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Primary small cell carcinoma of the ureter with associated hyponatremia and rapid progression to bladder involvement: a case report

Yu-Hsiang Chuang[1], Ghulam Mustafa Nandwani[1*], Magdelena Szewczyk-Bieda[2], Neil Kernohan[3] and Muhammad Zeeshan Aslam[2]

Abstract

Background: Primary small cell carcinoma (SmCCa) of the ureter is rare. The majority of patients present with visible haematuria. Diagnosis is confirmed by histopathology. Associated hyponatraemia in GU lesion can be due SmCCa can be useful for early diagnosis aggressive ureteric tumors. The current management includes radical surgery or radiotherapy with concomitant chemotherapy to improve survival and quality of life.

Case presentation: We present a case of a 77 years female who was found to have unilateral hydronephrosis with a 5 cm filling defect in the distal ureter on CT urogram. Further staging showed organ-confined disease. Serum sodium levels were low at presentation. At the time of planned nephroureterectomy (NU), cystoscopy revealed a bladder tumor obstructing the right ureteric orifice. TURBT was performed instead. After TURBT, there was marked hyponatremia and histology was small cell carcinoma (SmCCa). Paraneoplastic SIADH was the likely cause. Neoadjuvant chemotherapy (NACT) followed by radiotherapy (RT) was chosen for definitive treatment. This resulted in an excellent response supported by radiological evidence of almost complete resolution of the tumor.

Conclusion: The presence of genitourinary lesion and hyponatremia should raise suspicion of paraneoplastic SIADH. The case suggests the emphasis of histological diagnosis of the genitourinary lesion with existing hyponatraemia to provide better outcome with NACT followed by definitive treatment. We share our experience of NACT and RT in the management of ureteric SmCCa extension to the bladder.

Keywords: Small cell carcinoma, Ureter, Bladder, Hyponatremia, SIADH

1 Background

Primary small cell carcinoma (SmCCa) of the genitourinary (GU) tract is rare, accounting for less than 0.5% of all GU tumors [1]. SmCCa of the bladder accounts for less than 1% of all bladder cancers while SmCCa of the ureter is extremely rare [1]. Presentation of SmCCa of GU tract is no different from urothelial carcinoma. Ninety percent of the patients present with painless gross haematuria [1, 2]. Due to its aggressive nature, the prognosis of the disease is poor.

Diagnosis is usually confirmed by histopathological examination. The paraneoplastic syndrome can be a presenting or associated feature in patients with SmCCa. Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) in SmCCa of the lungs is well established but uncommon in extrapulmonary SmCCa [3]. There is no standard agreed management approach for GU

*Correspondence: Ghulam.Nandwani@nhs.scot

[1] Department of Urology, Ninewells Hospital and Medical School, Dundee DD9 1SY, UK
Full list of author information is available at the end of the article

SmCCa, however, multimodal treatment with chemotherapy and radical surgery or radiotherapy is the mainstay to improve survival and quality of life.

We report a case of SmCCa of the ureter which rapidly progressed to involve the bladder. Our patient had associated hyponatraemia at presentation and throughout the evaluation course, which was due to paraneoplastic SIADH.

2 Case presentation

A fit 77, non-smoker, female was evaluated for intermittently painless visible haematuria. There were no comorbidities or psychological issues. She did not have previous genetic analysis in view of no family history of cancers. General physical and abdominal examination was unremarkable. Flexible cystoscopy showed a normal bladder but oozing of blood from the right ureteric orifice. Serum creatinine and serum sodium at presentation was 66 mmol/L (eGFR > 60) and 126 mmol/L, respectively. She had no symptoms related to hyponatraemia at presentation. CT urogram (CTU) showed marked right hydronephrosis and hydroureter with a filling defect of 5 cm just above the vesicoureteric junction (Fig. 1). The urology multidisciplinary team meeting concluded that features were consistent with malignant neoplastic ureteric lesion and staging CT chest, abdomen, and pelvis (CAP) showed no evidence of metastasis or lymphadenopathy. In view of large ureteric lesion, normal renal functions and after full discussion of risk and benefits of surgical management, nephroureterectomy was planned.

Rigid cystoscopy at the time of planned right nephroureterectomy (6 weeks from the date of diagnosis) revealed a large lesion at the bladder base and right bladder wall. These findings suggested rapid extension of ureteric tumor in the bladder due to aggressive tumor. Both ureteric orifices were not visible, and a limited transurethral resection of bladder tumor (TURBT) was performed.

The histological features revealed a high-grade (G3) muscle invasive neuroendocrine small cell carcinoma. There was variable staining for cytokeratins, exhibiting dot like cytoplasmic staining for broad spectrum cytokeratins (AE1/3) but negative for another cytokeratin stain (MNF) as well for GATA3. The tumor cells were positive for synaptophysin and there was focal weak staining for CD56. The tumor was negative for TTF1 and CD45. (Fig. 2).

Subsequently, re-staging showed worsening hydronephrosis and a large mass measuring $4.2 \times 5.2 \times 4.2$ cm in the right posterior-lateral wall of the urinary bladder infiltrating into the perivesical fat consistent with the T3N0M0 stage of the disease (Fig. 3).

The patient developed marked hyponatraemia after TURBT (serum sodium of 117 mmol/L, serum osmolarity of 251 mmol/kg, urine sodium of 20 mmol/L and urine osmolarity 123 mmol/kg). The patient was euvolemic and had no neurological symptoms. Serum sodium levels improved to 129 mmol/kg with fluid restriction. Before presentation with visible haematuria, sodium levels were within the normal range. A decline in serum sodium levels from the normal ranges was seen since the onset of symptoms (Fig. 4). Serum cortisol and thyroid hormone levels were within the normal range. These results were supportive of the paraneoplastic syndrome of SIADH

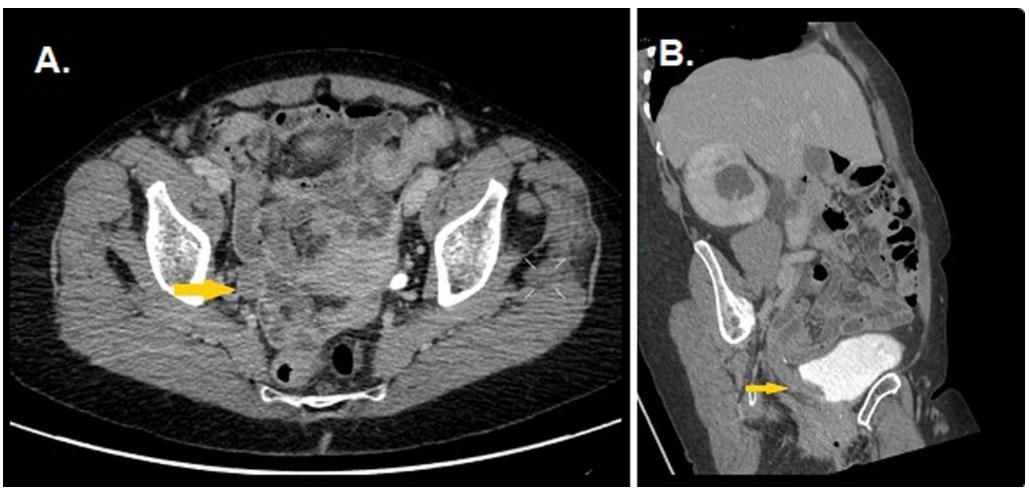

Fig. 1 (Pre NACT): Axial (**A**) and sagittal oblique (**B**) reconstructions from CECT in urographic phase showing enhancing lesion distending the right distal ureter (yellow arrow) with evidence of upstream hydroureter and hydronephrosis with delayed excretion from the right kidney (**B**)

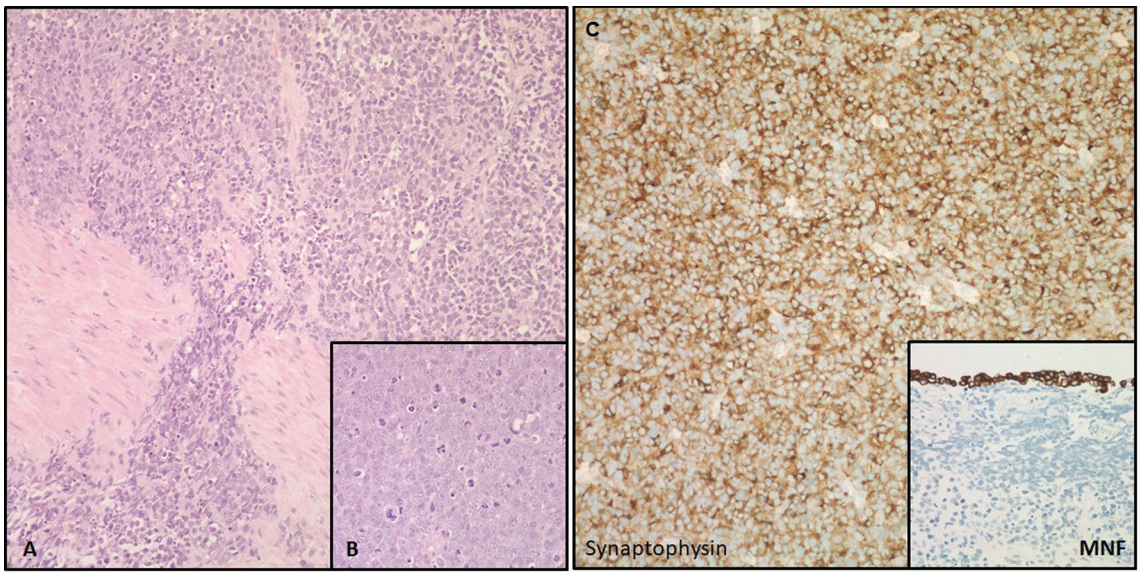

Fig. 2 A medium power view of the lesion (**A**) showing features of a high-grade malignant tumor that is muscle invasive. The tumor shows no overt evidence of urothelial differentiation, but the morphological features do suggest a neuroendocrine phenotype. A higher power view (**B**) demonstrates prominent proliferation with numerous mitotic figures, some atypical, together with evidence of apoptosis. The tumor shows widespread positive staining for synaptophysin (**C**)

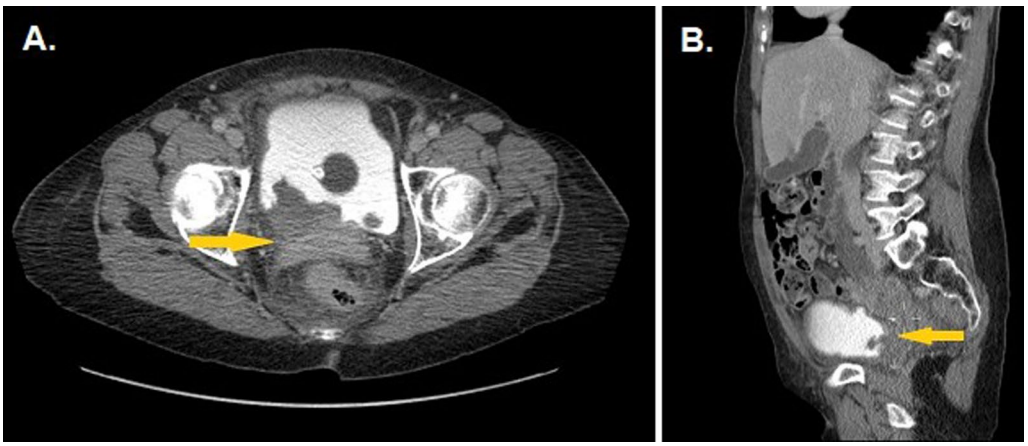

Fig. 3 (Pre NACT): Axial (**A**) and sagittal (**B**) reconstructions from CECT in urographic phase showing a progression from previous CT with large filling defect in the right lateral aspect of the urinary bladder infiltrating into base of bladder and loss of fat plane between the lesion and uterine cervix (yellow arrow)

secondary to SmCCa. DMSA scan showed a 19% split function in the right kidney. Percutaneous nephrostomy was not inserted as per the patient's preference. Six cycles of neoadjuvant chemotherapy (NACT)—Carboplatin and half dose of Etoposide were given due to reduced renal function (eGFR: 36 ml/min). Sodium levels improved and remained improved to normal range with NACT (Fig. 4).

Re-staging CT CAP after NACT showed an almost complete resolution of bladder and ureteric lesion (Fig. 5). Radical surgery and radiotherapy were discussed for definitive management via a multidisciplinary approach. The patient opted for radical radiotherapy and accepted no further invasive intervention. The patient completed consolidation radiotherapy (40 Gy in 15 fractions) to the bladder and lower ureter. Surveillance CT CAP and further surveillance showed no evidence of disease progression, at last, follow-up of 20 months.

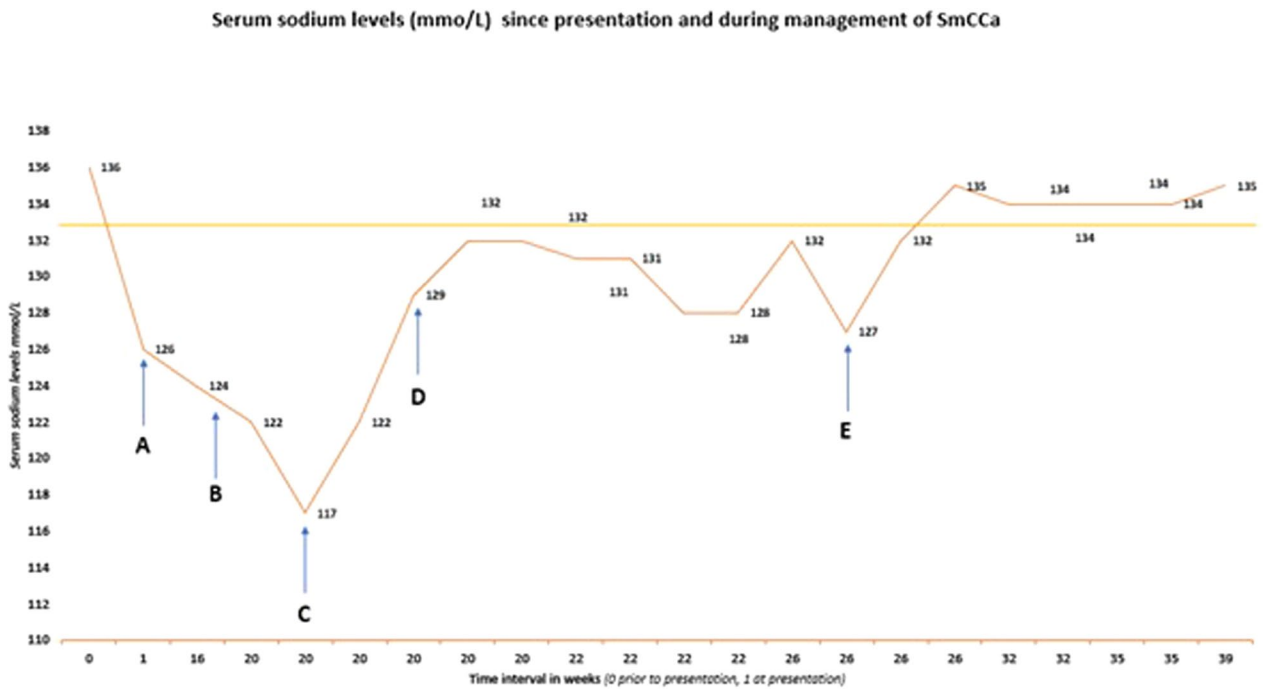

Fig. 4 Serum sodium level since presentation to treatment of SmCCa. Yellow straight line, lower limit of normal range (133 mmol/L); (A) first presentation of symptom; (B) pre-assessment clinic; (C) after TURBT; (D) after strict fluid restriction; (E) commencement of NACT

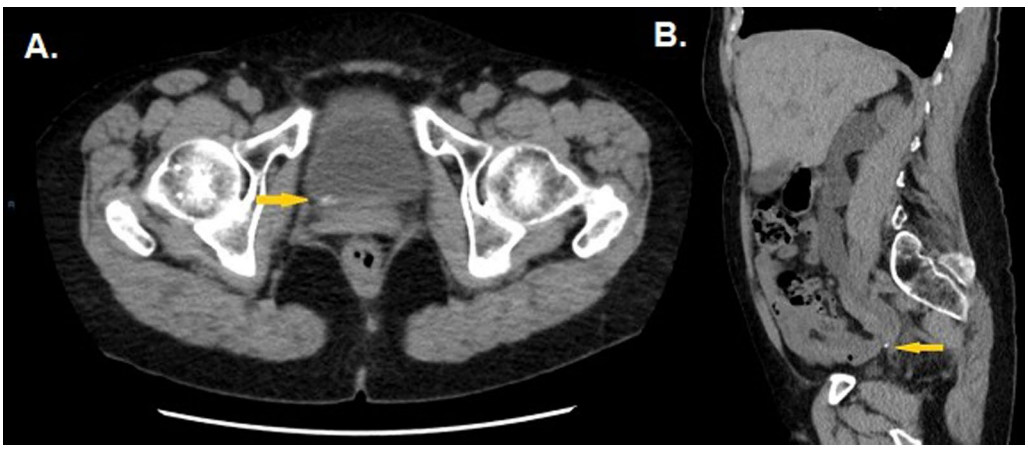

Fig. 5 (Post NACT): Axial (**A**) and sagittal (**B**) reconstructions from follow up CECT in portal venous phase showing almost complete resolution of the lesion with development of focal area of calcification (yellow arrow)

3 Discussion

SmCCa is highly aggressive cancer and also known as undifferentiated carcinoma, small cell anaplastic carcinoma, neuroendocrine small cell carcinoma and oat cell carcinoma. The most common site is lung however it can be found in any organ. GU SmCCa is uncommon. The most common site of SmCCa is the bladder (58.8%) and prostate (33.3%) [2]. Upper tract SmCCa is very rare (renal 4.4% and ureter 3.3%). The pathophysiology of GU SmCCa is unclear. It is possibly derived from the urothelium with neuroendocrine differentiation or from neuroendocrine cells that are already present in the urinary tract. An alternative hypothesis is that these cells originated from a multipotential stem cell with the potential to differentiate into various tissue types (transitional cell, squamous cell, neuroendocrine cell, etc.) [4].

Table 1 Summarized data from primary ureteric SmCCa reported in the literature

Authors	Age/Sex	Symptoms	Location	Staging	Pathology	Treatment	Follow up (months, status)
Present case	77 F	Haematuria	Right	T3N0M0	AE/AE3, Syn, CD56	NACT + RT	20 months, AWNR
Zhao et al	70 F	Flank pain	Left	T3N0M0	CgA, CD56, Syn, NsE	NU	9 months, DOD
Akshay et al	55 F	Flank pain, haematuria	Right	T3N2M0	Syn	NACT + NU	3 months, AWNR
Farci et al	79 F	Flank pain, haematuria	Right	T3N1M0	CgA, Syn, CD56	NACT (1cycle), SU	5 months, DOD
Sato et al	63 M	Flank pain	Right	T3N0M0	AE1/AE3, Syn	NACT + NU	6 months, AWNR
Jang et al	59 M	Haematuria	Left	T2N0M0	NsE, CD56, Syn, CgA	NACT + RT	10 months, AWNR
Ahsaini et al	54 M	Haematuria	Left	T2N0M0	NsE, CgA, Syn	NACT + NU	24 months, AWNR
Kozyrakis et al	78 M	Haematuria	Right	T3N0M0	CD56, Syn, CgA	NU	6 months, DOD
Kho et al	77 M	Flank pain	Left	T3N0M0	CgA	NACT + NU	4 months, DOD
Osaka et al	70 M	Flank pain	Left	T3N0M0	CD56, Syn	NACT + NU	38 months, AWNR
Rupert et al	72 M	Asymptomatic	Right	T3N0M0	CD56, Syn, CgA	NU + Chemo	22 months, AWR
Hensley et al	67 F	Flank pain, haematuria	Left	T4N1M0	Syn, CgA	NU + Chemo + RT	7 months, DOD
Ouzzane et al	66 F	Flank pain	Left	T3N0M0	CD56, CgA, Syn	Nil	5 months, DOD
Yang et al	70 F	Flank pain	Left	T3N0M0	CgA	NU	9 months, AWR

Only cases written in English and of proven primary SmCCa without synchronous neoplasms elsewhere in urinary tract or in different organs are reviewed

AWNR alive with no evidence of recurrence, *AWR* alive with recurrence, *DOD* dead of disease, *NU* nephroureterectomy, *SU* segmental ureterectomy, *M* male, *F* female, *NsE* neuron specific enolase, *CgA* Chromogranin A, *Syn* synaptophysin

It is most commonly found in the seventh decade, with a male to female ratio of up to 5:1 [1, 2]. Visible haematuria is the most common presentation and diagnosis is usually made on histopathological examination [3, 5]. Outcomes of GU SmCCa remain poor as it typically presents with locally advanced or disseminated disease. In a review, metastases were found in 40% of patients with median overall survival (OS) of 10.5 months [2]. Our patient was found to have a ureteric tumor which rapidly progressed to involve the bladder within 6 weeks from the diagnosis, suggesting an extremely aggressive tumor kinetic.

For primary SmCCa of the bladder, OS is 18 to 20.7 months with 3 years and 5 years OS 37.5% and 28.2%, respectively [6]. Age, gender, marital status, the ratio of the positive lymph nodes, size of the tumor, T stage, NACT and downstaging, have all been shown to be significantly associated with OS [2, 6]. The OS of SmCCa of the bladder treated with radiotherapy (RT) ranges between 20% and 70% while survival of 25% to 78% is reported with radical cystectomy (RC) [7–10]. NACT with Cisplatin-based chemotherapy showed better survival to (CSS 78%) patients who had RC only (CSS 36%) [10]. It is hard to compare long-term outcomes between NACT + RT and NACT + RC due to the lack of randomized controlled studies, however, both are associated with increased OS compared to monotherapy [10–12].

Due to the rarity of upper tract SmCCa, management guidance is only available from case reports. Majhail et al. reported a median OS of 8 months in 22 renal SmCCa. OS after RN and RN with chemotherapy was 5 months and 8.5 months, respectively [13]. Progression-free survival of 24 months to 38 months was reported when patients received platinum-based NACT before radical surgery. It seemed that multimodal treatment with platinum-based NACT followed by surgery provided a better outcome. A summary of ureteric SmCCa case reports is presented in Table 1.

Tumor related hyponatraemia is very with GU SmCCa and only six case reports in the literature described SIADH related hyponatremia associated with GU SmCCa [3, 5]. Five out of six studies showed association with prostate SmCCa. It was seen that SIADH associated with GU SmCCa resolved with chemo-radiotherapy or radical resection [3, 5]. In our case patient had normal sodium levels prior to the presentation with haematuria and hyponatremia was noted at presentation which became more severe after TURBT. Further investigations concluded that this was due to SIADH secondary to SmCCa. In our patient, sodium levels became normal after treatment with NACT and RT.

This case has provided sequential management outcomes since presentation to the last surveillance follow up for at least 20 months duration with good outcome. As this is rare to have SmCCa of ureter and even more rare to have associated SIADH with such tumor, it will add better understanding in management of these cancers. The case study is limited by retrospective data collection.

In summary, haematuria and hyponatremia were our patient's first clinical manifestations, leading to the discovery of SmCCa of the ureter. To our knowledge, this

case represents the only documented case of paraneoplastic SIADH attributable to ureteric SmCCa with progression to the bladder.

4 Conclusions

The presence of hyponatraemia and GU lesion should raise the suspicion of paraneoplastic SIADH secondary to SmCCa. Biopsy of GU lesion with such presentation could help in the decision of NACT before definitive surgical management. This case also demonstrated the effectiveness of NACT and RT in the management of ureteric SmCCa.

Abbreviations

CSS: Cancer Specific Survival; CT CAP: CT Chest, Abdomen and Pelvis; CTU: CT Urogram; CECT: Contrast Enhanced CT; GU: Genitourinary; NU: Nephroureterectomy; NACT: Neoadjuvant Chemotherapy; RT: Radiotherapy; RC: Radial Cystectomy; SmCCa: Small Cell Carcinoma; SIADH: Syndrome of Inappropriate Anti-Diuretic Hormone; TURBT: Trans Urethral Resection of Bladder Tumor; VUJ: Vesicoureteric junction.

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Author contributions

YC, performed data collection and drafted the manuscript. GMN, critically reviewed and edited manuscript. MSB, provided radiological input, edited CT images and reviewed manuscript. NK, provided pathological images and wrote pathological part of the manuscript. MZA, reviewed the manuscript and suggested changes. All authors read and approved the final manuscript.

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Declarations

Ethical approval and consent to participate

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Consent for publication

The patient has provided consent for the publication.

Competing interests

All the authors declare no competing interests.

Author details

[1]Department of Urology, Ninewells Hospital and Medical School, Dundee DD9 1SY, UK. [2]Department of Radiology, Ninewells Hospital and Medical School, Dundee DD9 1SY, UK. [3]Department of Pathology, Ninewells Hospital and Medical School, Dundee DD9 1SY, UK.

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