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CASE REPORT

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Hepatoid adenocarcinoma of the urinary bladder

An unusual neoplasm

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Abstract A new case of hepatoid adenocarcinoma was diagnosed in fragments obtained at transurethral resection (TUR) from a 71-year-old man who had complained of haematuria. The tumour was composed of trabeculae and small solid nests of polygonal atypical cells simulating hepatocarcinoma, together with glandular areas of an otherwise typical adenocarcinoma. Immunohistochemistry showed cytoplasmic reactivity to AFP, AAT, albumin and CAM 5.2. Membrane reactivity was seen in EMA immunostaining, and there was also positivity to polyclonal CEA following a canalicular pattern. Immunoperoxidase studies of hepatocyte growth factor (HGF) and its receptor, c-met, were positive. Their expression may be related to the aggressive behaviour of this tumour.

Key words Urinary bladder · Carcinoma · Hepatoid adenocarcinoma · Alpha fetoprotein

Introduction

Adenocarcinomas represent less than 2% of all urothelial neoplasms. Most cases arise in the dome of the bladder and are related to urachal remnants. These adenocarcinomas of urothelial origin present histological patterns similar to those observed in intestinal adenocarcinomas, with morphological variants including signet-ring carcinoma, clear-cell carcinoma and villous carcinoma [18].

Hepatoid adenocarcinomas in the urothelium are exceptional, only three cases having been reported in the literature: one in the renal pelvis [15] and two in the urinary bladder [24, 25].

The hepatoid variant of adenocarcinoma is defined by the reproduction of a pattern similar to that of hepatocarcinoma, with a combination of histopathological findings of solid nests and trabecular structures of polygonal atypical cells with wide granular cytoplasm and immunochemical expression of alpha-fetoprotein (AFP), alpha-1-antitrypsin (AAT) and albumin [13]. Polyclonal carcinoembryonic antigen (CEA) is expressed in approximately half of the cases with a canalicular staining pattern.

Since their original description in the stomach [12], which is the most common location, hepatoid adenocarcinomas have been reported in other organs, such as ovary [11], lung [2, 14], intestine [16] and adrenal gland [26], in addition to the above-mentioned cases in the urothelium.[1]

Clinically this variant of adenocarcinoma is characterized by its predilection for older patients, with an aggressive course and a poor prognosis. Early lymph node and visceral metastases are common [1, 16]. Most cases have high levels of AFP-circulating in the serum, although this is not a constant feature [16, 19, 20]. It is mandatory to rule out metastases from a hepatocarcinoma before a diagnosis of primary hepatoid adenocarcinoma is made.

We present a new case of hepatoid adenocarcinoma located in the urinary bladder, with immunohistochemical studies on hepatocyte growth factor (HGF) and its membranereceptor, c-met. These markers have been related to a more aggressive behaviour of the neoplastic process [3, 7, 10, 23].

Clinical history

The patient was a 71-year-old man with no unusual clinical antecedents, who complained of haematuria, right-flank pain and dysuria. Urography and cystoscopy disclosed a sessile, infiltrative tumour in the posterior wall of the bladder, which was excised by means of Transurethral resection (TUR).

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[1] While this work was under review Foschini et al. reported albumin gene expression in two adenocarcinomas with hepatoid differentiation. This expression is considered a valuable method of establishing hepatocellular differentiation. [Foschini MP, Baccarini P, Dal Monte PR, Sinard J, Eusebi V, Rosai J (1998) Albumin gene expression in adenocarcinomas with hepatoid differentiation. Virchows Arch 433:537–541]

Table 1 Source and dilution of the antibodies used and results of immunohistochemistry

Antiserum	Source	Dilution	Result
Alpha-fetoprotein	Dako	1/100	+
Alpha-1-antitripsin	Dako	1/500	+
Albumin	Dako	1/1000	+
CAM 5.2	Biomeda	1/40	+
CEA (polyclonal)	Dako	1/200	+
EMA	Dako	1/100	+
Chromogranin	Biomeda	1/50	∅
Neuron-specific enolase (NSE)	Biogenex	1/100	∅
Hepatocyte growth factor (HGF)	Sigma	1/500	+
c-*met*	Santacruz Biotech.	1/50	+

Ultrasonography and abdomino-pelvic CT revealed a tumour mass in the postero-basal bladder wall, together with a lobulated retroperitoneal mass suggestive of lymph node metastases, located in the left para-aortic lymphatic chain and measuring 3.5×5.5×10 cm. There was also a left iliac lymph node measuring 4×4 cm. No lesions were seen in the liver or in the rest of the abdomino-pelvic organs, including the rectal wall. There were high levels of circulating CEA (24.6 ng/ml) and CA 19.9 (193 mU/ml). Circulating levels of AFP were normal. Markers of hepatic function were also normal. Chest radiography ruled out pulmonary masses.

Chemotherapy was given, with some decrease in tumour size after 4 months. However, significant tumour mass and lymphatic metastases remained, and high levels of CEA and CA 19.9 were also present. The latest CT control disclosed new nodal metastases in the right iliac lymphatic chain.

Materials and methods

TUR fragments were fixed in 10% formaldehyde solution and embedded in paraffin. Multiple 3 μm sections were obtained with the use of a standard microtome and then stained with haematoxylin-eosin. Some sections were also stained with Alcian blue and periodic acid-Schiff (PAS).

Immunohistochemical study was performed with paraffin-embedded material using the avidin-biotin-peroxidase technique. The antisera used for immunohistochemistry and their working dilutions are shown in Table 1.

Pathological findings

The surgical specimen consisted of multiple greyish, soft TUR fragments, measuring 3.5×3 cm overall, all of which were processed.

Histologically there was a neoplastic proliferation of epithelial cells, mostly arranged in an organoid pattern, with multiple trabecular structures and small solid nests of polygonal cells (Fig. 1a, b). These cells showed pleomorphism, with large vesicular nuclei of clumped chromatine and prominent nucleoli. Cytoplasms were wide, eosinophilic and granular, with occasional hyaline, PAS-positive globules. More than ten mitoses in ten HPF were found. Some sections showed cellular aggregates with small central lumina, although no bile pigment was found.

Tumour nests grew in a diffuse manner, infiltrating the muscular layer of the bladder. There were multiple small foci of necrosis and haemorrhage. Lymphatic vessel invasion was seen focally. In some areas, the tumour had a glandular pattern with desmoplastic stroma, similar to that observed in typical adenocarcinomas.

The surrounding urothelium remained normal.

Immunohistochemical study showed cytoplasmic positivity in the tumour cells against AFP, AAT, albumin and CAM 5.2. EMA was expressed in a membrane pattern, and polyclonal CEA in a canalicular one. Tumour cells were also reactive to HGF, showing cytoplasmic immunostaining, its c-met receptor was also positive in a membrane pattern (Fig. 2a–d). There was no expression of NSE and chromogranin.

Discussion

Two malignant tumours are found in the literature under the term “hepatoid”: germ cell tumours with hepatoid areas, initially described by Prat et al. [22] and strongly positive to AFP but negative to CEA; and hepatoid adenocarcinomas, first reported by Ishikura et al. [12]. Both these tumours have the same phenotype as hepatocellular carcinoma, both histologically and immunohistochemically [13]. The morphological similarity consists in the presence of trabecular structures and solid nests of polygonal cells that resemble hepatocytes, with immunohistochemical expression of neoplastic hepatocellular markers, such as AFP, AAT and albumin, and also CEA in many cases. This pattern often coexists with an otherwise classical tubulo-papillary adenocarcinoma.

Since initial descriptions of it in the stomach [12, 13], several locations for hepatoid adenocarcinomas have been reported, including ovary [11], lung [2, 14], intestine [16] and adrenal gland [26]. Urological cases are rare and only three have been published: one in the renal pelvis [15] and two in the urinary bladder [24, 25].

Histologically, the current lesion was composed mainly of hepatocarcinoma-like areas merged in typical adenocarcinoma of tubulo-glandular pattern and surrounding desmoplastic stroma. No bile pigment was identified. Immunohistochemical expression of AFP, AAT, albumin and CAM 5.2 was found in the cytoplasm of the tumour cells, and there was membrane reactivity to EMA. Polyclonal CEA was expressed in a canalicular pattern, as in many hepatocarcinomas [5].

We also performed immunohistochemical staining for hepatocyte growth factor (HGF) and its receptor, codified by the proto-oncogene c-*met*. HGF showed a strong cytoplasmic positivity, its receptor c-*met* being expressed in a membrane pattern.

Before a diagnosis of hepatoid adenocarcinoma is made, the metastases of a hepatocarcinoma should be ruled out. In our case, appearances revealed by imaging techniques (ultrasonography and CT) and hepatic function markers were normal, indicating that this was a primary bladder tumour. Moreover, bladder metastases of

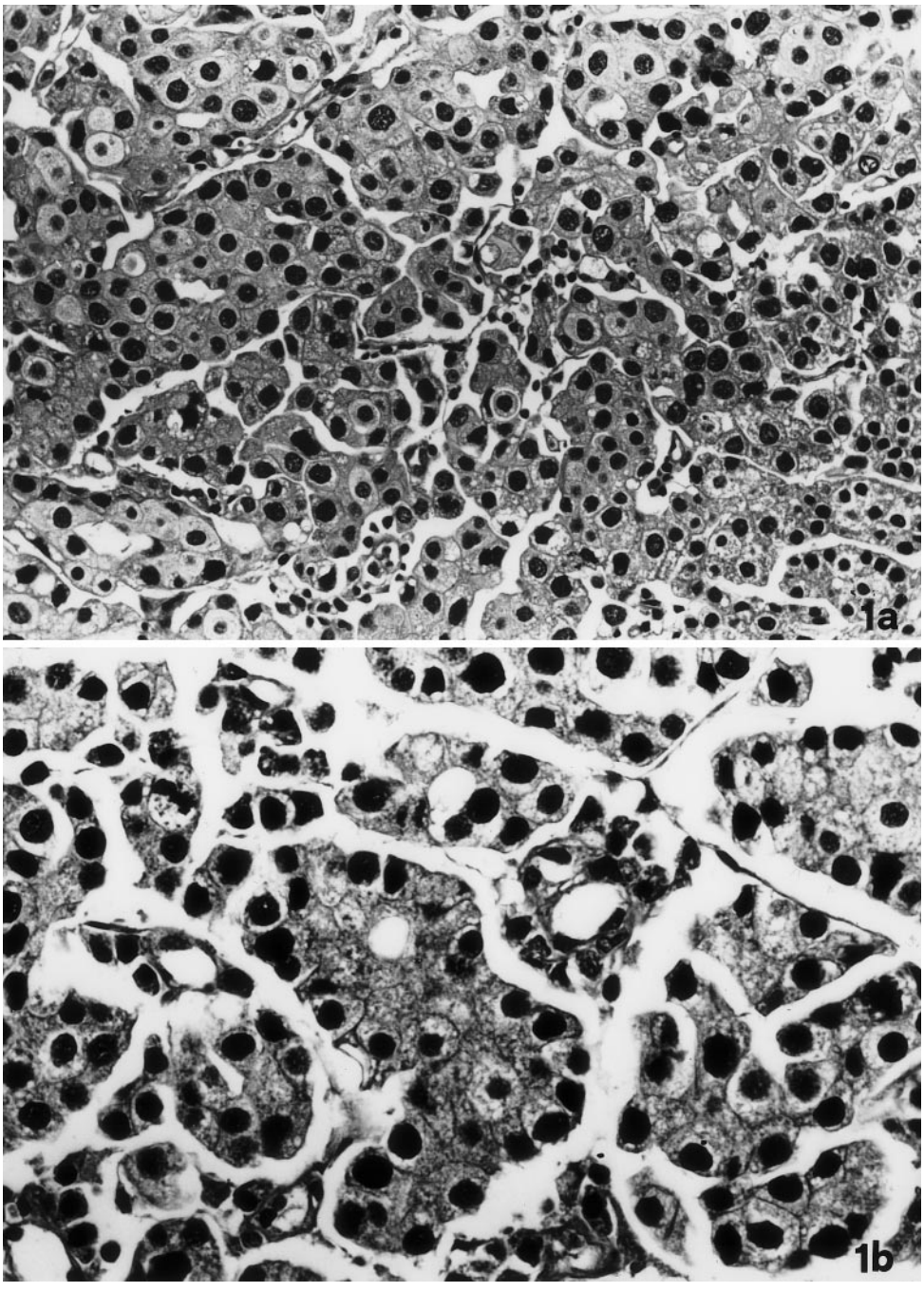


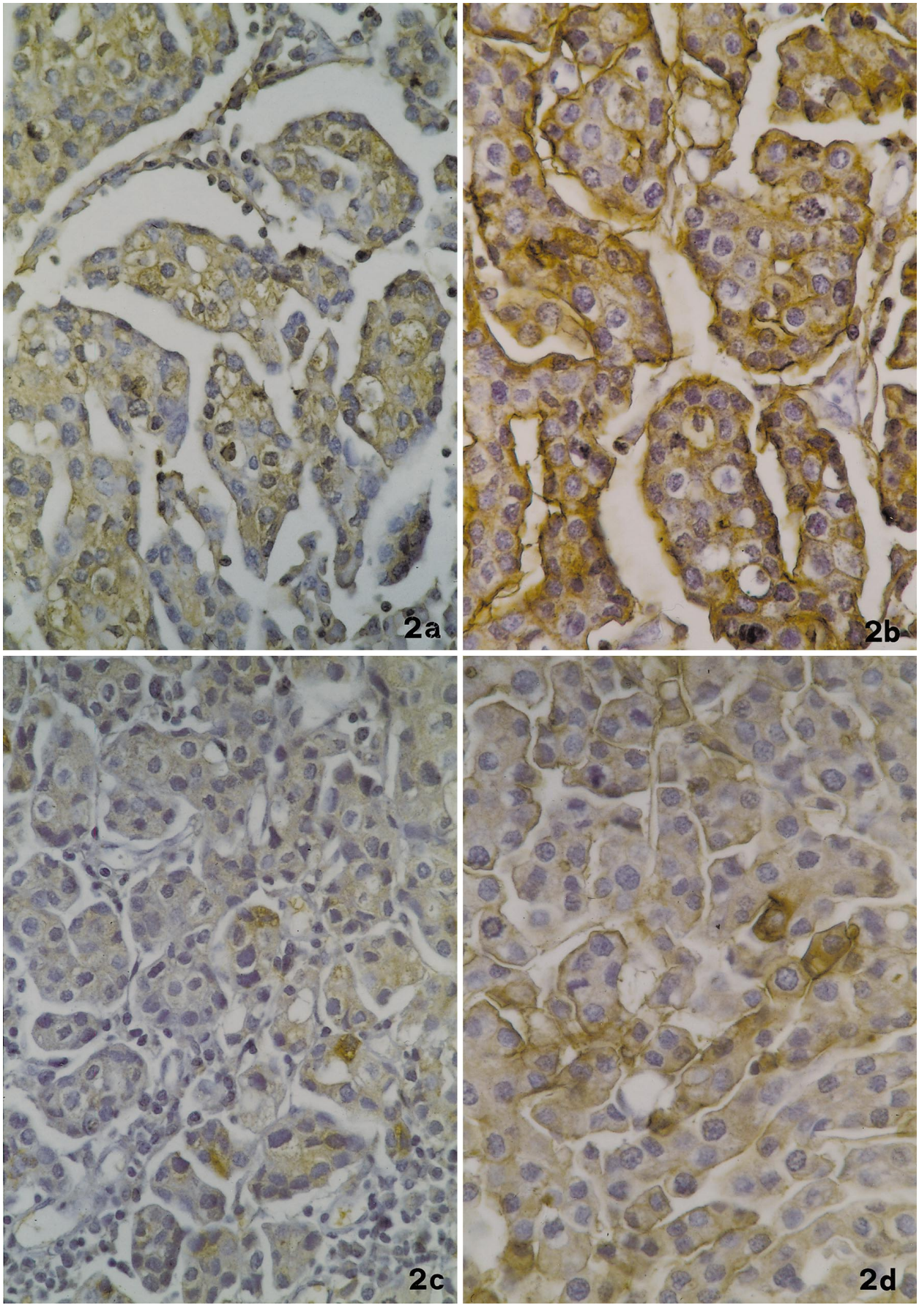
Fig. 1a, **b** Histopathological features of hepatoid adenocarcinoma of the urinary bladder: note the trabecular arrangement of polygonal neoplastic cells. H-E, ×200, ×400

hepatocarcinoma are very unusual and do not show a glandular pattern [8].

Hepatoid adenocarcinoma must be differentiated from other AFP-producing somatic tumours. These neoplasms have been described in many sites, especially in the gastrointestinal tract [1, 19, 20], but they lack the histological and immunohistochemical features of hepatoid adenocarcinoma. Furthermore, raised circulating levels of AFP do not always imply the activation of a hepatoid neoplasm [20]. However, hepatoid adenocarcinomas are not always accompanied by high levels of circulating AFP [16, 19]. In our case, the circulating AFP levels proved to be normal, although the cytoplasmic immunohistochemical expression of this marker was high in tumour cells.

Hepatoid adenocarcinomas usually present in elderly patients, being associated with a poor prognosis, with early development of nodal and visceral metastases [1,

Fig. 2 Immunocytochemical profile of hepatoid adenocarcinoma of the urinary bladder (ABC peroxidase). **a** Cytoplasmic positivity against AFP. ×200 **b** Expression of CEA with cytoplasmic and membranous-luminal staining. ×400 **c** Expression of HGF in a cytoplasmic pattern. ×200 **d** Membranous expression of c-met. ×400 ▶


2a
2b
2c
2d

16]. In our case the patient had retroperitoneal nodal metastases at the time of diagnosis.

HGF, also known as scatter factor (SF) is a cytokine that participates in cellular motility and angiogenesis, and acts also as a potent mitogen [4]. It has been detected in several normal and neoplastic tissues [3, 6, 9, 10, 17, 21], and its expression would not have any diagnostic value. It may have a prognostic significance, indicating a more aggressive biological behaviour. In fact, correlation between HGF-expression and a worse prognosis has been found in some neoplasms, with stronger local aggressivity and a higher metastatic rate [3, 7, 10, 23]. This may be determined by the fact that less differentiated and more invasive cell lines express higher levels of c-met receptors and respond to HGF with an increase in their motility and invasive capability [3].

Although they are exceptional in a urothelial location, hepatoid adenocarcinomas are tumours with an aggressive behaviour, which may be considered in the differential diagnosis of poorly differentiated neoplasms of urological origin, especially if there are high circulating levels of AFP.

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