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CASE REPORT

Peter Vermeulen · Lucien Hoekx · Cecile Colpaert
Jean-Jacques Wyndaele · Eric Van Marck

Biphasic sarcomatoid carcinoma (carcinosarcoma) of the renal pelvis with heterologous chondrogenic differentiation

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Abstract A case of a man with biphasic sarcomatoid carcinoma of the right kidney with chondrosarcomatous foci and with invasion of the pelvic mucosa and submucosa into the peripelvic adipose tissue is presented. In situ carcinoma of the urothelium of the right renal pelvis and proximal ureter was also noted. Comments on the nomenclature of malignant tumours with apparently mixed carcinomatous and sarcomatous phenotypes and a hypothesis on the histogenesis of these tumours are presented. Cytokeratin and p53 protein expression patterns, and the results of angiogenesis quantification are consistent with an epithelial-to-mesenchymal conversion induced by the stroma.

Key words Carcinosarcoma · Sarcomatoid carcinoma · Urothelial

Introduction

Sarcomatoid carcinomas of the ureter and of the renal pelvis are uncommon [18]. They are high-grade neoplasms with poor prognosis. Most of the reported cases present with invasion of the pelvic wall and contiguous invasion into the adjacent peri-pelvic adipose tissue. Metastases have been reported to develop in liver, heart, lungs and adrenals [5].

Even more uncommon are carcinosarcomas of the renal pelvis, which show foci of osteogenic, chondrogenic, rhabdomyoblastic or leiomyosarcomatoid differentiation [18]. One case of these interesting tumours is presented.

P. Vermeulen · C. Colpaert · E. Van Marck (✉)
Department of Pathology, University of Antwerp, University Hospital, Wilrijkstraat 10, B2650 Edegem-Antwerp, Belgium
Fax: +32-3-8214753

L. Hoekx · J.-J. Wyndaele
Department of Urology, University of Antwerp, University Hospital, Wilrijkstraat 10, B2650 Edegem-Antwerp, Belgium

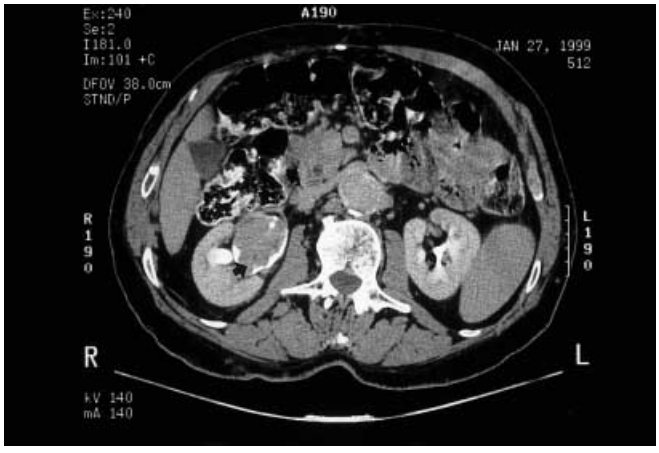

Fig. 1 Computed tomography showing a large solid mass in the pyelum of the right kidney (*arrow*)

Clinical history

U.H., a 77-year-old man, presented with painless and sterile macroscopic haematuria. Both physical examination and flexible urethrocystoscopic examination were negative. Ultrasound demonstrated a solid mass in the pyelum of the right kidney, which was confirmed by computed tomography (Fig. 1). During ureterorenoscopic examination, the pyelum and the calices of the right kidney could not be inspected due to a mechanical obstruction consisting of necrotic tissue at the junction between the pyelum and the ureter. The wash-out fluid obtained after catheterisation of the right pyelum revealed abundant malignant cells from a poorly differentiated carcinoma.

Based on these findings, a right nephroureterectomy was performed. At surgery, the pyelum was expanded by an oval tumour with a maximal diameter of 5 cm. The patient recovered well after the operation and remained without any evidence of disease for 8 months thereafter.

Materials and methods

The surgical specimen was fixed with 10% formaldehyde and representative samples were embedded in paraffin. Five-micron-thick sections were stained with haematoxylin and eosin. Immunohisto-

chemical analysis was performed using an indirect immunoperoxidase technique with diaminobenzidine (DAB) as chromogen and with the following primary antibodies: anti-p53 protein (DO-7, Dako; 1:100 dilution), anti-Ki67 (Ki67, Dako; undiluted), anti-CD31 (JC70, Dako; 1:20 dilution), anti-cytokeratin 20 (Ks20.8, Dako; 1:50 dilution), anti-cytokeratin 7 (CK7, Biogenex; undiluted), anti-low-molecular-weight cytokeratin (AE1, Biogenex; 1:80 dilution), anti-broad range cytokeratin (MNF116, Dako; 1:320 dilution), anti-epithelial membrane antigen (E29, Dako; 1:80 dilution) and anti-vimentin (V9, Biogenex; 1:160 dilution).

Microvessel density was assessed according to the guidelines of an international consensus report [20]. In brief, at low power magnification (×100), areas with a high density of CD31-positive structures were detected by scanning a complete tumour section. Whenever such an area was found, the magnification was changed to ×200 (field size of 1.2 mm^2). A countable microvessel was defined as any staining endothelial cell or cell cluster, clearly separated from adjacent microvessels. Neither vessel lumina nor the presence of red blood cells were necessary to define a microvessel. Small microvessels consisting of only one or two endothelial cells were also taken into account.

Pathological findings

Gross examination of the nephroureterectomy specimen showed a polypoid tumour with the base fixed at the urothelium of the most cranial calyx and with an exophytic extension into the lumen of the renal pelvis and the ureter. The maximal diameter of the tumour was 4.7 cm. The cut-surface was greyish white.

Microscopy revealed a tumour composed of a highly cellular stroma surrounding irregular, anastomosing and invasive epithelial cords (Fig. 2). These invasive cords extended downward from foci of in situ carcinoma of the overlying urothelium of the pelvic mucosa and contained small basaloid cells with scant cytoplasm at the periphery. Towards the centre of the cords, a squamous cell population was present showing single cell keratinization and horn pearls. Central necrosis focally resulted in microcysts. Mitotic figures were numerous. The tumour cell nests infiltrated into the peripelvic fat. The stroma surrounding the nests of squamous carcinoma was sarcomatous, containing numerous atypical non-cohesive spindle cells with a high mitotic activity. There were also foci of chondrogenic differentiation (Fig. 3). The carcinomatous lesions focally blended into sarcomatous areas, generating transitional zones between the two tumour components (Fig. 4).

Immunohistochemically, most of the carcinoma cells stained for epithelial membrane antigen (EMA), low-molecular-weight cytokeratin (LMWCK), broad range cytokeratin and cytokeratin 7. Some carcinoma cells stained for vimentin. Immunohistochemical staining for cytokeratin 20 was negative both in the carcinoma cells and in the sarcomatous stroma. Most of the sarcoma cells stained for vimentin and rare sarcoma cells stained for EMA, LMWCK, broad range cytokeratin and cytokeratin 7.

Expression of p53 protein was estimated by immunostaining and counting positive nuclei in the areas with highest expression. About 400 nuclei were evaluated in both the carcinomatous and the sarcomatous component.

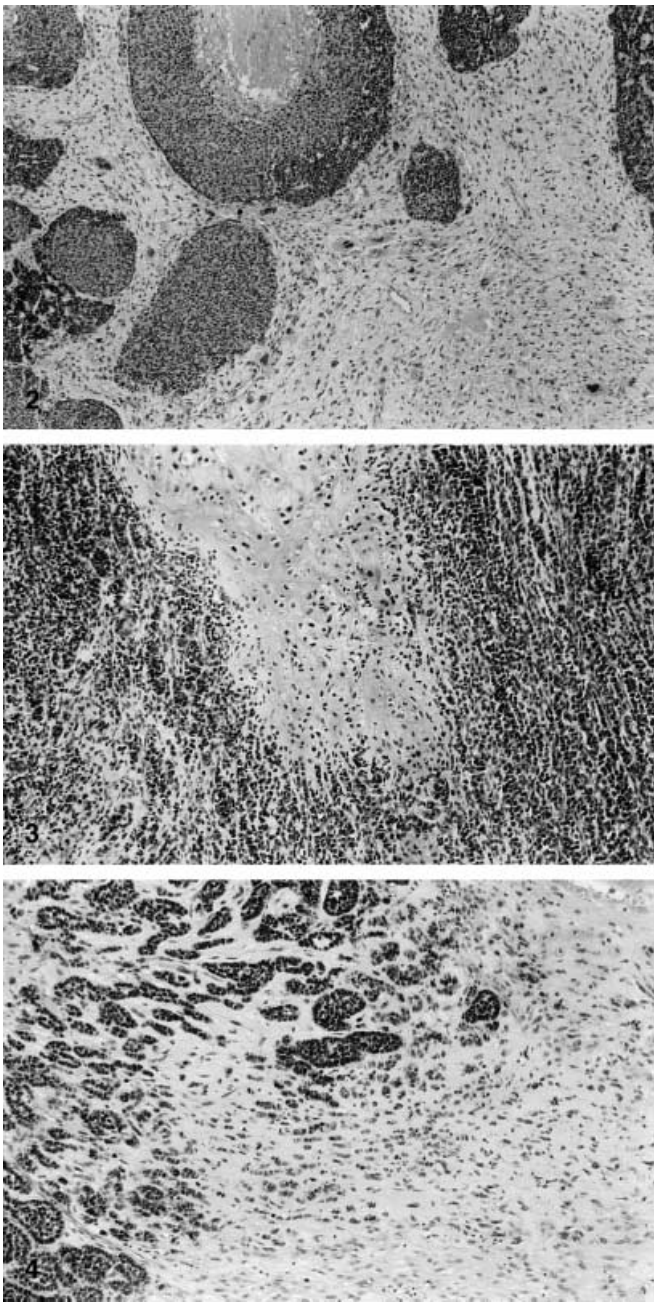

Fig. 2 Microscopic overview of the tumour composed of highly cellular stroma surrounding epithelial cords

Fig. 3 Central area of chondrogenic differentiation

Fig. 4 Transition of carcinomatous areas into sarcomatous components

The fraction of staining nuclei was highly comparable, being 60% and 62%, respectively. The same strategy was used for estimating the fraction of Ki67-positive nuclei. In the carcinomatous component, 31% of all nuclei were immunoreactive. In the sarcomatous component, only 7% of all nuclei stained.

The mean (±SD) microvessel density of the three most vascular areas in the purely sarcomatous compo-

nent was 133±20 microvessels per field, with a median value of 134. In the stroma of the tumour where the carcinomatous component predominated, the respective values were 75±22 and 83 microvessels per field, in areas with a comparable size to the analysed areas in the sarcomatous component. This difference was significant (Mann-Whitney U-test *P* value of 0.04).

Discussion

Sarcomatoid carcinomas involving the renal pelvis and ureter have rarely been reported [18]. The first case report outlining the fundamental role of immunohistochemistry in identifying the tumour type was published in 1984 [16]. In Japan, only the sixth case was reported in 1997 [12]. Recently, only 12 cases of sarcomatoid carcinoma could be retrieved from the combined archives of two large institutions, corroborating the low incidence of this tumour [1]. Half of the patients had died within about 1 year after diagnosis. Presently, there are no studies reporting prognostic factors.

Although the nomenclature used for these tumours in the literature is confusing, malignant tumours of the renal pelvis or ureter composed of both epithelial and spindle cell populations or with only the latter component can, according to Fletcher, be classified as follows [24]. If heterologous differentiation of the sarcomatous component is present, the name „carcinosarcoma“ is used. In „sarcomatoid carcinoma“, transitions between both tumour components are obvious, as opposed to carcinosarcoma where the interphases between both components are sharp.

Because of the heterologous differentiation of the sarcomatous component, the tumour we describe would clearly be a carcinosarcoma. There are, however, several arguments to adopt another nomenclature, based on the observation that the apparent mesenchymal malignant component is not truly a sarcoma. There is indeed no evidence supporting the conjoint tumorigenesis of the epithelial and mesenchymal elements [21]. On the contrary, a variable but definite fraction of the malignant mesenchymal cells have immunohistochemical and ultrastructural characteristics of epithelial cells and lack, for instance, vimentin expression. Cases with temporal evolution from low-grade transitional cell carcinoma to a tumour with a sarcomatous stroma have been reported [14]. Also, carcinosarcomas and sarcomatoid carcinomas show a comparable tumour biology, as both are observed in the same age group as conventional urothelial carcinoma and as there is no survival difference between patients with carcinosarcoma and those with sarcomatoid carcinoma of the urothelial tract [4]. Therefore, as suggested by Nappi et al., it might be more accurate to use the terms „biphasic sarcomatoid carcinoma“ for tumours composed of a carcinomatous and a sarcomatous component, whether or not with heterologous differentiation, and „monophasic sarcomatoid carcinoma“ for spindle cell carcinomas [13].

Some differential diagnostic considerations have to be made. In carcinoma with spindle cell stroma [9, 11], there is also a sharp demarcation between the spindle cells and the epithelial cells, but this pseudosarcomatous stromal reaction does not show an epithelial phenotype, nuclear anaplasia or aneuploidy [8]. In the present case, some sarcoma cells stained for EMA, LMWCK, broad range cytokeratin and cytokeratin 7. If only the sarcomatoid component is present, immunohistochemistry is needed to confirm the epithelial nature resulting in the diagnosis of a sarcomatoid carcinoma and to exclude a primary sarcoma [4]. Extensive sectioning of the tumour and surrounding mucosa may reveal an in situ or invasive epithelial component. In the present case, in situ urothelial carcinoma and invasive carcinoma with squamous differentiation were clearly present.

The immunohistochemical detection of p53 in both components of the tumour and the comparable cytokeratin 7–cytokeratin 20 staining pattern corroborates the carcinomatous origin of the sarcomatous component. In a study on the cytokeratin 7 and cytokeratin 20 immunophenotypes of epithelial tumours of various sites, all transitional cell carcinomas were cytokeratin 7 positive [15]. The sarcomatous component can be regarded as expressing the phenotype of embryonal epithelium, which is typified by the synthesis of both keratins and vimentin [6].

A divergent differentiation of carcinoma cells is usually explained by additional mutagenic events. However, a stroma can induce a stable phenotype independent of genetic alterations in the tumour cells. In mammary epithelial cells, matrix metalloproteinases (MMPs) can induce a cascade of epigenetic effects, eventually resulting in a stable loss of the epithelial phenotype: cleavage of E-cadherin from the cell-surface and disruption of cell–cell contact as well as the transition to a complete loss of cytokeratins and expression of vimentin [7]. Stromal cells, e.g. endothelial cells, have been shown to produce at least part of the MMPs necessary for tumour cell invasion [10]. Also, p53 protein expression, suggestive of a mutated and afunctional type of p53, was observed in both the carcinoma cells and in the sarcomatous tumour cells. Functional p53 suppresses angiogenesis by downregulating angiogenic factor expression, whereas afunctional p53 stimulates angiogenesis by both upregulating vascular endothelial growth factor and downregulating thrombospondin [2]. Hypothetically, an early genetic event, such as p53 gene mutation, in an in situ carcinoma of the urothelium might lead in the end to an epithelial-to-mesenchymal conversion resulting in a biphasic tumour. In the present case, the elevated microvessel density of the sarcomatous component relative to the carcinomatous component is in favour of this hypothesis.

In primary carcinomas of different sites, microvessel density has been shown to be positively associated with the risk of developing distant metastasis [20]. A recent study reports on the microvessel density in 21 carcinosarcomas and sarcomatoid carcinomas of the uterus [3]. In 20 of 21 tumours, the microvessel density in the epithelial component was found to be higher than that of the

mesenchymal elements, substantiating the high metastatic potential of the epithelial component in these tumours. Angiogenesis quantification has not been performed in sarcomatoid urothelial carcinoma, and metastases have rarely been investigated. Case studies mention metastases consisting of sarcomatous elements, carcinoma or sarcomatoid carcinoma [17, 19, 22, 23]. It would be worthwhile to evaluate whether microvessel density, and also the proliferation fraction, in the different components of the primary tumour is predictive of the phenotype of the metastases and of the risk of developing metastases.

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