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.

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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 Wilm's 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-cytoceratin, 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 Plains, 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

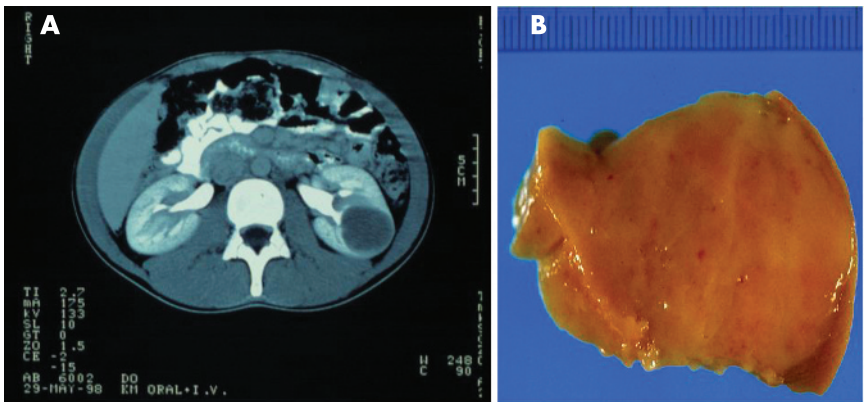

Figure 1 Metanephric adenoma of patient 1. (A) CT image of the well-defined tumour in the left kidney. (B) Macroscopic appearance of the tumour.

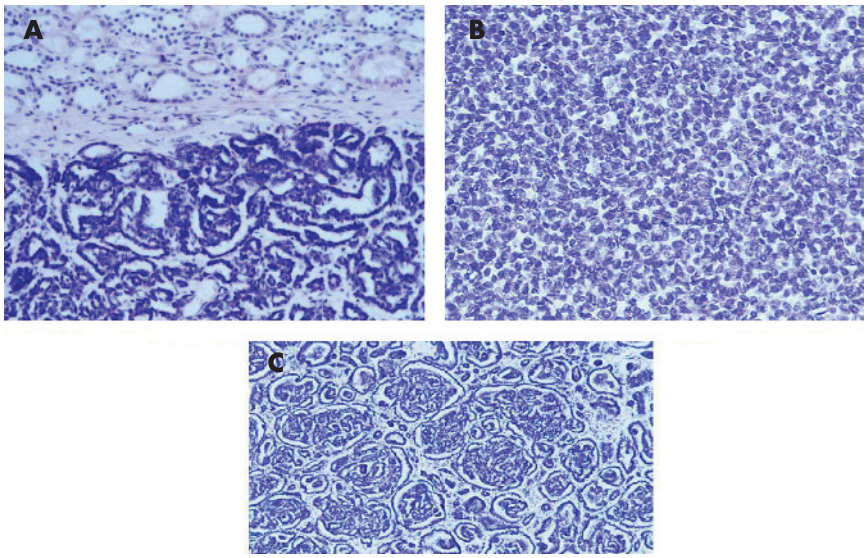

Figure 2 Histological features of patient 1. (A) Well-circumscribed tumour without capsule infiltration in adjacent renal parenchyma (H&E, magnification ×100). (B, C) The tumour is composed of small uniform epithelial cells forming small acini and glomeruloid structures (H&E, magnification ×200).

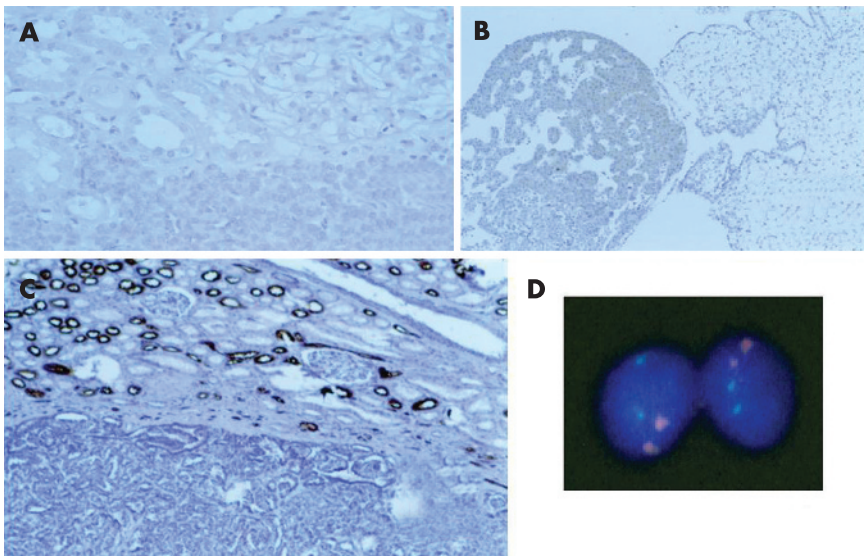

Figure 3 Immunohistochemical and molecular features of patient 1. (A, B) Negativity of the tumour of patient 1 with raised erythropoietin (EPO) serum levels for EPO and fetal liver as positive control. (C) Negativity of the tumour for epithelial membrane antigen (EMA; magnification ×100). (D) Fluorescence in situ hybridisation analysis for centromeres 7 (red) and 17 (green). For both centromeres two signals can be seen.

anomalies in chromosomes 1, 7, 9, 17, X and Y, and a normal CGH profile.

MA has been related to the proximal tubule of the fetal kidney owing to morphological, ultrastructural and immunohistochemical similarities.[2 8] Some authors state MA to be the benign counterpart of WT despite no deletion of the chromosome 11p13 region, an alteration typically found in WT.[3 10] MA has been linked to papillary RCC owing to certain overlaps of histological features and common molecular alterations, as gain of chromosomes 7 and 17 and loss of sex chromosomes have been reported.[4] However, MA shows no duplication of chromosomes 7 and 17q21.32, a consistent molecular feature of papillary RCC.[3] Thus, it is suggested that MA is a distinct entity. Fluorescence in situ hybridisation analysis could be used in addition to immunohistochemistry for distinguishing this benign tumour from its malignant counterpart.

About 50% of MA do not appear clinically symptomatic, while flank pain, haematuria and polycythaemia have been described.[7 10] The cause for the latter condition remains unclear. In our case, no expression of EPO could be demonstrated. Possibly, a mechanical irritation compromised renal blood supply, triggering EPO production.

Most authors describe MA as benign, and only one case of metastatic disease based on a supposed MA diagnosis has been reported.[1 11] The two cases presented here did not show any disease progression at 5 years. Thus, MA showing the typical features can safely be regarded as a benign tumour and treatment should consist of local resection.

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Malignant melanoma of the ciliary body presenting as extraocular metastasis in the temporalis muscle

A man in his 30s presented with an 18-month history of a painless 3×4 cm mass in his left temporalis muscle which had grown rapidly in the previous month. There were no neurological or ocular symptoms. Past medical history was unremarkable. The mass was excised and showed a metastatic pigmented malignant melanoma. Immunocytochemistry using antibodies HMB45 and MelanA were both positive. Postoperatively, the patient underwent adjuvant radiotherapy.

In search for a primary source an in situ superficial spreading pigmented malignant melanoma of the left leg was removed but was not regarded as the primary lesion. Ophthalmological examination detected a pigmented mass in the inferotemporal quadrant of the left iris/ciliary body with pigmented cells seeding the vitreous. Intraocular pressure of the left eye was markedly raised, and the iris architecture was distorted. Fundoscopy showed multiple hyperpigmented choroidal foci involving the posterior pole of the left eye (fig 1A). CT scans of the neck, thorax, abdomen and pelvis were all normal.

The enucleated left globe confirmed a primary pigmented malignant melanoma of the ciliary body, with maximum thickness of 2 mm (fig 1B). It focally involved the full thickness of the ciliary body, spread into the lateral aspect of the iris and invaded the trabecular meshwork. Multi-focal satellite-type nodules were found in the choroid, each surrounded by a dense lymphocytic response, predominantly made up of CD8-positive T-cells with a smaller number of CD20-positive B-cells (fig 2A). Within the ciliary body there were two distinct patterns of melanocytes. One spindle and round population, which appeared benign, had a low cell proliferation index using MIB1 labelling using Ki 67 and was in keeping with melanocytoma. The other population, arranged in clusters and more epithelioid, had a higher MIB1 labelling using Ki 67 cell proliferation index and showed malignant features (fig 2B). These cells were similar to those present in the metastatic lesion of the left temporalis muscle (fig 3). Several nerve branches within the choroid showed perineural invasion by melanoma. At the angle deep to the ciliary body, a focus of vascular intrascleral invasion was also present. The optic disc and nerve as well as the meninges around the optic nerve were free of invasion.

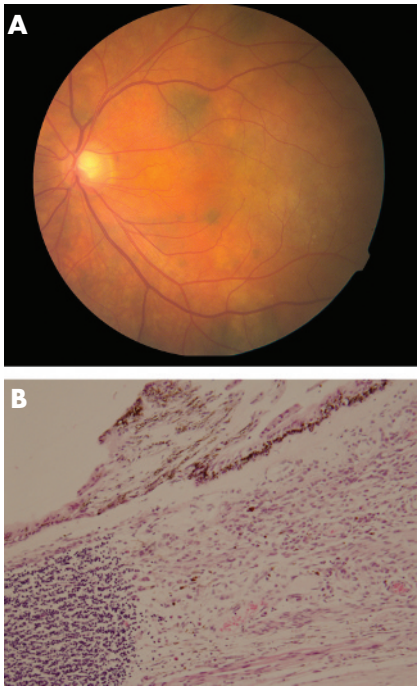

Figure 1 (A) Fundoscopy: note depigmented and pigmented nodules. (B) Ciliary body with underlying melanoma and lymphoid aggregate on left side (H&E ×200).

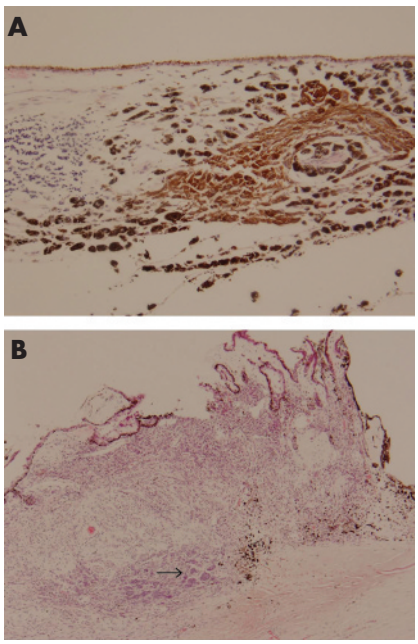

Figure 2 (A) Microscopy of the choroid showing pigmented satellite nodule with adjacent lymphoid aggregate (H&E ×100). (B) Full thickness of ciliary body showing partly pigmented malignant melanoma with epithelioid portion arrowed.

Discussion

This case illustrates an interesting histological presentation of a primary malignant melanoma of the ciliary body. Ciliary body melanomas comprise approximately 10% of uveal melanomas; they usually present with ocular symptoms and are amenable to local surgery. Of intraocular melanomas, iris melanomas have the best and ciliary body melanomas have the worst prognosis.[1] The median age at diagnosis ranges from 55 to 62 years.[1]

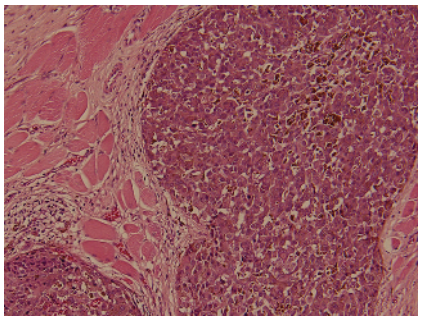

Figure 3 Epithelioid malignant melanoma (metastatic) in the temporalis muscle (H&E ×100).

In ocular melanoma, metastasis is usually haematogenous and in 95% of cases the initial site is the liver.[2 3] Liver metastasis is especially frequent with ciliary body melanomas.[4] In contrast to cutaneous melanomas, uveal melanomas do not have direct access to the lymphatics and thus cannot initially spread to regional lymph nodes.[5] In the present case, several nerve branches within the choroid showed perineural invasion by the tumour, and extraocular metastasis to the left temporalis muscle was found. This might have resulted from perineural invasion of the zygomaticotemporal branch of the maxillary nerve which exits the orbit through the zygomaticotemporal fossa and ends in the infratemporal fossa, the location of the metastasis.[6] Perineural spread of ocular melanoma has been well documented previously.[7 8] Vascular spread might also account for metastasis in this case.

Histologically, the multi-focal satellite spread in the choroid and the pronounced lymphocytic immune response around the tumour were highly unusual. Satellite metastasis and central regression is more frequently found in cutaneous melanomas.[9 10] A literature search has failed to identify previous reports of this type of ''satellite'' spread in ciliary body melanoma.

Malignant transformation of choroidal melanocytomas to malignant melanomas has been reported several times.[11–13] In all of these, the presenting features were due to the primary tumour, characterised by ocular symptoms and neurological deficits. In this case the metastatic lesion in the left temporalis muscle was the only clinical sign at presentation.

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