Case Report

Non-functional muscle-invasive bladder paraganglioma—a case report

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Background: Extra-adrenal pheochromocytoma (paraganglioma) of the urinary bladder is a rare tumor, accounting for 0.05% of bladder tumors and less than 1% of all paragangliomas. In the genitourinary tract, paragangliomas are most commonly found in the bladder. These tumors have aggressive malignant potential, so complete surgical resection for localized disease is important. Paragangliomas may be non-functional or functional with catecholamine secretions. Although these tumors are rare and difficult to distinguish from urothelial carcinoma (UC), intraoperative manipulation of these tumors may lead to a catecholamine surge and intraoperative complications. Preoperative or early intraoperative recognition of this tumor would facilitate appropriate alpha blockade to minimize morbidity.

Case Description: Herein we report a rare non-functional paraganglioma arising from the bladder of a 46-year-old male. This case is notable for the location of the mass, requiring a 70-degree cystoscopic lens for complete visualization near the bladder neck, and for the identification of a golden-yellow sessile mass during the resection. Upon visualization of this mass, the operation should be paused for close hemodynamic monitoring and assess for signs of hypertensive crisis prior to continuing without alpha blockade.

Conclusions: Suspected localized bladder paraganglioma cases should be optimized hemodynamically and managed surgically. Visualization of a sessile bladder mass on gross examination with golden-yellow tumor during the resection should prompt suspicion for a paraganglioma. Biochemical evaluation with serum or urine catecholamines, metanephrines, and normetanephrines should be performed to assess for tumor functionality.

Keywords: Paraganglioma; non-functional paraganglioma; variant histology bladder cancer; case report

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Introduction

Pheochromocytoma of the urinary bladder, also known as bladder paraganglioma, is a rare condition, accounting for 0.05% of bladder tumors and less than 1% of all paragangliomas (1). These originate as tumors of chromaffin cells and usually arise from the adrenal medullae; in 10% of cases, they are extra adrenal (1).

In the genitourinary tract, paragangliomas are most commonly found in the bladder (79.2%), urethra (12.7%), pelvis (4.9%), and ureter (3.2%). Up to 50% of cases which present as Ta or T1, progress to extravesical spread or distant metastasis (2,3). Given the poor prognosis and high rates of disease progression, complete surgical resection for localized disease is paramount.

Bladder paragangliomas can be functional due to

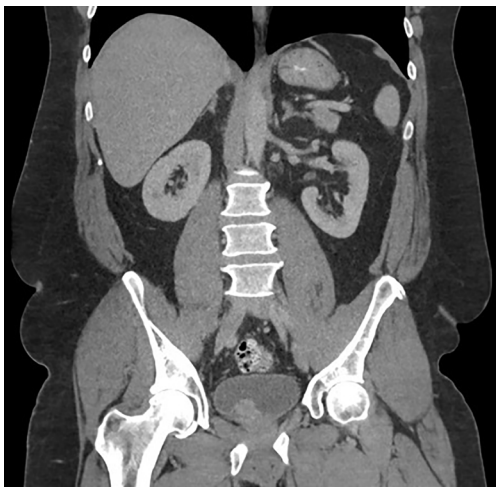

Figure 1 CT abdomen/pelvis, prior to any TURBT, demonstrating an enhancing mass along the right inferior urinary bladder. CT, computed tomography; TURBT, transurethral resection of bladder tumor.

Highlight box

Key findings

- Paraganglioma of the bladder is a rare sessile tumor that may be non-functional or functional tumors. They appear golden brown in color during resection, which is unique from urothelial carcinoma of the bladder.

What is known and what is new?

- These paraganglioma tumors secrete catecholamines when they are manipulated intraoperatively, which may result in complications such as hypertensive crisis.
- This manuscript demonstrates intraoperative findings of the sessile bladder tumor, which appears distinct compared to urothelial carcinoma on gross examination. Transurethral resection will reveal a unique golden-yellow paraganglioma tumor color, which is not typically present in urothelial carcinoma and other variant histologies.

What is the implication, and what should change now?

- Paraganglioma is a rare variant histology bladder tumor that may be not be visualized due to its sessile shape, which may be mitigated by the use of a 70-degree cystoscopic lens. Visualization of any golden-yellow color within a bladder tumor during resection should prompt immediate cessation of the operation to assess for signs of catecholamine surge and perform alpha blockade. A hormonal and metastatic evaluation should be performed after identification of a paraganglioma bladder tumor.

catecholamine secretion, causing atypical symptoms such as micturition syncope, paroxysmal hypertension, palpitations, tachycardia, and sweating. If not suspected preoperatively, bladder paragangliomas can elicit hypertensive crisis during surgical resection (4). Although these tumors are rare and difficult to distinguish from urothelial carcinoma (UC), early recognition of this tumor preoperatively would allow appropriate preoperative alpha blockade to minimize morbidity (5).

The following case describes a non-functional, muscle-invasive, bladder paraganglioma that was successfully managed with transurethral resection after multiple prior non-diagnostic biopsies. We provide visual cues to help differentiate bladder paraganglioma from UC intraoperatively, and demonstrate endoscopic surgical techniques to adequately resect and stage this subtle, yet aggressive tumor. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-50/rc).

Case presentation

A 46-year-old male was referred for evaluation of an incidental bladder mass identified on computed tomography (CT) imaging for a complaint of persistent, non-specific, right-sided abdominal pain. The enhancing mass measured 1.8 cm × 2.7 cm × 2.0 cm and was located on the right inferior urinary bladder wall (*Figure 1*).

He had a 5-pack year tobacco smoking history with two prior episodes of gross hematuria, and underwent two prior cystoscopies with transurethral biopsies at an outside institution. On both occasions, the pathology identified benign urothelium. A CT of the bladder from his most recent presentation identified enlargement of his anterior bladder mass to 3.4 cm × 2.6 cm. Past medical history was significant for asymptomatic sinus tachycardia, with self-reported heart rates up to 140 beats per minute and a pulmonary embolus in 2009. He also reported one syncopal episode.

All procedures performed in this study were in accordance with the ethical standard of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Verbal informed consent was obtained from the patient for the publication of this

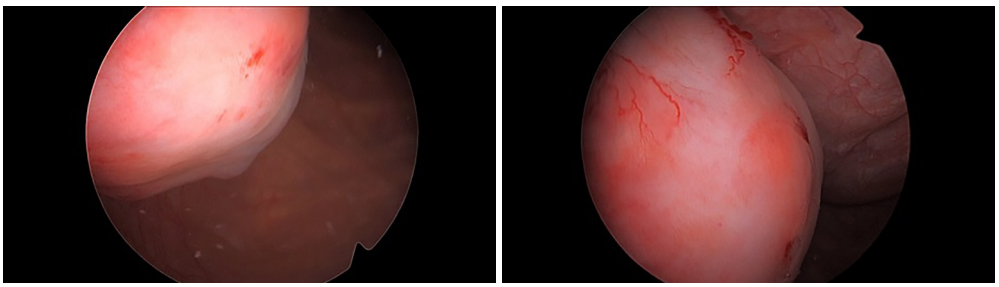

Figure 2 Cystoscopic views of the sessile tumor with a 70-degree lens, which was unable to be appreciated using a 30-degree lens.

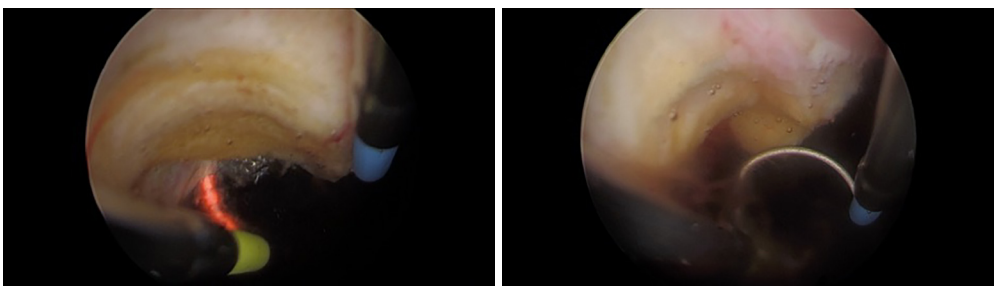

Figure 3 Golden-yellow paraganglioma tumor color during transurethral resection.

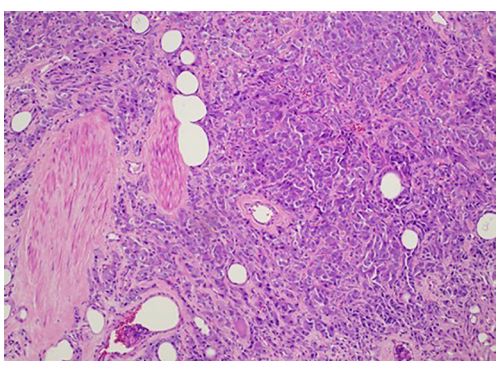

Figure 4 H&E stain of paraganglioma tumor invading muscularis propria, original magnification ×40. H&E, hematoxylin & eosin.

case report and accompanying images.

Surgery

After extensive counseling and discussion regarding the findings, this patient underwent a transurethral resection of bladder tumor (TURBT). The bladder mass was not readily identified upon initial visualization with a 30-degree rigid cystoscope. Use of a 70-degree lens revealed a well-circumscribed, smooth mass at the right anterior lateral wall, measuring approximately 4 cm in diameter (*Figure 2*). The overlying mucosa appeared hypervascular compared to the surrounding mucosa. The mass was resected with a bipolar loop resectoscope, which immediately revealed a golden-yellow solid mass beneath the mucosa (*Figure 3*). The mass was resected until normal-appearing detrusor muscle was visualized. The golden-yellow mass extended from the bladder neck towards the prostatic base. Deep resections were obtained to rule out prostatic stromal invasion. All visible tumor was thoroughly resected at the conclusion of the case. The patient was hemodynamically stable throughout the resection, maintaining a normal blood pressure and pulse rate.

Pathology

Hematoxylin and eosin staining identified the diagnosis of a muscle-invasive paraganglioma (*Figure 4*). Paraganglioma cells display characteristic Zellballen or nesting patterns with delicate fibrovascular stroma and granular basophilic cytoplasm, representing the neurosecretory glands of the tumor. *Figures 5*,*6* show positive staining in the neurosecretory granules for chromogranin and synaptophysin, respectively. *Figure 7* shows S100-positive sustentacular cells, which were not very prominent in this case.

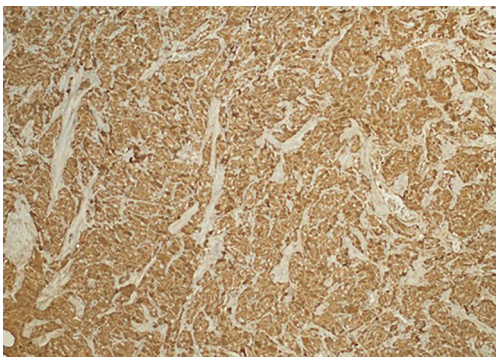

Figure 5 Chromogranin stain showing positive neurosecretory granules, original magnification ×40.

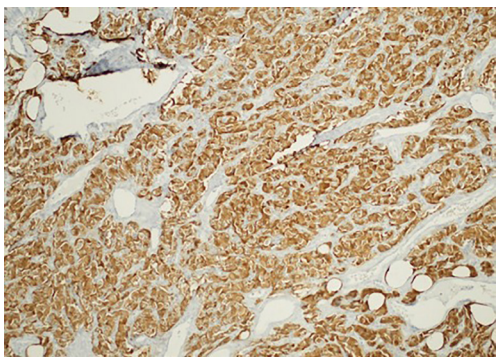

Figure 6 Synaptophysin staining the neurosecretory granules (cytoplasm brown), original magnification ×40.

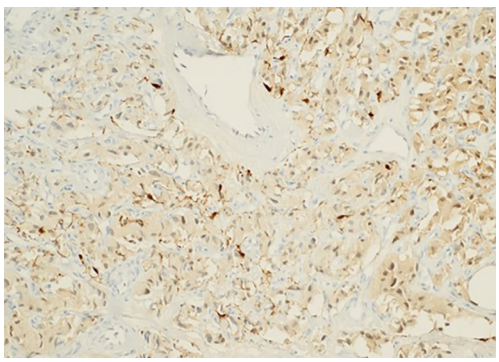

Figure 7 S100 staining the peripherally located sustentacular cells (nucleus and cytoplasm dark brown), original magnification ×40.

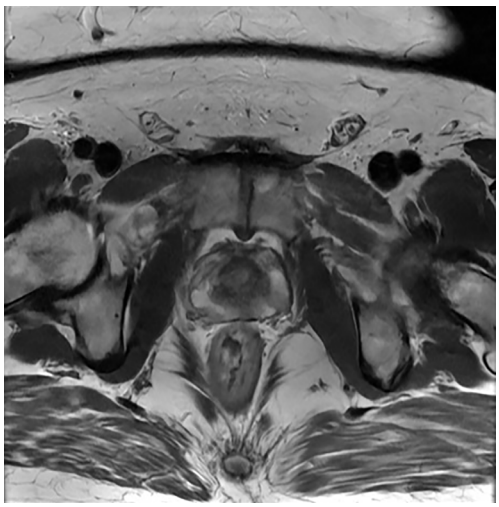

Figure 8 MRI abdomen/pelvis, 4 months post-resection of the diagnostic TURBT, showing nonspecific right bladder neck wall enhancement, but without infiltration into perivesical fat, pelvic lymphadenopathy, or osseous metastatic disease. MRI, magnetic resonance imaging; TURBT, transurethral resection of bladder tumor.

Radiology

Based on the finding of a muscle-invasive tumor, post-resection magnetic resonance imaging (MRI) was performed which identified residual bladder wall enhancement, but no lymphadenopathy or visceral/osseous metastases (*Figure 8*). Additionally, a positron-emission tomography (PET) study, performed using 18F-fluorodeoxyglucose, did not identify any avidity to suggest active disease sites.

Follow-up

A metabolic evaluation was performed, which revealed normal levels of plasma normetanephrine, metanephrine, and urine catecholamines (epinephrine, norepinephrine, dopamine). Given the non-functional hormonal profile and radiographic size stability from 2019–2022, the patient chose surveillance with serial imaging instead of re-staging TURBT or radical cystoprostatectomy.

A repeat PET-CT scan performed 6 months post-resection did not identify metabolically active masses.

Discussion

We present the case of a non-functional, muscle-invasive, bladder paraganglioma that was successfully managed with a TURBT after multiple prior non-diagnostic biopsies. During transurethral resection of this tumor, a submucosal golden-yellow mass characteristic of paraganglioma was identified and resected until no visual tumor was present. His tumor was not hormonally active on metabolic workup, and 6-month follow-up did not show any signs of disease progression.

Prior to definitive extirpative therapy, clinicians should maintain differential diagnosis for submucosal bladder masses that includes benign etiologies such as fibroma, fibrosarcoma, leiomyoma, leiomyosarcoma, hemangioma, paraganglioma, and neurofibroma; malignancies such as urothelial cell carcinoma, squamous cell carcinoma, and small cell carcinoma of the bladder, as well as inflammatory-mediated conditions such as granulomatous inflammation and amyloidosis (6). Diagnostic differentiation between these varied etiologies should include imaging as well as serum and urine metanephrines, catecholamines, and vanillylmandelic acid (VMA), especially if the patient presentation includes endocrine symptoms raising suspicion for a functional tumor (7).

Various diagnostic imaging modalities are available for suspected bladder paraganglioma, including ultrasound, which can be used with color Doppler to investigate vascularity. CT urogram is the gold standard when assessing for gross hematuria or a bladder mass, which will also identify pelvic lymphadenopathy. MRI is more useful than CT to estimate the depth of bladder tumor invasion, and is currently being explored in the setting of Vesical Imaging-Reporting and Data System (VI-RADS) (8). Metaiodobenzylguanidine (MIBG) scintigraphy is highly specific for neuroendocrine tumors but has limited sensitivity, allowing for a high false-negative potential (7). Once a diagnosis is confirmed histologically, this can be considered as part of a metastatic workup if a regional or distant lesion is visualized on CT chest/abdomen/pelvis imaging.

Urine and plasma metanephrines may serve as a useful diagnostic tool when pheochromocytoma is suspected. Plasma metanephrines are preferred for initial screening due to higher sensitivity and convenience; however, they are susceptible to false positives and are expensive. In contrast, 24-hour urine metanephrines are highly specific and are less influenced by acute changes in physiology, but are less convenient for patients. According to Waingankar *et al.*, the sensitivity and specificity for plasma metanephrines are 97% and 96%, while urinary catecholamines are 79% and 96%, respectively (7). We advocate for initial screening with the highly sensitive plasma free metanephrines, and subsequent confirmatory testing with the highly specific 24-hour urine catecholamines and metanephrines. We have included a summary of case reports and case series published 2022–2024 to summarize the biochemically active prevalence in bladder paragangliomas (*Table 1*).

Surgical resection continues to be the standard of care for localized bladder paraganglioma. On direct visualization, these tumors typically appear as smooth, well-circumscribed masses with normal overlying urothelium. These features are subtle in comparison to the pedunculated or papillary appearance of typical UC tumors. Surgical resection can involve a transurethral approach or partial cystectomy for tumors of appropriate size and location. The transurethral approach is preferred for tumors <3 cm and should include close hemodynamic monitoring and alpha blockade when indicated to avoid an intraoperative hypertensive crisis. Complete surgical resection that removes all viable tumor offers the patient's best chance for disease free survival, as metastatic tumors are predominantly managed with palliative care.

In our index patient, the mass had been biopsied with benign results twice prior to our resection, which was likely due to inadequate visualization. The change to a 70-degree lens in this case allowed adequate delineation of this sessile mass due to its location in the anterior bladder, which was far more subtle compared to a typical papillary UC tumor. The diagnosis of a bladder paraganglioma, while unexpected due to its rarity, was delayed due to these inadequate and inaccurate prior resections.

Another aspect of this case was the additional sampling of the prostate base and bladder neck to rule out prostatic stromal invasion. Tumors with ≥ T3 stage have been associated with poor prognosis, and prostatic stromal invasion (T4 disease) would likely have necessitated a radical cystectomy (1,2). Fortunately, this tumor did not progress and remained localized until an adequate resection could be performed.

Pre-operative alpha blockade is typically only pursued in cases of suspected or known bladder paraganglioma, which represent few of the reported cases. Since this malignancy

Table 1 Case reports/series 2022–2024 of bladder paragangliomas with biochemical activity

Author	Year	Biochemically active patients	Total patients
Padilla Bermejo (9)	2024	0	1
Song (10)	2024	0	1
Orsini (11)	2024	1	1
Chen (12)	2024	1	1
Youssef (13)	2024	1	1
Zhao (14)	2024	15	29
Pang (15)	2024	28	73
Hassan (16)	2024	0	1
Zare (17)	2024	1	1
Chen (18)	2024	0	1
Pérez Barón (19)	2024	1	1
Vos (20)	2024	N/A	1
Kita (21)	2023	0	1
Gauci (22)	2023	1	1
Kratiras (23)	2023	0	1
Alaklabi (24)	2023	1	1
Takahashi (25)	2023	1	1
Co (26)	2023	0	1
Tan (27)	2023	1	1
Yu (28)	2023	N/A	1
Wang (29)	2022	1	1
Zhang (30)	2022	N/A	1
Aksakallı (31)	2022	0	1
Yoon (32)	2022	11	32
Tomkins (33)	2022	1	1
Cai (34)	2022	7	20
Ji (35)	2022	0	1
Wang (36)	2022	0	1
Ejaz (37)	2022	2	2
Hald (38)	2022	0	1
Sonderer (39)	2022	1	1
Yu (40)	2022	48	77
Chen (41)	2022	0	1
Xiong (42)	2022	1	1
Matsuzawa (43)	2022	1	1
Thia (44)	2022	0	1
Rajkumar (45)	2022	1	1

N/A, not applicable.

is rarely suspected, preventative steps are seldom taken to avoid hypertensive crises. Early intraoperative recognition of a golden-yellow submucosal mass (classically associated with pheochromocytoma) should prompt a cessation of the resection with close hemodynamic monitoring to avoid a hypertensive crisis, which can introduce significant morbidity due to sudden catecholamine release in patients with functional tumors (4,5,46). The hypertensive crisis can manifest with changes in the patient's vital signs [e.g., tachycardia, hypertension (>180/120 mmHg), diaphoresis, and increased body temperature]. These findings can cause neurological emergencies such as acute subarachnoid hemorrhage, intracerebral hemorrhage, hypertensive encephalopathy, and acute ischemic stroke, cardiovascular emergencies such as acute heart failure and aortic dissection, and obstetric emergencies such as pre-eclampsia can also occur. In rare cases, untreated or undetected hypertensive crisis can lead to multi-system organ failure (4). Uslar *et al.*, in a four-decade retrospective review of extirpative surgeries to treat paraganglioma, noted a 42% overall incidence of intra-operative hypertensive crises, with a reduction from 50% in the decade spanning 1990–2000 to 23% in the years 2010–2019 (47). Beilan *et al.* considered 80 studies of bladder paraganglioma from 1980 to 2012 encompassing 106 patients, 65 (61.3%) of whom presented with an increase in catecholamine, metanephrine, or VMA levels (1). Visualization of this golden-yellow submucosal mass and/or hypertensive crisis during resection should raise concern for paraganglioma and prompt further workup with serum and/or urine metanephrines.

Patients diagnosed with a bladder paraganglioma should be followed closely for recurrence, since 15–20% of these tumors are malignant and have metastatic potential (48). Due to the rarity of the presentation and lack of high-quality evidence, limited large scale studies are available to guide surgeons that encounter this malignancy. Based on the pathophysiology involved, plasma and urine metanephrines, catecholamines, and VMA should be included in its surveillance (7). MIBG scintigraphy can be considered for patients with a high index of suspicion for distant metastases or in patients for whom PET-CT imaging has been performed and is equivocal or positive (49). In a retrospective study of 110 patients with histopathologically confirmed bladder paraganglioma, Yu *et al.* found a 4-year overall survival of 81% and a cancer-specific survival of 91%, with higher mortality rate in patients with synchronous metastases (40). Based on prior studies, our index patient is unlikely to have high disease-

specific mortality despite the finding of muscle-invasive disease due to the absence of synchronous metastases and the non-functional status of the tumor.

A definitive surveillance protocol has not been recommended; however, prior studies have recommended a combination of blood/urine studies and cross-sectional imaging. Plasma and urine metanephrines are tested 3 months after definitive paraganglioma resection, even if these values were not elevated preoperatively. Cross-sectional imaging in the form of CT chest/abdomen/pelvis is performed every 6–12 months for the first few years postoperatively, since recurrence rates may be as high as 15–20% (50).

Due to the rarity of bladder paraganglioma, it is unlikely that prospective, randomized studies comparing the effects and survival rates of different treatment modalities will be feasible. Additionally, meta-analyses of case reports are unlikely to be representative due to selection bias. Future studies can focus on subgroup analyses including large patient cohorts from academic centers or large databases to further elucidate the long-term prospects of patients found to have urinary bladder paragangliomas.

The patient was satisfied with his care through endoscopic resection. In the context of two prior negative transurethral biopsies and slow growth in radiographic size, the patient decided to refuse a re-staging TURBT or radical cystoprostatectomy. He believed that additional surgery was "overkill" in the context of his prior experiences and interventions.

Conclusions

Herein, we report a rare non-functional extra-adrenal pheochromocytoma (paraganglioma) arising from the bladder of a 46-year-old man. This case is notable for the location of the mass, requiring a 70-degree cystoscopic lens for complete visualization near the bladder neck, and for the identification of a golden-yellow sessile mass during the resection. Upon visualization of this mass, the operation should be paused for close hemodynamic monitoring and assess for signs of hypertensive crisis prior to continuing without alpha blockade.

Based on a review of the literature, suspected localized cases should be optimized hemodynamically and managed surgically. A preoperative biochemical evaluation with serum or urine catecholamines, metanephrines, and normetanephrines should be performed to assess for tumor functionality. The surveillance and follow up of bladder paragangliomas should be multidisciplinary, involving endocrinology, internal medicine, urology, and medical oncology.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-50/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-24-50/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-50/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Verbal informed consent was obtained from the patient for the publication of this case report and accompanying images.

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