

Case of the Month

'Case of the Month' from the University of Verona, Italy—navigating the medical and surgical challenges of urinary bladder paraganglioma: insights from a clinical case

Lorenzo Pierangelo Treccani^{1,2} , Francesco Artoni^{1,2}, Claudio Brancelli^{1,2}, Alessandro Veccia² , Mirko D'Onofrio^{1,3}, Isabella Pichiri^{1,4}, Matteo Brunelli^{1,5}, Riccardo Giuseppe Bertolo^{1,2}  and Alessandro Antonelli^{1,2}

¹University of Verona, ²Department of Urology, AOUI Verona, ³Department of Radiology, GB Rossi University Hospital, ⁴Division of Endocrinology, Diabetes and Metabolic Diseases, and ⁵Section of Pathology, AOUI Verona, Verona, Italy

The Case Report

A 44-year-old woman came to us with a history of two paravesical masses, monitored via radiological imaging for 10 years.

The patient's medical history revealed multiple episodes of pulmonary embolism after orthopaedic surgery since the age of 22 years. The patient tested negative for any form of coagulopathy. To note, the patient had developed hypertension at a young age, necessitating polypharmacotherapy, accompanied by additional adrenergic symptoms such as flushing, limb tremors, panic attacks, and palpitations.

The first diagnosis of bladder masses occurred incidentally during a routine abdominal ultrasonography scan performed in the setting of an episode of suspected cystitis. Subsequent cystoscopy revealed two bulges on the left lateral wall, covered by normal bladder mucosa. The patient was followed up with repeated ultrasonography scans; neither clinical nor radiological alterations were noted until the patient reported an episode of gross haematuria in 2022. Subsequent abdominal CT scan and MRI (Figs 1 and S1) revealed a solid mass, 4.5 cm in maximum size, located near the posterior left bladder wall (in contact with but not infiltrating, the cervix) and another mass measuring 2.1 cm near the left lateral bladder wall.

Operative cystoscopy with biopsy was performed, which caused a hypertensive crisis complicated by acute pulmonary oedema, which required intubation and admission into the intensive care unit. The biopsy specimen's final pathology examination confirmed a bladder paraganglioma.

Further investigations during the hospital stay included a thorough cardiological evaluation (echocardiography, coronary CT-angiography), which suggested an atypical Takotsubo syndrome.

Takotsubo syndrome, also known as stress cardiomyopathy or 'broken heart syndrome', is a temporary heart condition that

often mimics the symptoms of a heart attack. It is typically triggered by severe emotional or physical stress. The syndrome gets its name from the Japanese word 'takotsubo', which means 'octopus pot', due to the distinctive shape of the left ventricle seen in imaging tests during the condition [1].

Blood tests (serum chromogranin A, metadrenalines, and normetadrenaline) and urine analysis (urinary metadrenaline and normetadrenaline) revealed elevated levels of chromogranin A and normetadrenaline, while metadrenaline levels remained normal. A whole-body CT scan excluded distant metastases. Positron emission tomography (PET)/CT using gallium-tetraazacyclododecane tetraacetic acid (⁶⁸Ga-DOTA)-conjugated somatostatin receptor–targeting peptide and ¹⁸F-dihydroxyphenylalanine (DOPA) revealed hyper-fixation at the level of the masses, along with two small ileal foci and a right breast nodule (Fig. 2). These extravesical localisations were excluded from being metastatic. Genetic evaluation revealed a succinate dehydrogenase B subunit (*SDHB*) mutation linked to familial paraganglioma (paraganglioma type PGL4) [2].

After a careful multidisciplinary evaluation, given the masses' size and the patient's age, the patient was counselled for bladder-sparing robot-assisted laparoscopic surgery (summarised in Video S1).

Prior to the operation, the patient first received alpha-blockade, followed by beta-blockade, and underwent aggressive intravenous fluid resuscitation while being treated in the endocrinology department. The surgery began by placing a left ureteric single-J stent in a retrograde fashion during cystoscopy. The robot-assisted laparoscopic phase started with incising the peritoneum at the level of the vesico-uterine pouch. The bigger mass was identified: its pedicle was first isolated, clipped, and divided. Only after controlling the pedicle was the dissection of the mass carried out. Notwithstanding the additional care, during the dissection of the main mass, a hypertensive crisis occurred (270/

Fig. 1 The contrast-enhanced arterial phase of abdominal CT, in axial, sagittal, and coronal planes, showcases the two bladder masses: the bigger slightly hyperdense and the smaller distinctly hyperdense.

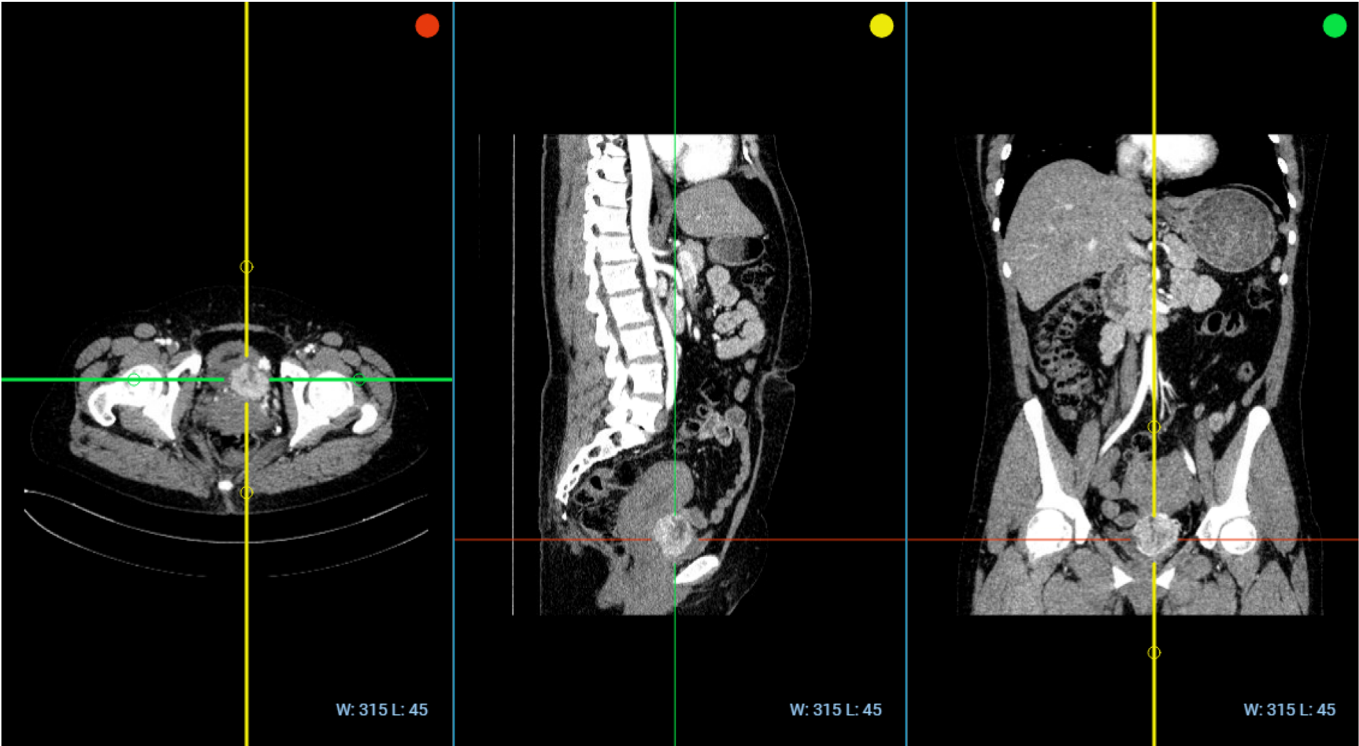
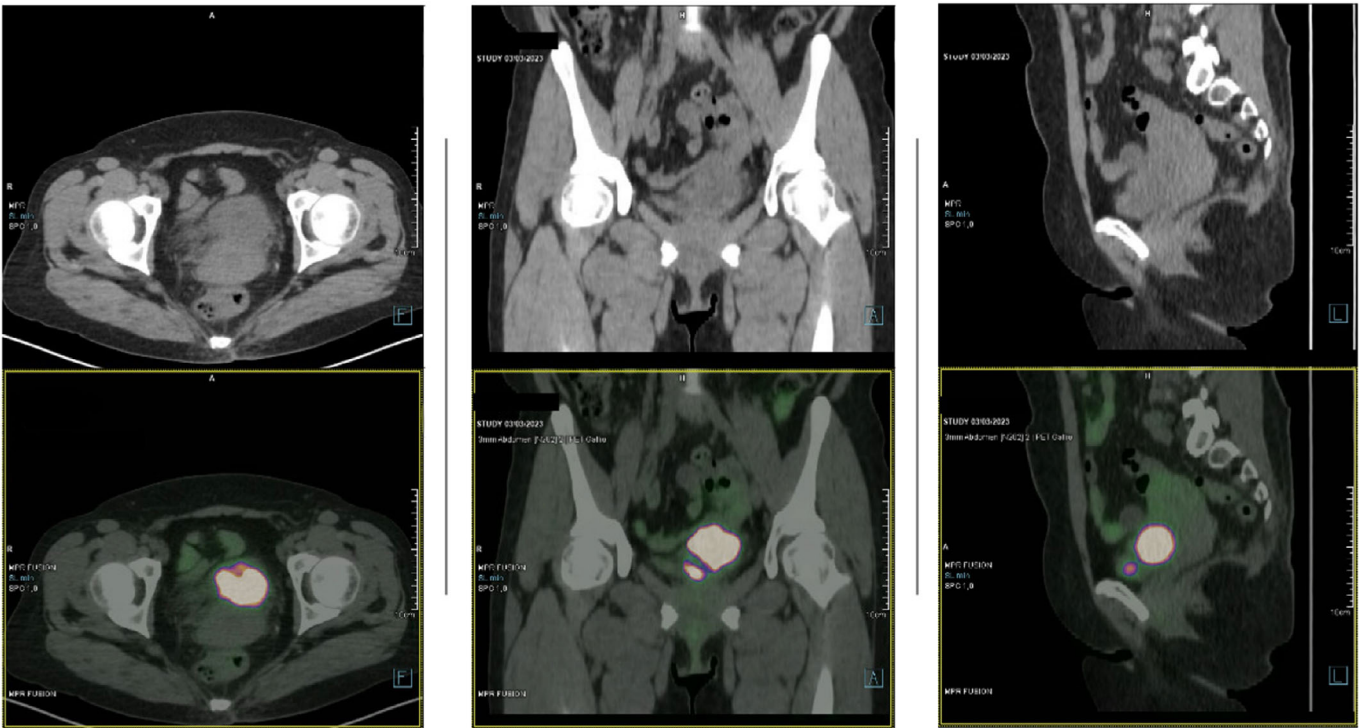


Fig. 2 The ^{68}Ga -DOTA-conjugated somatostatin receptor-targeting peptide imaging in (left to right) axial, coronal, and sagittal planes, showcasing the two bladder masses.



150 mmHg) with initial pulmonary oedema. The surgical procedure had to be paused, and the robot had to be undocked for ~10 min to allow for intensive care manoeuvres. The patient was positioned in an anti-Trendelenburg position. Beta-blockers and sodium nitroprusside were administered. The initial response was severe hypotension; however, normal blood pressure values were achieved only after the titration of the nitrate. In the case of nitrates, the titration involves starting with a low dose and gradually increasing it based on the patient's response regarding blood pressure, heart rate, and symptoms until the desired effect is achieved.

Once haemodynamic stability was achieved, the robotic part continued with the completion of the excision of the bigger mass, performed by a combination of extra- and transvesical approaches.

The second smaller mass was identified during the transvesical approach: first, the pedicle was secured. Second, the mass was excised with an extravesical approach. During the excision of the smaller mass, no intraoperative anaesthesiological adverse events occurred. The bladder defect was sutured in a double-layer fashion.

The postoperative course was uneventful. A drain and a Foley catheter were kept *in situ* for 2 and 10 days, respectively; the ureteric stent was removed after 7 days.

The pathological and immunohistochemical examination revealed a well-differentiated tumour, showing the typical cell-nests, synaptophysin, and chromogranin positive, suggesting paraganglioma (Fig. 3). Genetic analysis revealed mutations of *SDHB*, which are associated with an aggressive

clinical presentation of paraganglioma (and pheochromocytoma).

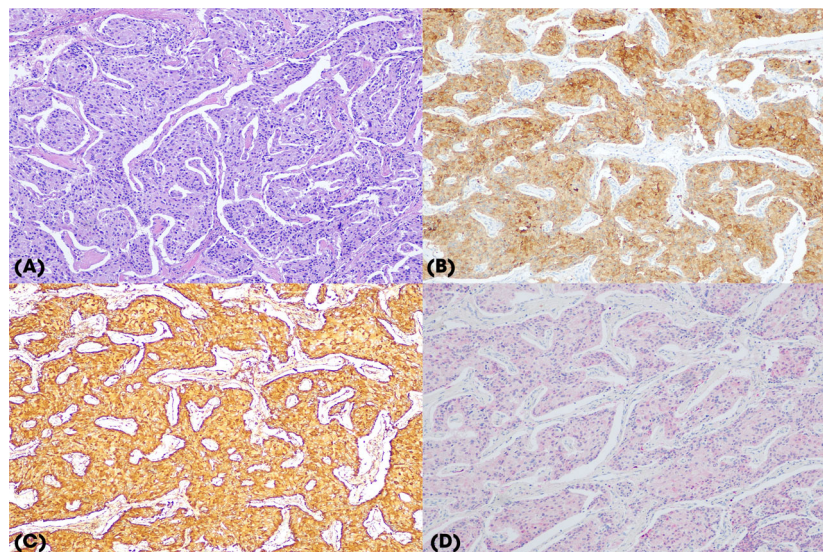
Discussion

Urinary bladder paraganglioma is rare, accounting for 0.05% of all bladder neoplasms. Paraganglioma is the denomination of any extra-adrenal pheochromocytoma. It is estimated that ~10% of all pheochromocytomas are extra-adrenal, and ~10% of these occur within the bladder wall. The tumour originates from the chromaffin tissues of the sympathetic nervous system located in the detrusor muscle of the urinary bladder; most commonly, they are located at the dome or the trigone. Paragangliomas can occur at any age, but the mean age at diagnosis is 43 years [3].

They are typically benign, but a variable percentage of cases can be malignant, mostly when associated with hereditary syndromes such as the *SDH* mutation (familial paraganglioma syndromes). Malignancy is associated with younger age, larger and multiple masses, and metastases [3].

Signs and symptoms depend on whether the tumour is functional or non-functional. Functional tumours secrete catecholamines (adrenaline and noradrenaline), causing a variety of presenting symptoms (hypertensive crises, headache, palpitations, hot flushes, and sweating). These could also be present only when provoked by micturition (micturition syncope), defecation, sexual activity, ejaculation, or bladder/urethral instrumentation. The most common bladder-specific sign is painless haematuria, although it is non-specific. Biochemistry plays a key role in functional tumours: plasma and urine catecholamines and

Fig. 3 Haematoxylin and eosin staining of bladder paraganglioma tumour (A) showing characteristic nests of cells ('Zellballen') with eosinophilic cytoplasm and round nuclei. Synaptophysin (B) and chromogranin (C) staining was strongly positive, while S100 staining (D) was positive in patches.



metadrenalines (more sensitive and specific) levels are usually elevated. Chromogranin A is also often elevated [3].

The primary tumour is usually diagnosed through cross-sectional imaging (either CT or MRI): common findings at MRI are a well-circumscribed round vascularised lesion that is hyperintense in T2 ('lightbulb sign'). The best PET/CT imaging for diagnosing paragangliomas is typically ^{68}Ga -DOTA-conjugated somatostatin receptor-targeting peptide. This imaging technique uses gallium-68 labelled with DOTA-Tyr3-octreotate, a somatostatin analogue. It targets somatostatin receptors, often overexpressed in neuroendocrine tumours, including paragangliomas. While ^{68}Ga -DOTA PET/CT is highly regarded, other imaging techniques such as ^{18}F -fluorodeoxyglucose (FDG) PET/CT and ^{131}I -metaiodobenzylguanidine (MIBG) scintigraphy may still be used in specific scenarios: ^{18}F -FDG PET/CT is useful for paragangliomas that do not express somatostatin receptors; however, it is less effective for small, indolent tumours; ^{131}I -MIBG scintigraphy is primarily indicated for pheochromocytomas, but can also be used for paragangliomas that uptake MIBG. Unfortunately, it may miss non-functioning paragangliomas or those not taking up MIBG [4].

Cystoscopy, when performed, shows normal mucosa and an underlying mass bulging it. Transurethral manipulation and biopsy of functional paragangliomas could lead to potentially life-threatening cardiac events due to massive catecholamine release. This was the case of the first interventional cystoscopy performed at another institution before the patient came to us.

For the same reason, an endoscopic, transurethral approach as a treatment option should be avoided. As such, it often leads to incomplete resection and a high risk of perioperative cardiac events, particularly when a correct histopathological or clinical diagnosis has yet to be made [5]. Moreover, the endoscopic approach lacks the control of the vascular pedicle of the mass that a surgical approach (either open, laparoscopic, or robot-assisted) guarantees.

For these medical reasons, preoperative care is fundamental. About 2 weeks before surgery, alpha-blockade should be started, preferably with an irreversible alpha-blocker such as phenoxybenzamine. This molecule irreversibly binds to the alpha receptors, rendering any potential intraoperative catecholamine release from tumour manipulation 'harmless', as it would require *de novo* synthesis of alpha receptors for the catecholamines to exert their effect. Beta-blockade should be introduced (mainly to treat side effects from alpha-blockade) only after reaching the appropriate alpha-blockade. Otherwise, it would increase the affinity of catecholamines for the α_1 receptors. Finally, 1–2 days before surgery, aggressive intravenous hydration to restore the intravascular volume should be initiated to avoid postoperative severe hypotension given the prolonged effect of alpha-blockade [6].

After proper preparation, surgical excision is the mainstay treatment because paraganglioma is chemo-radioresistant. A radical excision of the mass should be performed whenever feasible. This is usually achieved through a partial cystectomy. Indeed, the bladder mucosa at the base of the mass should always be removed. In selected cases (large masses, metastases, suspected malignancy), radical cystectomy can be indicated. Pelvic lymph node dissection should be performed when a radical cystectomy is indicated, although there is not sufficient evidence supporting this choice [7].

Histopathological examination shows polygonal cells arranged in a nested fashion ('Zellballen'), surrounded by a fibrovascular matrix [8]. This pattern could trick the pathologist's eye and be confused with a nested variant of TCC. Immunohistochemistry shows positivity for chromogranin A, synaptophysin, and GATA binding protein 3 (GATA-3); cytokeratins are negative [3].

A summation section of the most relevant diagnostic evaluation, medical, and anaesthesiological information is provided as Data S1 at the reader's convenience.

In summary, our case report underscores that not all patients with gross haematuria should be treated equally. Specifically, the presence of a mass bulging on the bladder mucosa in a younger patient with adrenergic symptoms should suggest at least considering the possibility of a bladder paraganglioma. This could help reach a correct diagnosis before any invasive manoeuvre is performed. Moreover, it would avoid potentially fatal perioperative adverse events or incomplete excision of the mass typical of transurethral resections performed before confirming paraganglioma diagnosis [9].

Once surgical removal of a diagnosed bladder paraganglioma is indicated, despite cautious premedication of patients, the experience of the surgeon, and necessary surgical precautions in handling these formations before controlling their vascular pedicles, it must be remembered that surgery is not straightforward when such paragangliomas are functional. This holds true both from a technical standpoint and, more importantly, considering its potential anaesthesiological implications.

Acknowledgements

None.

Disclosure of Interests

The authors have no conflict of interest.

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Correspondence: Riccardo Bertolo, Azienda Ospedaliera Universitaria Integrata Verona, AUOI Verona, Borgo Trento

Hospital, University of Verona, Piazzale A. Stefani 1, 37126 Verona.

e-mail: riccardogiuseppe.bertolo@univr.it

Abbreviations: DOTA, tetraazacyclododecane tetraacetic acid; FDG, fluorodeoxyglucose; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; *SDHB*, succinate dehydrogenase B subunit.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Axial T2-weighted MRI of the pelvis shows two masses within the left posterior bladder wall; the sequence shows the bigger mass to be hyperintense ('lightbulb sign').

Data S1. Supplementary material.

Video S1. Summary of the case report and the bladder-sparing robot-assisted laparoscopic surgical excision of the paragangliomas.