CASE REPORT

Bladder perivascular epithelioid cell tumours

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Dr Rami Abou Ghaida,
ra172@aub.edu.lb**SUMMARY**

Perivascular epithelioid cell tumours, better known as PECOMAs, are a very uncommon pathological finding. In English medical literature it has rarely been reported. In the genitourinary system, mostly urinary bladder, the incidence is as low as 10 cases described since 2003 until now. In this case report, we present a urinary bladder PECOMA with a detailed pathological description and a review of literature.

BACKGROUND

This case will be the 11th described in the registry of bladders perivascular epithelioid cell tumours (PECOMAs).

CASE PRESENTATION

The patient was a 54-year-old man, previously healthy, heavy smoker (50 pack-years) who presented with gross painless haematuria on May 2012. He denied any previous lower urinary tract symptoms, fever or chills. The haematuria subsided on its own with conservative management (increased fluid hydration).

INVESTIGATIONS

Workup included an ultrasound and MRI of the kidneys and bladder that showed a suspicious right anterior wall bladder tumour (figure 1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included leiomyoma/leiomyosarcoma (ruled out by positive HMB45 staining), sarcomatoid carcinoma (ruled out by negative cytokeratin stains) and inflammatory myofibroblastic tumour (ruled out by positive smooth muscle markers, HMB45 and negative ALK).

TREATMENT

The patient underwent a transurethral resection of a bladder tumour in an outside hospital. The pathology read outside was consistent with a smooth muscle tumour. Immunohistochemical stains were not performed. The patient was then scheduled for a right partial cystectomy at our institution. The final pathological diagnosis was Spindle/epithelioid neoplasm with smooth muscle and melanocytic differentiation consistent with PECOMA. Histological features favour benign/low-grade behaviour.

OUTCOME AND FOLLOW-UP

Follow-up until April 2013 by cystoscopy and CT of the chest/abdomen/pelvis with intravenous and PO contrast showed a disease-free survival with no urological sequel from the partial cystectomy operation.

The segment of resected bladder measured 5×3×3 cm. It contained a well-circumscribed mass measuring 3×2.5×1.5 cm which was tan white, friable involving the entire thickness of the bladder wall. Histologically, the tumour involved the entire thickness of the muscularis propria and extended to the perivesicular fat. The tumour predominately had a pushing border but was focally infiltrative. It was composed of a monotonous population of spindle cells with focal epithelioid areas. The spindle tumour cells had elongated nuclei with blunt edges, abundant eosinophilic cytoplasm and showed mild-to-moderate cytological atypia with occasional mitosis (1 mitosis in 30 HPFs). The epithelioid cells had a nested pattern and clear cytoplasm. Focal areas showed granular brown pigment positive for iron stain. The tumour had numerous thin-walled blood vessels. There was no necrosis or vascular invasion seen (figure 2).

Immunohistochemically, the tumour cells demonstrated strongly positive for HMB45 (melanocytic marker) and smooth muscle actin (SMA), MyoD1 and caldesmon (smooth muscle markers) they failed to stain with other melanocytic markers (Melan A, S100), epithelial markers (CKAE1/AE3, CK7, CK20) GIST (CD117), neuroendocrine (synaptophysin) and inflammatory myofibroblastic tumour (ALK) markers (figure 3). CD34 was

Figure 1 MRI pelvis showing a right anterior bladder wall tumour.

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Figure 2 (A) Low-power view of urinary bladder PECOMAs showing focal infiltrative growth pattern (H&E×40). (B) The tumour shows a monotonous population of spindle cells with elongated nuclei and abundant eosinophilic cytoplasm (H&E×200). (C) Admixture of epithelioid and spindle patterns (H&E×200).

negative in tumour cells but highlighted numerous vascular channels. The proliferation index (Ki67) was 10%. All stains were performed with a positive and negative control.

DISCUSSION

The majority of primary bladder tumours are predominantly malignant tumours originating from the urothelium. However, there are several non-urothelial bladder tumours that can originate from any cell lineage. The latter include postoperative spindle cell nodule, inflammatory myofibroblastic tumour, leiomyoma/leiomyosarcoma, haemangioma, neurofibroma and perivascular epithelioid cell tumours, known as 'PECOMA'.

A review of the literature revealed only 10 cases of PECOMA involving the bladder reported in the English literature. Perivascular epithelioid cell tumours (PECOMAs) are defined as a family of mesenchymal tumours composed of histologically and immunohistochemically distinctive perivascular epithelioid cells that do not have a normal anatomic homologue.¹ They are mesenchymal neoplasms that show dual differentiation with both melanoma and smooth muscle characteristics. This is demonstrated pathologically by a spindle and epithelioid tumour with immunohistochemical positivity for melanoma markers (HMB45, Melan A tyrosinase and microphthalmia transcription factor) in addition to smooth muscle markers (SMA, MSA, calponin and caldesmon).

Initially described by Pea and colleagues as unusual cells in both angiomyolipoma and clear cell sugar tumour of the lung.¹ They are also now recognised as the cell of origin in lymphangiomatosis and unusual clear cell PECOMAs of the uterus, pancreas, thigh, heart and other sites.² PECOMAs are associated with tuberous sclerosis complex; the PECOMA cells can show

loss of heterozygosity in the TSC1 and/or TSC2 region which play a role in the regulation of the Rheb/mTOR/p70S6K signal pathway.^{3–5}

PECOMAs have been described in variety of sites starting from the base of skull down to the thigh.^{5–6} PECOMAs of the bladder are very rare. With only 10 cases reported in the English medical literature (table 1).

This rare tumour has a large pathological differential diagnosis which includes all spindle cell proliferations. The most common spindle cell neoplasm in the bladder is the sarcomatoid variant of urothelial carcinoma which is similar to the usual urothelial carcinomas except that it exhibits spindle cell morphology. This diagnosis is readily made by demonstrating origin from the urothelium and by positive immunohistochemical staining for cytokeratins. Other non-epithelial spindle cell proliferations include leiomyoma and leiomyosarcoma, malignant melanoma, clear sarcoma, inflammatory myofibroblastic tumour, postoperative spindle cell nodule and schwannoma. Immunohistochemistry is invaluable in arriving at the correct diagnosis. PECOMAs demonstrate positive immunostaining for markers of both myoid and melanocytic differentiation.⁷

PECOMAs are malignant tumours and bladder PECOMAs are no exception; their clinical behaviour varies widely from complete remission to local, distal metastasis and even death. PECOMAs are thus clinically ubiquitous tumour. Their presentation is similar to other bladder tumour and preoperative suspicion is almost impossible based on symptoms or imaging. In case of bladder PECOMAs, surgical resection represents the only curative option. This treatment modality was extrapolated from extragenitourinary PECOMAs since chemotherapy or radiation therapy have been inefficient in the different clinical trials.

Figure 3 Immunohistochemical profile: the tumour cells demonstrated strong and diffuse cytoplasmic positivity for HMB45 (A), smooth muscle actin (B) and caldesmon (C) (original magnification ×200).

Table 1 All bladder PECOMAs reported in literature

Author	Age/ gender	Pathology	Immunohistochemistry
Kalyanasundaram (2005)	19/F	Perivascularly arranged cells with granular eosinophilic fluffy cytoplasm, round-to-oval nuclei and prominent nucleoli	Positive for HMB45, negative cytokeratin, vimentin, S-100
Pan (2003)	33/F	Clear to eosinophilic, epithelioid and spindled cells arranged in fascicles or packets	Positive for HMB45 and smooth muscle actin but negative for S-100 protein, Melan-A, desmin and pan-cytokeratin
Parfitt (2006)	48/M	Epithelioid but occasionally spindled, with abundant cytoplasm that varied from eosinophilic and granular to clear	Positive for HMB45 (cytoplasmic), Melan-A (cytoplasmic) and smooth muscle actin (membranous, smooth muscle myosin heavy chain, desmin and CD117— S100 protein, cytokeratin (AE1/AE3, 8/18), vimentin, muscle-specific actin, myoglobin, CD31, CD34 and WT-1
Weinreb (2005)	39/M	Pleomorphic eosinophilic cells containing larger nuclei and prominent nucleoli, focal single cell necrosis and isolated mitotic figures	Positive for HMB45, S-100, smooth muscle actin, MSA
Sukov (2009)	36/M	Clear to partially eosinophilic cytoplasm, epithelioid and spindled cells	Positive for smooth muscle actin, HMB45, tyrosinase negative, Melan-A and desmin
Sukov (2009)	37/M	Large epithelioid cells with clear to finely granular, eosinophilic cytoplasm. A small component showing spindle cell	Negative for HMB45 and negative for high-molecular weight cytokeratin, pankeratin, vimentin, synaptophysin, chromogranin, CD56, Melan-A, S-100, inhibin and smooth muscle actin
Sukov (2009)	26/F	Fascicles of spindled cells with eosinophilic cytoplasm intermixed with epithelioid cells with clear cytoplasm arranged in a nested pattern	Negative for smooth muscle actin and vimentin, HMB45 tyrosinase negative for Melan-A, S-100, c-kit, muscle-specific actin and cytokeratin
Pianezza (2008)	24/F	Spindle cells, the cytoplasm was eosinophilic or clear	Positive for HMB45, S-100, caldesmon and actin positive. Negative for MART-1, CD34, K903, pankeratin, calretinin, CD99, ALK-1, C-Kit and desmin
Shringarpure (2012)	39/M	Spindled and epithelioid clear cell neoplasm	Positive for HMB45, vimentin, S-100, MSA, smooth muscle actin, negative cytokeratin and desmin
Kyrou (2012)	44/F	Bundles of uniform cells with variably clear or eosinophilic cytoplasm. In many areas the cells appeared to be epithelioid, whereas focally they were more spindled	Positivity for protein S-100 ,HMB45 negative for EMA, keratin and desmin

A full clinical or genetic workup for tuberous sclerosis is not necessary in case of bladder PECOMAs, since no association has been reported in the medical literature unlike cases of extrauro-genital PECOMAs. PECOMAs commonly involve mTOR

activating mutation. Many hypothesis that mTOR inhibitors, such as sirolimus, might benefits patients clinically especially in locally invasive and metastatic diseases. Until now, no randomised control trial has been conducted to prove the effectiveness of mTOR inhibitors as a treatment modality in PECOMAs. Its use remains based on case reports; physician should not omit the high cost burden when choosing this treatment modality option.

Learning points

- Owing to the rarity of perivascular epithelioid cell tumours (PECOMAs) in general and their extreme rarity in the bladder reliable criteria to determine their biological behaviour are lacking. Folpe *et al* proposed criteria for prediction of malignant behaviour in PECOMA. It included size greater than 5 cm, infiltrative growth, high cellularity, high nuclear grade, necrosis, vascular invasion and mitotic rate greater than or equal to 1/50 high power fields.
- Tumours with only nuclear pleomorphism ('symplastic' features) or size greater than 5 cm are classified as having uncertain malignant potential.⁷
- Wide surgical resection is the main treatment of PECOMAs, as most of tumours are malignant.
- Up to the date this review was written, no role for chemotherapy and/or radiotherapy in treatment of PECOMAs was confirmed. The use of mTOR inhibitors (ie, sirolimus) needs to be consolidated by randomised controlled trials.
- The pathological behaviour and prognosis has only been extrapolated from existing and reported cases. We advise on close follow-up by cystoscopy every 6 months and a yearly CT of the abdomen and pelvis. The optimal follow-up, timing and modality, will not be possible, except after a significant number of reported cases and analysis of their natural course of disease.

Competing interests None.

Patient consent Obtained.

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