disease without involving the residual thyroid tissue or local lymph nodes (9). Progression towards metastatic disease can be very slow and it may take years before it manifests, hence a high degree of clinical suspicion and long term follow up is warranted.

Metastatic Hürthle cell carcinomas can present with a wide range of biochemical abnormalities. In our case the patient presented with a persistently low FT4, elevated IGF-1 and thyroglobulin, and severe hypercalcemia. Animal studies have shown that thyroglobulin and IGF-1 play important roles in biosynthesis of thyroid hormones (10,11). Both in vitro and in vivo rat studies suggested that thyroglobulin downregulates the synthesis of thyroid hormones and also reduces the uptake of iodide by the follicular cells irrespective of TSH concentration (12,13). This could partly explain why our patient has a low FT4 concentration and a lack of radioactive iodine uptake. In addition, normal thyroid tissue possesses type 1 and type 2 iodothyronine deiodinase enzymes which results in catalyzation of FT4 to FT3 by outer ring deiodination (14). A few studies have shown overexpression of type 1 and type 2 deiodinases in large and metastatic follicular cell carcinomas causing rapid conversion of FT4 to FT3 with a subsequently raised FT3/FT4 ratio, whilst maintaining a TSH concentration within the reference range (15,16). These authors showed that resection of the tumor resulted in normalization of the FT3/FT4 ratio. Our case also showed similar biochemistry (see Table 1) and there was some recovery of FT4 after completion thyroidectomy and thyroxine replacement with accompanied mild triiodothyronine (T3) toxicosis (FT3 = 6.7 pmol/L). However, this pattern of biochemistry is very unusual and only there are only a few related case reports in the literature with metastatic follicular thyroid carcinoma (15,16). To our knowledge, this is the first case where this phenomenon has been reported in a metastatic Hürthle cell carcinoma.

Table 3
Further Biochemical Results

Growth hormone suppression test	GH (µg/L)	Glucose (mmol/L)
-30 minutes	2.8	5.8
-10 minutes	2.51	5.6
0 minutes	2.77	5.6
30 minutes	1.95	6.8
60 minutes	2.52	8.5
90 minutes	2.46	8.7
120 minutes	1.82	9.1
150 minutes	0.92	7.0
Other tests		
Insulin-like growth factor 1 (normal, 5.8-25.5 nmol/L)	29	
Adjusted calcium (normal, 2.10-2.60 mmol/L)	3.28	
Parathyroid hormone (normal, 1.6-6.9 pmol/L)	1.1	
Parathyroid hormone-related peptide (normal, <1.8 pmol/L)	<1	
Phosphate (normal, 0.8-1.45 mmol/L)	1.59	
25-hydroxyvitamin D (nmol/L)	50	
1,25-dihydroxyvitamin D (normal, 55-139 pmol/L)	258	
24,25-dihydroxyvitamin D (nmol/L)	2.6	
1,25-dihydroxyvitamin D:24,25-dihydroxyvitamin D ratio	99	
Vasoactive intestinal peptide (normal, <30 pmol/L)	6	
Pancreatic polypeptide (normal, <300 pmol/L)	68	
Somatostatin (normal, <150 pmol/L)	48	
Gastrin (normal, <40 pmol/l)	123	
Chromogranin A (normal, <60 pmol/L)	58	
Glucagon (normal, <50 pmol/L)	43	
Chromogranin B (normal, <150 pmol/L)	110	
Fibroblast Growth Factor-23 (normal, <100 RU/mL)	8890	
Serum iodine (normal, 0.32-0.63 µmol/L)	0.22	
Thyroglobulin (ng/ml) (antithyroglobulin negative)	38200	
Calcitonin (normal, <11.8 ng/L)	<1.0	
Abbreviation: GH = growth hormone.		

This finding is in contrast to consumptive hypothyroidism caused by type 3 iodothyronine deiodinase activity triggering degradation of FT4 and FT3 into inactive metabolites, reverse T3 and 3,3'-diiodothyronine, respectively, by inner ring deiodination. Overexpression of type 3 iodothyronine deiodinase has been reported with hepatic hemangiomas and nonvascular tumors as a rare form of acquired consumptive hypothyroidism, in which both FT4 and FT3 are low with elevated TSH and require supraphysiologic doses of thyroxine to achieve a euthyroid state (17). However, we were unable to assess iodothyronine deiodinase activity in the resected thyroid tissue or the liver biopsy which we acknowledge is a limitation.

Approximately 80% of malignancy related hypercalcemia is mediated by PTHrP, with approximately 20% driven by osteolytic bony metastasis, and a small percentage attributed to ectopic 1,25-hydroxylase activity and ectopic PTH (18,19). In our case, the absence of PTHrP, PTH, and skeletal disease suggested the hypercalcemia was likely due to ectopic 1-alpha-hydroxylase activity resulting in the elevated 1,25-dihydroxyvitamin D concentrations and malignant hypercalcaemia. This phenomenon is well described in cases of sarcoidosis, lymphomas, and ovarian germ cell tumors (20-22), but has not been previously reported in the literature with metastatic Hürthle cell thyroid carcinoma. It is also interesting to note that

the patient's FGF23 was elevated but did not suppress the 1,25-dihydroxyvitamin D concentrations, as previous work has reported negative feedback of FGF23 on renal 1-alpha-hydroxylase activity (23). This severe hypercalcemia proved resistant to conventional treatment with intravenous fluids, glucocorticoids, bisphosphonates, calcitonin, cinacalcet, and denosumab. Previous work has shown that targeting the 1-alpha-hydroxylase activity with the azole group of antifungals can achieve normocalcemia in granulomatous diseases (22). The use of somatostatin analogues for malignant humoral hypercalcemia has also been reported with good results (24). However, in the present case, the patient deteriorated swiftly and we were unable to try these treatments.

The curative management of Hürthle cell carcinomas is chiefly surgical. Radioactive iodine has shown improved survival rates in iodine avid tumors (25); however, only up to 53% of metastatic tumors are iodine avid (26). Indium-111 octreotide scintigraphy has some role in the diagnosing and monitoring of metastatic disease in noniodine avid metastatic disease (27). There is a limited role for palliative radiotherapy, such as the use of radioligand therapy, with somatostatin analogues, or kinase inhibitors, which have been used with variable results (27-31).

Hürthle cell carcinomas are more aggressive in nature than other differentiated thyroid neoplasms, with a greater propensity to metastasize to distant sites (6). Bhattacharya et al (5) reported a nonsignificant reduction in survival rates between nonmetastatic Hürthle cell carcinomas and follicular thyroid cancer with an overall survival time of 109 months. Due to the relative rarity of Hürthle cell carcinomas and its unpredictable behavior, there are varied opinions on how best to manage them, with more consistency being advocated with a longer term follow-up (32).

CONCLUSION

In summary, our case illustrates that Hürthle cell carcinoma can manifest with various biochemical abnormalities, including isolated low FT4, severe hypercalcemia, and ectopic growth hormone excess, and can present in distant organs aggressively after a prolonged period of dormancy. Clinicians should consider this as a potential diagnosis when presented with unusual biochemistry if a Hürthle cell carcinoma has been previously diagnosed, no matter how long ago.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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