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Varied clinical presentations of genitourinary tuberculosis: A case series at a tertiary Philippine hospital

Lilibeth Lim-Navarro[1], Almira Jose Amin-Ong[1]

Abstract:

Genitourinary tuberculosis (GUTB) represents a critical aspect of extra-pulmonary tuberculosis (TB). While it is the second most common form of this disease, its diverse clinical presentations pose a substantial challenge. This report, titled "Varied Clinical Presentations of Genitourinary Tuberculosis: A Case Series from a Tertiary Philippine Hospital," aims to shed light on the intricacies of GUTB diagnosis, treatment, and its broader implications. In this case series, we present five unique clinical scenarios. Cases 1, 2, and 3, having completed TB treatment, developed spontaneous genitourinary fistulae. Case 4 was initially managed as interstitial cystitis, while Case 5 underwent diverticulectomy for a urethral diverticulum. The diagnosis of GUTB as the underlying cause in these cases, despite conventional treatment, highlights the diagnostic challenges posed by this disease. All five patients, experienced irritative voiding symptoms and recurrent urinary tract infections with limited improvement following antibiotic therapy. Imaging studies consistently revealed upper urinary tract involvement. Importantly, only one case exhibited histologic evidence of granuloma suggestive of GUTB, and microbiologic confirmation of *Mycobacterium tuberculosis* infection was obtained in only two cases. This underscores the need for a multidimensional diagnostic approach. The findings in this case series emphasize that GUTB diagnosis, often reliant on clinical findings supported by imaging studies and suggestive cystoscopy findings, remains critical for prognosis, even in the absence of microbiologic confirmation. Beyond the individual cases, this series offers insights into the complexity of GUTB, raising questions about the overall management and implications for TB control.

Keywords:

Diagnostic challenges, endemic tuberculosis, genitourinary tuberculosis, spontaneous genitourinary fistula, tuberculosis control

Introduction

Tuberculosis (TB) remains a significant public health concern in the Philippines, with 500 affected individuals per 100,000 people, underscoring the ongoing challenges in disease management and control within the nation.[1] Following peripheral lymphadenopathy, genitourinary TB (GUTB) stands out as the second most prevalent form.[2,3]

GUTB poses a distinctive diagnostic challenge due to several factors, including the typically paucibacillary nature of the disease and the nonexclusive nature of histopathologic findings, such as granulomatous reaction.[3]

This case series presents five instances of GUTB documented over a recent 5-year period, each characterized by nonspecific clinical presentations, varying disease intensity, and prolonged durations.

The inclusion criteria for these cases were guided by the need to capture the

[1]Department of Obstetrics and Gynecology, Division of Urogynecology and Pelvic Reconstructive Surgery, UP-Philippine General Hospital, Manila, Philippines

Address for correspondence:
Dr. Almira Jose Amin-Ong, Philippine General Hospital, Taft Avenue, Ermita, Manila 1000, Philippines.
E-mail: almondrei@gmail.com

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diversity and clinical challenges associated with GUTB. By examining these cases, this study seeks to provide valuable insights for clinicians, researchers, and policymakers, ultimately contributing to a more comprehensive understanding of GUTB and its impact on the broader TB control efforts in the Philippines.

Case Report

Case 1 is a 39-year-old G3P3 (3003) with a 1-year history of urinary incontinence. The patient was treated for pulmonary TB (PTB) 2 years prior.

On physical examination, a vaginal defect was seen with egress of urine. Urine studies reveal sterile pyuria and hematuria, with negative acid-fast bacilli (AFB) test. Recurrent and relapse of urinary tract infections (UTIs) showed urine culture growth of *Klebsiella* sp, *Pseudomonas* sp., and *Eschericia coli*. On upper tract imaging, findings include an enlarged left kidney with ureterohydronephrosis, with poor function of the right kidney on renal glomerular filtration rate (GFR) scan.

Cystoscopic findings a bladder defect continuous with the vagina. Bladder biopsy reported chronic granulomatous inflammation with Langhans type giant cells. Microbiologic findings for *Mycobacterium tuberculosis* (MTB) yielded negative results. After completing, anti-Koch's medications, the patient reported no improvement of urinary symptoms with further enlargement of the fistula and deterioration of the kidney function. The patient was advised nephrectomy, cystectomy, and left ileal conduit. The patient did not consent to surgery and was lost to follow-up.

Case 2 is a 38-year-old G2P2 (2002) who reports urgency, weak urine stream, and vaginal leakage for 2 years. She was previously managed as a case of GUTB after presenting with gross hematuria. The patient also has systemic lupus erythematosus (SLE) presenting with joint pains. She also had a history of abnormal uterine bleeding (AUB) probably secondary to steroid use for SLE. Vaginal examination showed urethral stricture, poor vaginal pliability, no vaginal defect but with positive swab test suggestive of vesicovaginal fistula. Urinalysis showed sterile pyuria. Urine culture reports for her recurrent UTI showed growth of *Staphylococcus saprophyticus* and *Proteus* sp. Repeat urine microbiologic studies for GUTB are now negative.

Urinary tract imaging studies show severe cystitis, vesicovaginal fistula and vesicourachal diverticulum, right ureteropelvocaliectasia, and right hydronephrosis (Grade IV). A fistulous tract is seen connecting the superoposterior urinary bladder wall with the adjacent anterior wall of the vaginal canal. Filling cystometry show cystometric capacity of 30 mL only.

The operative plan is for diagnostic cystourethroscopy, transvaginal repair of vesicovaginal fistula with flap interposition, possible augmentation cystoplasty.

Case 3 is a 25-year-old G1P0 (0010) with a 1-year history of vaginal leakage and enuresis. Two years prior, she had previously completed anti-Koch's medicine for PTB. The patient is being monitored for AUB (oligomenorrhea) probably secondary to prolactinemia due to renal insufficiency. Vaginal examination revealed proximal vaginal narrowing, no vaginal defect, but with positive swab test suggestive of vesicovaginal fistula. Urine studies reveal pyuria and hematuria, while urine culture showed recurrent cystitis attributed to *Klebsiella* sp, *Pseudomonas* sp. and *E. coli*. Microbiologic MTB tests are negative. Imaging shows bilateral hydronephrosis and ureteral dilatation, more severe on the left. Renal GFR scan showed poor function of the left kidney.

Cystoscopy shows that the right ureteral orifice is dilated with golf hole appearance and right vesicoureteral reflux but with no evidence of obstruction on retrograde pyelogram. The left ureteral orifice was not seen, with evidence of left focal calyceal dilatation, perinephric abscess, and infundibular stenosis on antegrade pyelogram. No defects were seen on cystoscopy or vaginoscopy.

Biopsies of urethra, bladder, vagina, and tissues surrounding the vaginal defect showed acute on chronic inflammation with no granuloma or malignant process. Her vesicovaginal fistula is being managed conservatively with a catheter in place, vaginal and bladder tissue optimization, and anti-muscarinics for the vesicoureteral reflux. If with persistence of genitourinary fistula (GUF), the operative plan is for diagnostic cystourethroscopy, transvaginal repair of vesicovaginal fistula with flap interposition.

Case 4 is a 45-year-old G3P3 (3003) with a 2-year history of bladder pain related to bladder fullness, episodes of hematuria, and recurrent cystitis. The patient has no previous PTB. She had recurrent UTI for 2 years, with urine culture growth of *Klebsiella* sp and *Pseudomonas* sp but with minimal and temporary improvement after completing antibiotics. On physical examination, pelvic floor tenderness and trigger points were identified, but no gross lesions or abnormal findings were seen. Urine studies revealed hematuria, pyuria and bacteriuria, urine culture showed nosocomial infection, and negative urine AFB test. Imaging studies showed cystitis, right mild pelvocaliectasia, mid-ureteral, and ureterovesical strictures.

Cystoscopic findings of glomerulation, petechiae, and Hunner's ulcers which bled upon distention supported the diagnosis of interstitial cystitis. Biopsy of bladder and urethral tissues showed chronic inflammation. The patient underwent hydrodistention three times at monthly intervals and was given anti-muscarinics and pain relievers which only afforded minimal and temporary relief. On repeat work-up, urine AFB tested positive, for which she completed anti-Koch's treatment. Patient reports improvement in quality of life with no bladder pain and hematuria and improvement of irritative urinary symptoms.

Case 5 is a 58-year-old G1P1 (1001) with a 6-month history of a palpable vaginal mass and urgency. The patient has no known PTB. She had three bouts of UTI within 6 months, with no improvement after completing antibiotics. On physical examination, a suburethral cystic mass is seen at the mid to distal anterior vagina with discharge of urine per urethra on gentle expression. Urine studies showed pyuria and bacteriuria, while her urine culture reported growth of *Klebsiella* sp. and *Pseudomonas* sp. Transvaginal and transperineal ultrasound reveal a suburethral mass inferior to the urethra, suggestive of a urethral diverticulum and right ureteropelvocaliectasia.

Cystoscopic findings reveal the areas of trabeculation on the trigone and posterolateral bladder walls, two posterior urethral wall defects, leading to a single diverticulum. The surgeon obtained a diverticular sac, with biopsy report consistent with urethral diverticulum. However, 1-month postoperative, the patient had recurrence of urgency and urge incontinence, unrelieved by antibiotic treatment for cystitis and unresponsive to trial anti-muscarinics. On further work-up, urine AFB was positive, and patient was started on anti-Koch's medication. The patient completed anti-Koch's medicine with improvement of urgency and urge incontinence and no recurrence of vaginal mass.

Discussion

The pathophysiology of GUTB relies on hematogenous dissemination, ascending infection, and lymphatic spread.[3] Untreated lesions may form tubercular abscess and the kidney is replaced by caseous material with resulting fibrosis, strictures, and renal failure.[4,5] Therefore, prompt GUTB diagnosis is critical to avoid delay in treatment leading to severe damage of the urinary tract and debilitating genital tract injuries.

This case series is in continuation of an earlier report by Lirazan and Amin-Ong.[6] The authors aim to further analyze patient characteristics, symptomatology, physical examination, diagnostic and histopathologic findings and correlate it with history of previous or ongoing PTB or Extra PTB (EPTB), response to Anti-Koch's treatment and clinical course. Thereafter, the authors would like to come up with recommendations from our hospital experience.

Out of the five cases, four women were within the reproductive age [Table 1]. Two of the reported cases had menstrual abnormalities – one from steroid use for SLE flares and other from renal insufficiency. These menstrual irregularities are beyond the scope of this case series and will not be discussed further. Two women were identified to have hypertensive disease but nephropathies were not known before GUTB diagnosis.

Three of the five cases had previous diagnosis of PTB or GUTB [Table 1]. The knowledge of TB infection in the past medical history provides an important clue in a large number of cases. In our case series, GUTB symptoms became apparent within 3 months to 2 years after TB diagnosis. In some reported cases, it could take more than 40 years before GUTB becomes evident.[5]

Despite varying presentations of the five cases (urinary incontinence, gross hematuria, vaginal discharge, bladder pain, and suburethral mass), some common findings can be observed. All women had irritative voiding symptoms [Table 2] and recurrent UTI with temporary and minimal improvement of symptoms after antibiotics. In addition, all GUF cases had known/recent TB infection and two out of these three women have end stage renal disease (ESRD).

All women had imaging findings suggestive of upper tract involvement [Table 3]. KUB intravenous (KUB IVP) findings reported in our study, range from bilateral renal parenchymal disease, with predominance of right ureteropelvocaliectasia, and all report sub-optimally filled bladders precluding assessment of fistula presence. A KUB ultrasonography was done in case 2 due to ESRD.

Ultrasound reports in our study reveal normal sized uteri, cervix, endometrium and ovaries in all patients. Pelvocaliectasia was seen in all patients, with predominance on the right. The GUF cases of urethrovaginal and vesicovaginal fistula were documented on transvaginal ultrasound.

Computed tomography (CT) imaging was done in four cases – showing right hydronephrosis in 3 cases, enlarged left kidney in two cases. Three cases suggest GUF (two vesicovaginal fistula, one urethrovaginal fistula). CT was not done in case 5, due to nonsuspicion of upper tract involvement at the time of imaging request.

On urethroscopy and cystoscopy – all women had pale and fibrotic urethral mucosa and small bladder

Table 1: Summary of patient demographics, symptoms, physical examination, imaging, laboratory results and outcome

	Age; OB score	Chief complaint and urinary symptoms	History of pulmonary TB	UTI	Physical exam	Upper tract imaging	Cystoscopy	Microbiologic test	Biopsy	Management	Anti-Koch's medication	Diagnosis and outcome
Case 1	39; G3P3 (3003)	Incontinence Frequency urgency enuresis	PTB - 2 years prior	Recurrent	Vaginal defect		Urethrovaginal fistula	Negative	Chronic inflammation with Langhan's type cells	Nephrectomy, cystectomy, left ileal conduit (no consent)	Incomplete for PTB Intermittent×6 months due to allergic reaction for GUTB	Urethrovaginal fistula Genitourinary TB End stage kidney disease Lost to follow up
Case 2	38; G2P2 (2002)	Gross hematuria Frequency urgency Weak urine stream	GUTB - 3 months prior	Recurrent	Vaginal defect Urethral stricture Poor vaginal pliability		For procedure	Negative	For procedure	If with genitourinary fistula on cystoscopy and no active TB infection For transvaginal repair of vesicovaginal fistula with flap interposition, possible augmentation cystoplasty	Completed×6 months for GUTB	Vesicovaginal fistula Genitourinary TB For diagnostic cystourethroscopy and vaginoscopy
Case 3	25; G1P0 (0010)	Vaginal discharge Frequency urgency enuresis	PTB - 3 years prior	Recurrent	Vaginal defect Proximal vaginal narrowing		Bladder diverticulum Intact bladder with blebs and severe trabeculations	Negative	Acute on chronic inflammation, no granuloma or malignant process	Conservative management, catheter in place, tissue optimization, anti-muscarinic If with fistula recurrence For Latzko repair with Martius flap	Completed×6 months for PTB	Vesicovaginal fistula Genitourinary TB End stage kidney disease Improvement with no vaginal discharge
Case 4	45; G3P3 (3003)	Bladder pain hematuria Frequency urgency Weak urine stream	None	Recurrent	Pelvic floor tenderness		Hunner's ulcers Glomerulations	Positive urine AFB (6 months after hydrodistension with no relief of irritative voiding symptoms)	Chronic inflammation	Anti-Koch's medication	Completed×6 months for GUTB	Genitourinary TB Improved functional capacity of 50 mL from previous of<10 mL
Case 5	58; G1P1 (1001)	Palpable vaginal mass Frequency urgency Weak urine stream	None	Recurrent	Suburethral cystic mass		Urethral diverticulum Intact bladder with severe trabeculations	Positive urine AFB (3 months after diverticulectomy with no relief of irritative voiding symptoms)	Consistent with urethral diverticulum	Anti-Koch's medication	Completed×6 months for GUTB	Genitourinary TB Improved functional capacity of 200 mL from previous of<30 mL

UTI: Urinary tract infection, TB: Tuberculosis, GUTB: Genitourinary TB, PTB: Pulmonary TB, AFB: Acid-fast bacilli, OB: Obstetric score

Table 2: Urinary and vaginal symptoms symptoms

Case	Frequency	Nocturia	Urgency	Urge UI	Stress UI	Enuresis	Straining to void	Poor stream	Incomplete emptying	Dysuria	Hematuria
1	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No
2	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No
4	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No

UI: Urge incontinence

Table 3: Upper tract imaging

Case	Significant findings
1	Bilateral hydroureteronephrosis[c]
2	Right ureteropelvocaliectasia[c]
	Right hydronephrosis[c]
3	Bilateral hydronephrosis[a-c]
	Right pelvocaliectasia[a-c]
4	Left pelvocaliectasia[b, c]
	Left ureteral strictures[b, c]
5	Right pelvocaliectasia[b]

[a]KUB-IVP, [b]Pelvic ultrasound, [c]CT scan. CT: Computed tomography, KUB-IVP: KUB-Intravenous

capacities. However, no bladder defects were visualized in the vesicovaginal fistula cases. This was probably secondary to limited distention of the contracted bladders, severe trabeculations and overall moth-eaten appearance [Table 4].

In the acute GUTB stage, patients present with irritative bladder symptoms which usually resolve after pharmacologic treatment [Tables 5 and 6]. However, cases may still progress to chronic stages of GUTB. Despite correct diagnosis and completing treatment, small bladder capacities and evidence of upper tract involvement may persist.[4,6] For example, two cases were already in ESRD within few months to 2 years from onset of GUTB symptoms [Table 7]. Our case series report proves that whenever a pattern of chronic renal inflammatory disease is recognized, GUTB should be highly considered.

To our knowledge, only one other case series of GUTB patients is published locally. Rosales *et al*.[7] included 61 patients GUTB in a Tertiary Hospital from 1987 to 1994. Mean durations of illness to diagnosis were 30.4 months in females versus 3 to 24 months in our report. Bacteriologic, radiologic and histopathologic means were the most common diagnostic modalities used. They concluded that the above modalities utilized were not uniformly employed – a sentiment that the authors of this study share.

We reviewed the 2020 Department of Health Manual of Procedures for National TB Program[8] and 2016 clinical practice guidelines (CPG) on EPTB.[9] Current guidelines suggest that active microbiologic or histopathologic evidence is encouraged prior to initiating or re-starting TB medication.[8,9]

It is recommended that patients with relapse suspicion should be referred to the nearest Xpert® MTB/rifampicin (RIF) facility for RIF susceptibility testing. Category II regimen (2HRZES/1HRZE/5HRE) should only be among confirmed or in circumstances where Xpert® MTB/Rif services cannot be performed (i.e. no access or no sputum specimen).[8,9]

While waiting for the results or if above tests are not available, patient may be empirically retreated with Category II regimen (World Health Organization, 2010).[10,11] Some case reports showed clinical improvement with 6 months of TB treatment with adjunctive surgical intervention. Reconstructive surgery is an option for patients with sequelae of GUTB such as contracted bladder or fistula formation that is unlikely to regress with anti-Koch's medication alone.[9,12,13] The 2016 CPG suggests at least 3–6 weeks of anti-TB therapy before surgery to allow the inflammatory process to settle, the disease to stabilize and assess surgical intervention post-TB treatment.[9]

Based on the experiences gained from the five cases presented in this series, the authors propose several recommendations for the effective approach to patients presenting with urinary symptoms and clinical suspicion of GUTB:

1. The need for a multidisciplinary clinical registry of GUTB cases in all Tertiary Referral Hospitals is underscored, encompassing urogynecology, urology, adult and pediatric nephrology, and infectious disease services. These five cases were initially seen in various clinics spanning months to years from onset of symptoms to GUTB diagnosis. Some literature[13-15] have reported on the implications of these circumstances, with repeated tests and medications, which might contribute to noncompliance with follow-up appointments in some patients and ultimately lead to delay in treatment. The authors believe that a comprehensive registry can help streamline the triage of these patients, facilitating a more efficient and patient-centered approach
2. We recommend a minimum of 3 years of regular follow-up for PTB and EPTB patients enrolled in the multidisciplinary clinical registry. Such an extended follow-up period is essential for tracking disease

Table 4: Cystourethroscopic findings

Case	Urethra	Bladder	Ureteral orifices	Others
1	1 cm×0.5 cm defect on the posterior distal urethral wall 0.3 cm from external urethral meatus with communication to the distal vagina	Hyperemic Trabeculations	Not seen	None
2	For procedure	For procedure	For procedure	For procedure
3	Pale and fibrotic	Pink, red, and yellow blebs seen Bladder diverticulum	Right ureteral orifice with golf hole appearance Left ureteral orifice appears stenotic	No vaginal wall defects No vaginal wall defects
4	Normal	Petechiae Hunner's ulcers	Patent	Hunner's ulcers which bled upon hydrodistention
5	2 posterior urethral wall defects, 0.8 cm and 0.5 cm from the bladder neck leading to a single diverticulum	Trabeculations	Patent	Obtained a 3 cm×2 cm×1.5 cm diverticular sac with smooth walls, no lithiasis within

Table 5: Urinalysis sediment analysis

Case	RBC	WBC	Epithelial cells	Mucus thread	Bacteria	Pathogen
1	>20/hpf	>50/hpf	Not in report	Not in report	Not in report	*Klebsiella* sp. *Pseudomonas* sp. *E. coli*
2	3/hpf	19/hpf	3/hpf	1/hpf	18/hpf	*S. saprophyticus* *Proteus* sp.
3	25/hpf	151/hpf	1/hpf	23/hpf	315/hpf	*Klebsiella* sp. *Pseudomonas* sp. *E. coli*
4	218/hpf	87/hpf	1/hpf	4/hpf	17/hpf	*Klebsiella* sp. *Pseudomonas* sp.
5	0–1/hpf	Too many to count	Few	Few	Few	*Klebsiella* sp. *Pseudomonas* sp.

E. coli: Escherichia coli, S. saprophyticus: Staphylococcus saprophyticus, RBC: Red blood cell, WBC: White blood cell

Table 6: Urine cytology

Case	Cytology report
1	Not done
2	Acute on chronic inflammation, with occasional benign epithelial cells
3	Acute on chronic inflammation, with occasional benign epithelial cells
4	Few reactive squamous epithelial cells partially obscured by severe acute inflammation No definite neoplastic or atypical cells seen
5	Negative for malignant cells Acute inflammatory pattern with scattered benign epithelial cells

Table 7: Renal glomerular filtration rate scan

Case	Right kidney	Left kidney	BSA normalized GFR
1	21.8 mL/min (29%)	52.1 mL/min (70%)	No report
2	Not done	Not done	Not done
3	22.3 mL/min (77%)	6.3 mL/min (22%)	BSA-normalized GFR - 35 mL/min (lower limit for age 88 mL/min)

GFR: Glomerular filtration rate, BSA: Body surface area

recurrence or progression despite completion of medication. The unique experiences of these five cases emphasize the importance of prolonged monitoring for better patient outcomes

3. When female patients exhibit unresponsiveness to conventional management and present with irritative urinary symptoms, such as frequency, dysuria, urgency, incontinence, recurrent cystitis, and sterile pyuria, combined with supportive imaging and cystoscopy findings, clinical suspicion of GUTB should be entertained unless proven otherwise

The comprehensive work-up should encompass the following:

a. Imaging (Chest X-ray, KUB-IVP, CT imaging, transvaginal/transperineal ultrasound in cases of chronic kidney disease)
b. Urine studies (urinalysis, urine cytology)
c. Microbiologic MTB investigation (Xpert® MTB/Rif, AFB studies, and tissue cultures from relevant

tissues such as sputum, urine, stool, endometrium, urethral, bladder, and vagina, as needed)

d. Renal function tests and renal GFR scans to monitor the progression of ESRD
e. A two-step approach involving diagnostic cystourethroscopy, retrograde/antegrade pyelogram, and biopsy if considering surgical intervention for GUF.

4. In cases necessitating surgical intervention, it is imperative to establish the presence of active disease, relapse, or re-infection before proceeding with surgery. This precaution is critical to ensure that surgery is the most appropriate and effective course of action
5. For cases with a high clinical suspicion of GUTB, the authors endorse the World Health Organization's recommendation to initiate treatment 3 to 6 weeks prior to surgery. This approach can help reduce the risk of complications and optimize patient outcomes
6. In cases requiring surgical intervention, tissue optimization and control of co-morbidities should be achieved at least 2 to 4 weeks before the procedure. These measures are essential for improving surgical outcomes and ensuring the best possible recovery for the patient.

Through these recommendations, the authors aim to share the insights gained from their specific experiences with the presented cases, ultimately enhancing the approach to GUTB cases and advancing patient care and TB control efforts.

Conclusion

The findings of this study emphasize that clinical diagnosis, complemented by supporting imaging studies and suggestive cystoscopy findings, remains a cornerstone of GUTB prognosis. Whether or not microbiologic confirmation is attainable, this approach is instrumental in preventing irreversible renal function loss and significantly improving the quality of life for affected individuals.

This study provides valuable insights into the diagnosis and management of GUTB, providing clinicians with a more comprehensive understanding of this complex disease, with recommendations to improve timely and effective decisions in GUTB patient care.

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Name	Role
Almira J. Amin-Ong, MD	Supervising consultant and co-author
Lisa T. Prodigalidad-Jabson	Case consultant
Joanne Karen S. Aguinaldo, MD	Case consultant

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Lilibeth M. Lim Navarro, MD - Concepts, Investigation, and Manuscript writing.

Almira J. Amin-Ong, MD - Concepts, Design, Definition of intellectual content, Manuscript writing.

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Conflicts of interest

There are no conflicts of interest.

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