Virchows Arch (2012) 460:353–356
DOI 10.1007/s00428-012-1211-5

CASE REPORT

Urothelial carcinoma of the renal pelvis with simultaneous trophoblastic and malignant clear cell endodermal-type differentiation

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Received: 23 January 2012 / Accepted: 6 February 2012 / Published online: 24 February 2012

Embryonal-type differentiations in urothelial neoplasms are uncommon [1, 2]. These frequently underdiagnosed phenomena may include either the presence of trophoblastic areas or, even more rarely, admixed yolk sac tumour patterns (YST) [2]. We present for the first time the association of both trophoblastic and malignant endodermal-type elements within an aggressive high-grade urothelial carcinoma (HGUC). Due to the presence of the endodermal component, which had cells with a prominent clear cytoplasm, a differential diagnosis with other papillary and clear cell renal neoplasms was necessary.

Paper presented at the 23rd Congress of the european Society of Pathology. Helsinki, Finland, August 27-September 1, 2011

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Clinical history

A 47-year-old male presented with intense pain in the lumbar region. Seventeen years previously, he had been treated for a non-seminomatous testicular tumour with lung and liver metastases. He eventually underwent a right orchidectomy followed by platinum-based chemotherapy. Follow-up showed only residual mature teratomatous tissue in the biopsy material from the remaining testicle.

On his recent admission, elevated levels of serum β-hCG of 9,897.06 mUI/ml (normal 0–2.6 mUI/ml) and a lactate dehydrogenase of 1,280 U/L (normal 0–480 U/l) were found. Serum α-foetoprotein (AFP) was negative. A CT scan showed a large, ill-defined retroperitoneal mass involving the left kidney and ureter. There was marked infiltration of the psoas, and lung and vertebral metastases were prominent. No lesions were detected in the left testicle after both clinical and ultrasonographical exploration. A left ureteronephrectomy with resection of the surrounding tissues was performed. Patient refused chemo- or radiotherapy and 18 months after diagnosis is alive but has a large residual mass and pulmonary metastases.

Materials and methods

The ureteronephrectomy specimen was bivalved and fixed overnight in 10% buffered formalin and routinely processed. Seven tissue blocks were taken, and H&E-stained sections were analysed. Immunohistochemistry was performed on representative sections with the antibodies shown in Table 1.

Table 1 Antibodies used in this study

Antibody	Clone	Vendor
AFP	Polyclonal	DAKO, Glostrup, Denmark
Glypican 3	1G12	Bio Mosaics, Burlington, VT
SALL4	Sc-101147	Santa Cruz Biotechnology, Inc
CDX2	AMT 28	MasterDiagnostica, Granada
HepPar-1	OCH1E5	DAKO, Glostrup, Denmark
β-hCG	polyclonal	DAKO, Glostrup, Denmark
hPL	polyclonal	MasterDiagnostica, Granada
α-Inhibin	R1	DAKO, Glostrup, Denmark
Cytokeratin 20	K_s20.8	DAKO, Glostrup, Denmark
Cytokeratin 7	Ovtl 12/30	DAKO, Glostrup, Denmark
p63	4A4	MasterDiagnostica, Granada

Results

The nephrectomy specimen showed a dilated pelvis harbouring a solid 6×4.7-cm mass which infiltrated the adjoining kidney parenchyma, perirenal fat and the psoas muscle. Microscopically, a solid HGUC originating from the pelvis had numerous scattered syncytiotrophoblasts, which were also present in the numerous tumour emboli (Fig. 1a). In close transition with the urothelial tumour (Fig. 1b), a complex tubulopapillary neoplasm lined by tall, vacuolated, clear, atypical cells (Fig. 1c) was seen protruding into the pelvic space.

Immunohistochemical markers differentiated the cytokeratin 7 (CK7) and p63-positive (Fig. 2a) urothelial component from the trophoblastic cells which were positive for β-hCG, α-inhibin (Fig. 2b) and human placental lactogen (hPL). In contrast, the clear cell tubulopapillary cells had a characteristic primitive endodermal immunophenotype positive for glypican 3 (GLY3), CDX-2 and SALL4 (Fig. 3a–c) which, however, failed to stain for AFP, a fact which precluded a diagnosis of glandular yolk sac tumour. Cytokeratin 20 and HepPar-1 were negative.

Discussion

The capacity of urothelial carcinomas to differentiate into various cell lineages is well recognized. Amongst others, glandular, squamous, neuroendocrine and lymphoepithelioma-like patterns are relatively frequent in the bladder [1].

The rare trophoblastic differentiation in transitional tumours represents a variant of carcinomas associated with a poor prognosis [1, 3, 4]. Immunohistochemistry performed in the present case demonstrated the coexistence of atypical transitional cells with a characteristic CK7 and p63 positivity showing both syncytio- and intermediate trophoblastic differentiations, the former positive for β-hCG and α-inhibin and the latter for hPL. This highly specific immunophenotype helped to differentiate this variant of urothelial carcinoma from other giant cell-containing tumours [1].

This case also showed the concomitant presence of a clear cell tubulopapillary growth that merged with the urothelial neoplasm. This aberrant component had a characteristic primitive endodermal immunophenotype which was positive to SALL4, a stem cell marker [5],

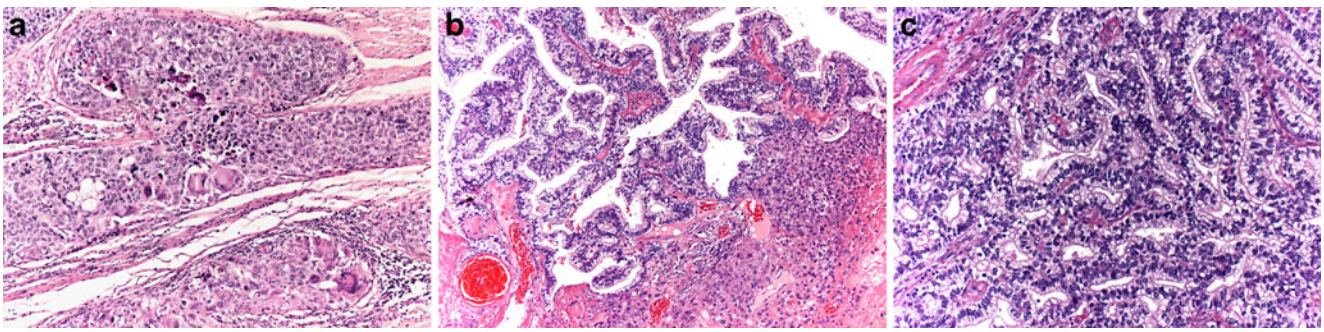

Fig. 1 Pelvic urothelial tumour with abundant syncytiotrophoblasts (**a**), merging with a tubulopapillary growth (**b**) lined by cells with prominent clear cytoplasm (**c**)

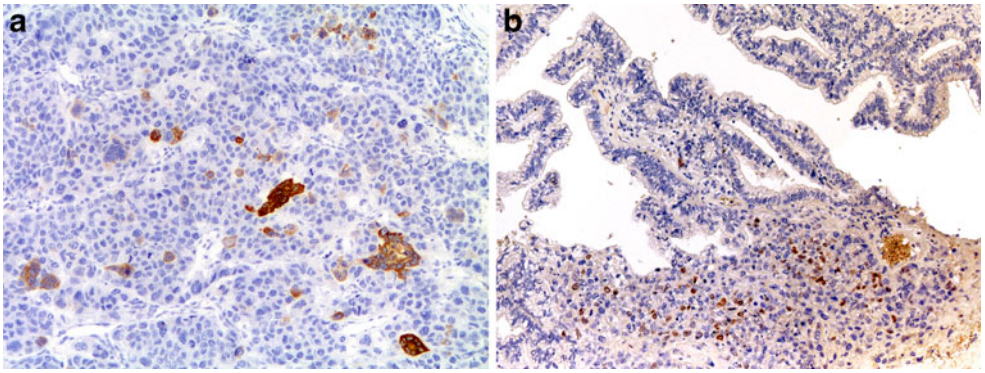

Fig. 2 Trophoblastic component of urothelial tumour is positive for α-inhibin (**a**). p63 positivity in urothelial neoplasm (**b**) contrasts with its negativity in the clear cell areas

and to GLY3, a marker for both yolk sac and liver cell tumours [6]. Both antibodies are always co-expressed in yolk sac tumours [7].

The primitive malignant endodermal or YST-type differentiation may be present in somatic, non-embryonal tumours of the female genital tract [8, 9], although it can also develop in the sinonasal area, stomach, colon, etc., where it is also associated with both high-grade tumours and a poor prognosis [7]. In the urinary tract, this association has been reported in rare, isolated cases of AFP-producing adeno- or transitional cell carcinomas and demonstrated by AFP stains only. Histologically, these cases consistently reveal the presence of a distinctive vacuolated epithelium with a characteristic AFP-positive immunophenotype [2]. The higher sensitivity of recently introduced antibodies such GLY3 [6] and SALL4 [5] has facilitated the demonstration of areas of primitive endodermal differentiation (YST) [7] present in various mixed tumours. In our case, tubulopapillary areas showed an incomplete primitive endodermal phenotype due to presence of a strong GLY3 and SALL4 positivity in the absence of AFP staining, a more specific but less sensitive marker of endodermal differentiation [6]. Furthermore, CDX2, an intestinal type differentiation marker [10], was also positive in our case, supporting an intestinal differentiation in the malignant primitive endodermal component [7, 11]. This immunophenotype helped to differentiate the endodermal tubulopapillary areas from both clear cell renal cell carcinoma (negative for CK7 and p63 but positive for renal cell carcinoma marker, vimentin and CD10) and from the newly introduced entity of tubulopapillary clear cell carcinoma (positive for CK7 and vimentin but negative for CD10, alpha-methyl CoA racemase and renal cell carcinoma marker) [12, 13].

Simultaneous placental and endodermal-type differentiations have not been previously reported in association with transitional cell carcinomas. The non-germ cell origin of some embryonal-type tumours, arising from somatic type neoplasms, has been recently reviewed [7], and an origin from pluripotent malignant stem cells present in the somatic tumour has been proposed [14]. We believe that the relationship of this complex renal tumour with the previous testicular tumour is coincidental, as there was a successful response to chemotherapy with no short-term recurrence; furthermore, the present lesion showed an intimate admixture of somatic and embryonal histological patterns reflecting tumour heterogeneity rather than a metastasis.

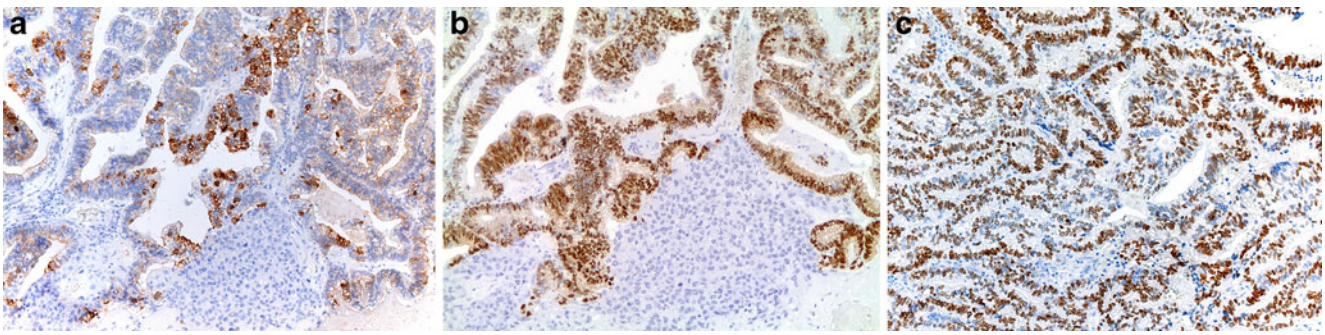

Fig. 3 Clear cell tubulopapillary areas with a primitive endodermal phenotype are positive for GLY3 (**a**), CDX2 (**b**) and SALL4 (**c**)

Conflict of interest None.

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