CASE REPORTS

Hürthle cell follicular carcinoma of the thyroid gland presenting with diffuse meningeal carcinomatosis and evolving to anaplastic carcinoma

Hürthle cell follicular carcinoma (HCFC) of the thyroid gland is a malignant tumour composed predominantly or entirely of oncocytes (also called "Hürthle" or "Askenazy" cells),¹ arranged in a follicular/trabecular pattern without the cytological changes found in papillary carcinoma.^{1,2} Although most studies have demonstrated that HCFC and follicular thyroid carcinoma share similar clinical behaviour and prognosis,³ recently the World Health Organization (WHO) has classified HCFC as a separate and distinct entity.⁴ Anaplastic thyroid carcinoma accounts for 5–10% of all thyroid cancers and represents the most aggressive thyroid tumour almost invariably associated with a fatal outcome.⁵ Most anaplastic thyroid carcinoma cases show evidence of a pre-existing differentiated, or poorly differentiated, thyroid carcinoma.^{2,5} At present, to our knowledge, the secondary leptomeningeal localisation of thyroid HCFC has not yet been reported in the literature.

Case report

We describe the case of a 56-year-old woman who was admitted to the hospital due to a 3-day history of partial seizures, unsteady walk with frequent falls and dysarthria. She had no history of either neck irradiation or thyroid diseases in her family. Fifteen years before, laboratory and imaging investigations disclosed a euthyroid goitre with a 15 mm hypoechoic, scintigraphically "cold", nodule in the left thyroid lobe. She was not submitted to fine-needle aspiration biopsy, and was given L-thyroxine thyroid stimulating hormone suppressive treatment for about 1 year. On admission, the neurological examination was normal, although the Mini Mental State Evaluation (MMSE) showed only a mild cognitive impairment with deficiency of working memory. A few days later, generalised seizures and lethargy developed. Laboratory testing and imaging procedures were performed. Blood count, renal liver and thyroid function tests, and acid-base equilibrium were normal, whereas erythrocyte sedimentation rate was elevated at 35 mm/h. Cerebral MRI documented a cortical hyperintensity on T2-weighted sequences, enhancing after gadolinium administration. Cytological examination of the liquor obtained by lumbar puncture showed clusters of large polygonal cells exhibiting hyperchromatic, markedly atypical nuclei with prominent "cherry pink" nucleoli and abundant eosinophilic granular cytoplasm resembling oncocytes (fig 1A). Immunocytochemical reaction against thyroglobulin, calcitonin and thyroid transcription factor-1 (TTF-1) stains was negative. Treatment with dexamethasone 16 mg/d intravenously and oxcarbazepine was started. Investigations performed to detect the source of oncocytes, including whole body CT, scintigraphy of the skeleton and thyroid ultrasound, revealed several metastatic lesions at the lumbar spine and a 22 mm hypoechoic, hypervascularised nodule with undefined margins in the left thyroid lobe.

Thyroid fine needle aspiration biopsy yielded highly cellular material composed of follicular-patterned Hürthle cells lacking nuclear features of papillary carcinoma and finally interpreted as Hürthle cell follicular neoplasm. A biopsy of a lumbar spine lesion was obtained. The smears from lumbar spine biopsy featured a neoplasm composed of oncocytes arranged in small follicles, showing marked atypias and frequent mitotic figures; tumour cells were positive for thyroglobulin (fig 1B) and TTF-1, and negative for calcitonin and chromogranin: the histological diagnosis was "bone metastasis from HCFC of the thyroid". The patient underwent total thyroidectomy without complications. Histological examination of thyroid specimen demonstrated a well-circumscribed, partly encapsulated, lesion in the left lobe. The neoplasm was mostly composed of Hürthle cells arranged in small follicles with scanty colloid (fig 1C), widely invasive into the tumour capsule and vessels. Oncocytes were polygonal to square in shape, had distinct cell borders and abundant eosinophilic granular cytoplasm; nuclei were large, with frequent multinucleation, marked atypias and mitotic activity, and prominent cherry pink nucleoli, in the absence of grooves, clearing, crowding or pseudoinclusions. The neoplasm stained positively for thyroglobulin, TTF-1 and cyclin D1, whereas it was negative for cytokeratin, S100 protein, Melan A, HMB-45, ret/PTC, CT, p21, p27, and p53 stainings. In some discreet areas of the neoplasm, contiguous to oncocytes and intermingled with them, a haphazard proliferation of giant pleomorphic, unusual cells was seen (fig 1D). These elements were polygonal to spindle-shaped, contained pale

eosinophilic cytoplasm and large, irregular, markedly atypical nuclei. At immunohistochemical examination, these cells showed positive reaction to p53 and cyclin D1, but did not stain with thyroglobulin, TTF-1, cytokeratin, S100 protein, Melan A, HMB-45, ret/PTC, CT, p21, and p27. The final diagnosis was consistent with HCFC of the thyroid gland, including foci of anaplastic thyroid carcinoma. Soon after thyroidectomy, the patient was given L-thyroxine 100 mcg/d. A 5-mCi ¹³¹I whole body scan was obtained following administration of recombinant thyroid stimulating hormone (Thyrogen), 0.9 mg intramuscularly in two consecutive days; unfortunately, no radioiodine uptake was detected throughout the body. The patient died 4 months after diagnosis.

Discussion and conclusions

The present report is of particular interest because, to the best of our knowledge, it represents the first documentation of a HCFC of the thyroid presenting with diffuse meningeal carcinomatosis and evolving to anaplastic thyroid carcinoma. The evidence of foci of anaplastic thyroid carcinoma within a HCFC in our patient strongly supports the hypothesis that most anaplastic thyroid carcinoma cases derive from the loss of differentiation of a pre-existing differentiated neoplasm;^{2,5} so far, papillary thyroid carcinoma has been indicated as the main precursor of anaplastic thyroid carcinoma.^{2,5} In this case, the neoplasm displayed overexpression of cyclin D1 and underexpression of p21 and p27 in both HCFC and anaplastic thyroid carcinoma areas, as well as p53-positive thyroglobulin-negative

Figure 1 (A) Liquor cytology: clusters of large polygonal cells exhibiting hyperchromatic, markedly atypical nuclei with prominent "cherry pink" nucleoli and abundant eosinophilic granular cytoplasm, resembling oncocytes (H&E stain, original magnification $\times 40$). (B) Bone biopsy (spine): a neoplasm composed of thyroglobulin-positive oncocytes arranged in small follicles, showing marked atypias and frequent mitotic spindles was detected within bone trabeculae (thyroglobulin stain, original magnification $\times 20$). (C) Histological examination of thyroidectomy: Hürthle cell follicular carcinoma. Oncocytes were arranged in small follicles with scanty colloid, were polygonal to square in shape, had abundant eosinophilic granular cytoplasm, and large nuclei with marked atypias. (D) Histological examination of thyroidectomy: on the top, contiguous to oncocytes and intermingled with them, a haphazard proliferation of giant pleomorphic, unusual cells was seen.

Take-home messages

- Thyroid Hürthle cell follicular carcinoma (HCFC) may evolve to anaplastic thyroid carcinoma.
- Differential diagnosis should always include secondary leptomeningeal localisation of thyroid HCFC when cytological examination of the liquor shows clusters of large polygonal cells resembling oncocytes.

cells within anaplastic thyroid carcinoma: a pattern reflecting the progressive tumour undifferentiation.⁶ The aggressive behaviour of the neoplasm in our patient, showing bone metastases, meningeal carcinomatosis and no radioiodine uptake, likely represented the clinical aspect of such cellular events.

Carlo Maria Stucchi

Department of Neurology

Valentina Vaccaro

Department of Internal Medicine, Azienda USL Modena, Italy

Anna Magherini

Department of Neurology, Ospedale S. Agostino-
Estense, Modena, Italy

Carmela Di Gregorio

Section of Pathology, Azienda USL Modena, Italy

Gabriele Greco

Department of Neurology

Virginia A Livolsi

Department of Pathology, University of Pennsylvania,
Philadelphia, USA

Giampaolo Papi

Department of Internal Medicine, Azienda USL Modena, Italy

Correspondence to: Dr Giampaolo Papi, MD,
Dipartimento di Medicina Interna, Ospedale
"Ramazzini", Via S. Giacomo, 2, 41012 Carpi (MO),
Italy; papi@giampaolo@hotmail.com

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Metanephric adenoma of the kidney: a clinicopathological and molecular study of two cases

Metanephric adenoma (MA) is a benign kidney tumour, accounting for about 0.2% of adult renal epithelial neoplasms.¹ Development of MA from tubules of the fetal kidney and relationship with Wilms' tumour (WT) were postulated despite lack of chromosome alterations typically found in WT.^{2,3} MA has been linked to papillary renal cell carcinoma (RCC) and the differentiation can be challenging in routine pathology. It has been suggested that MA is a distinct tumour entity with specific genetic alterations.⁴ Many cases do not seem clinically symptomatic.

Clinical presentation

A white teenage boy presented with polycythaemia (haemoglobin 25 g%) and an erythropoietin (EPO) level of 105 mU/ml (8.0-34.0 mU/ml) in a routine medical check-up. Bone-marrow biopsy ruled out haematological disorders. A CT scan demonstrated a contrast-enhancing mass 4 cm in diameter in the lateral middle section of the left kidney. An encapsulated, homogeneous, light-brown coloured tumour was removed and sent in for frozen section. The further course was uneventful.

A woman in her 40s, otherwise healthy, presented with subjective weakness. CT showed a mass 3 cm in diameter with contrast enhancement of the right kidney. The patient underwent a transperitoneal resection of the tumour; the further course was uneventful. No signs for disease progression are found after 5 years in either case.

Macroscopic and histological presentation

Macroscopically, both tumours appeared well circumscribed, round and homogeneous, measuring 3.5 and 3 cm, respectively, in diameter. Both tumours had a light brown cutting surface without cystic lesions, haemorrhage or necrotic areas (fig 1).

Histologically, both cases showed a well-circumscribed tumour without any capsule, with tightly packed uniform small epithelial cells forming small acini, tubules and focally glomeruloid structures (fig 2). The cells had a high nuclear to cytoplasmic ratio, with homogeneous chromatin distribution and no cellular

atypia. The uniform and round nuclei showed no mitoses.

Immunohistochemistry

An avidin-biotin peroxidase method with diaminobenzidine was used after microwave antigen retrieval of formalin-fixed paraffin wax-embedded material in an NEXUS immunostainer (Ventana, Tucson, Arizona, USA). Both tumours stained positive for pan-cytokeratin, CK7 and vimentin, and negative for epithelial membrane antigen (EMA), CK19 and p53. Case 2 stained negative for EPO (fig 3).

Molecular methods and results

Fluorescence in situ hybridisation was performed for tumour cells microdissected from frozen sections as described previously.⁵ Centromeric probes for enumerations of chromosomes 1, 7, 9, 17, X and Y were used (Vysis, Des Plaines, Illinois, USA). At least 200 cells were counted for every chromosome. Both tumours had two signals for every investigated centromere in >90% of cells. Comparative genome hybridisation (CGH) was performed as described previously.⁶ Both tumours showed a normal CGH profile without any losses or gains of chromosomal material (fig 3).

Discussion

Macroscopically, MA appears well circumscribed, round, solid and soft, with a light brown surface. Histologically, it features small uniform epithelial cells of an acinar, tubular, glomeruloid or papillary growth pattern with a high nuclear to cytoplasmic ratio. The nuclei are oval, with inconspicuous chromatin distribution and display little mitoses.^{1,7} The two cases presented here display the macroscopic and histological features typical of MA.

Despite no consistent immunohistochemistry staining patterns, there is frequent focal positivity of CK7 and CD57 and positivity for vimentin, but negativity for EMA and S-100.^{7,8} This marker profile can be used in differential diagnosis of papillary RCC and WT, as papillary RCC is positive for EMA and CK7.⁹ Both tumours in our study showed the typical behaviour of MA and could be discriminated from WT and RCC.

Most reports show normal karyotypes for MA.^{7,8} Our two cases showed no numerical

Figure 1 Metanephric adenoma of patient 1. (A) CT image of the well-defined tumour in the left kidney. (B) Macroscopic appearance of the tumour.