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Case report

Tiny but Nasty: A case report and a review of the literature on *Ureaplasma parvum* peritonitis

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ABSTRACT

Ureaplasma parvum, a member of the *Mollicutes* class, is a rare but significant pathogen in extragenital infections. This case report is the tenth known case of *Ureaplasma* spp. peritonitis, occurring in a 36-year-old female post extensive surgery for metastatic sigmoid colon adenocarcinoma. Following the intervention, the patient exhibited post-surgical peritonitis with fever despite empirical broad-spectrum antibiotics. Conventional bacterial and fungal cultures remained negative, prompting the use of 16 S rRNA polymerase chain reaction (PCR) for diagnosis. *Ureaplasma parvum* was detected in both peritoneal and perihepatic fluid samples, and in the urine, leading to the initiation of doxycycline therapy. The patient responded positively to the treatment, with complete resolution of symptoms and no recurrence observed during a four-year follow-up. This report underscores the clinical challenge posed by *Ureaplasma* spp. due to its resistance to common antibiotics and difficulty in cultivation. It highlights the importance of molecular diagnostics in identifying such pathogens in culture-negative cases and the necessity of considering *Ureaplasma* spp. especially in female patients with persistent peritonitis post-urogenital procedures or surgeries. The case also reflects on the limited data regarding antimicrobial susceptibility, emphasizing the need for tailored therapeutic approaches based on local resistance patterns and the clinical context. Ultimately, this case contributes valuable insights into the diagnosis and management of *Ureaplasma* spp. peritonitis, advocating for heightened clinical suspicion and appropriate molecular testing to ensure effective patient outcomes.

Introduction

Ureaplasmas represent a group of ubiquitous self-replicating bacteria belonging to the class *Mollicutes* and are among the smallest known free-living organisms with the unique ability to metabolize urea as a source of energy [1,2] (Fig. 1). Clinically relevant species include *Ureaplasma parvum* and *Ureaplasma urealyticum*, which are part of the human microbiota and can be isolated from both female and male genital tracts, with varying frequencies, often correlating with sexual activity [3]. These organisms primarily cause urogenital tract infections, such as non-gonococcal urethritis, and adverse pregnancy outcomes, including chorioamnionitis and premature rupture of membranes [4,5]. They are rarely implicated in extragenital infections, such as septic arthritis [6], infective endocarditis [7,8], osteomyelitis [7,9], sternal wound infections [10] and peritonitis [11–14].

The treatment of infections caused by *Ureaplasma* spp. is complicated by the lack of a peptidoglycan cell wall and their inability to synthesize folic acid, which confers intrinsic resistance to β-lactams and other cell wall-targeting agents, as well as to sulfonamides and trimethoprim [4,5]. They require complex growth media for cultivation, such as A8 agar or 10B broth; hence, diagnosis and susceptibility testing can be challenging, as routine bacterial cultures often fail to isolate these organisms [15]. Diagnosing extragenital infection requires a high index of suspicion and is often established through molecular testing, such as 16 S

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ribosomal RNA (rRNA) polymerase chain reaction (PCR).

In this report, we describe a case of peritonitis caused by *Ureaplasma parvum* in a patient following extensive surgery for sigmoid colon adenocarcinoma. To our knowledge, this is the tenth case of *Ureaplasma* spp. peritonitis reported in the literature.

Case report

The patient is a 36-year-old woman with a history of metastatic, moderately differentiated sigmoid colon adenocarcinoma that had spread to the liver, omentum, spleen, and bilateral ovaries. She had previously completed ten cycles of a combination chemotherapy regimen consisting of folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX), and bevacizumab. She was admitted to our facility for a complex surgical intervention, which included liver wedge resection, left colectomy with primary anastomosis, splenectomy, hysterectomy with bilateral salpingo-oophorectomy, intra-abdominal debulking, and bilateral ureteral stent placement.

On the first postoperative day, she had multiple low-grade febrile episodes (38.2 °C). Physical examination revealed minimal wound dehiscence and diffuse abdominal tenderness on superficial and deep palpation without guarding. Vital signs showed a blood pressure of 119/83 mmHg, a heart rate of 113 beats/min, and an oxygen saturation of 97 % on room air. Laboratory tests showed a total white blood cell (WBC) count of 16.8 $\times$ 10^9/L (reference range 3.4–9.6 $\times 10^9$/L), a lactic acid level of 1.0 mmol/L (reference range 0.5–2.2 mmol/L), a hemoglobin level of 8.9 g/dL (reference range 13.2–16.6 g/dL), and a C-reactive protein (CRP) level of 238 mg/dL (reference range $\leq$ 8.0 mg/L). Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin were within normal limits. Two sets of peripheral blood cultures were obtained. Urinalysis revealed 1–3 WBCs per high-power field with no bacteria seen on microscopy.

At this stage, the differential diagnosis was broad. However, intravenous (IV) piperacillin/tazobactam was started empirically due to concerns for a complicated healthcare-associated intra-abdominal infection, given the extensive nature of the surgery. On postoperative day seven, the patient's fever recurred, peaking at 39.1 °C, despite ongoing antibiotic therapy, and her white blood cell (WBC) count increased to 24.4 $\times$ 10^9/L An abdominal computed tomography (CT) scan was obtained with results shown in Fig. 2. A 12 French catheter was placed into the superior hepatic fluid collection. Additionally, paracentesis was performed with aspiration of 190 mL of serous fluid. Ascitic fluid analysis showed 6809 nucleated cells/mL, 83 % of which were neutrophils. No malignant cells were observed on cytological examination. The ascitic fluid creatinine (Cr) was 1.50 mg/dL (serum Cr 1.53 mg/dL), making a urinary leakless likely. Fluid from both sites was

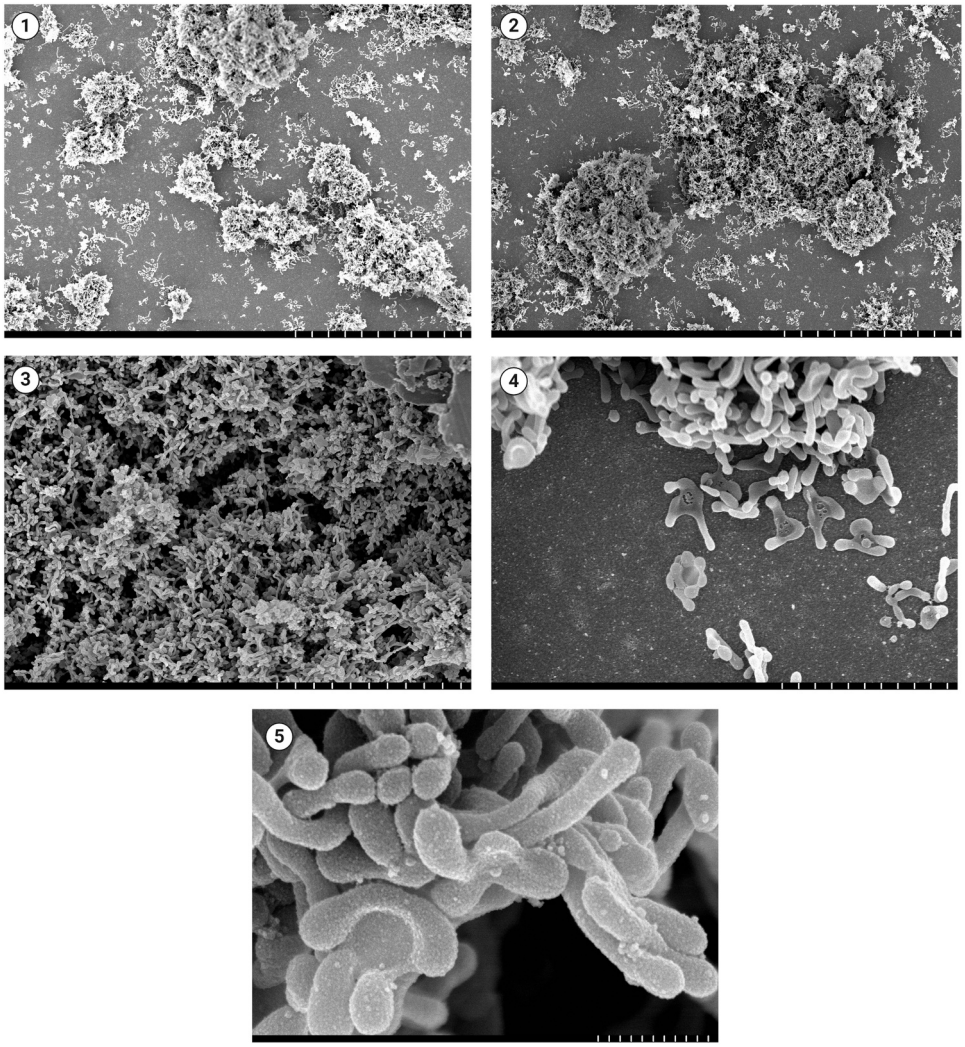

Fig. 1. Scanning electron micrographs showing aggregates of *Ureaplasma* spp. colonies forming biofilms with self-produced matrix components at different magnifications (picture 1, 30 μm; picture 2, 30 μm; picture 3, 10 μm; picture 4, 3 μm; picture 5, 500 nm. Courtesy of Derek Fleming, PhD – Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA).

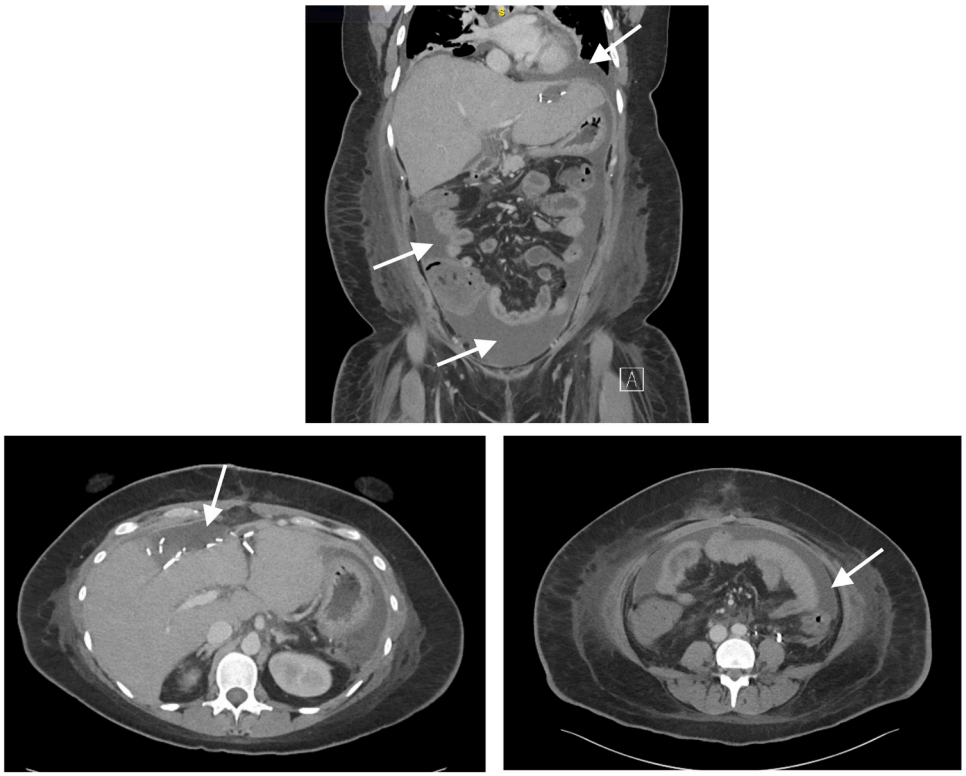

Fig. 2. CT scans showing abdominal ascites (white arrows), with a large fluid collection in the left upper quadrant surrounding the stomach and anterior pelvis (coronal plane, upper; axial plane lower right) in addition to an anterior loculated perihepatic fluid collection (axial plane, lower left).

sent for fungal and bacterial cultures. She was noted to have new onset post-operative diarrhea; therefore, *Clostridioides difficile* stool PCR was obtained and returned negative. The antimicrobial regimen was empirically broadened to include IV caspofungin and IV vancomycin, but there was no clinical response after 72 h, and she continued to have high-grade fevers.

Blood and abdominal fluid fungal and bacterial cultures remained negative. The differential diagnosis at that time was expanded to include post-surgical intra-abdominal infection involving common gastrointestinal pathogens but without adequate source control; post-surgical intra-abdominal infection caused by atypical and/or fastidious pathogens, including *Mycobacteria* spp*, Trichomonads, Mycoplasma* spp.; or non-infectious causes such as drug-induced fever. Subsequently, 16 S rRNA PCR was performed on stored peritoneal and perihepatic fluid samples, and the results were positive for *Ureaplasma parvum* in both samples. For completion, a urine sample was sent for in-house PCR testing and returned positive results for *Ureaplasma parvum* but negative for *Ureaplasma urealyticum,* while a blood sample PCR was negative for both. The organisms failed to grow in specialized cultures for susceptibility testing.

Doxycycline (100 mg orally twice daily) was initiated, resulting in a gradual resolution of the fever and a progressive decrease in WBC count. Piperacillin/tazobactam, vancomycin, and caspofungin were discontinued, and the abdominal drain was removed following serial CT scans and sinograms confirming the resolution of the perihepatic fluid collection. The patient completed an extended eight-week course of doxycycline, concurrent with chemotherapy, with complete resolution of her symptoms and no evidence of recurrence after one year of follow-up.

Discussion

Ureaplasma spp. peritonitis is an emerging clinical challenge, with documented cases primarily affecting females, often following surgical or urogenital manipulation. Nine cases of *Ureaplasma* spp. peritonitis have been reported in the literature to our best knowledge (Table 1). All patients were women, and their median age was 35 years (range 28–50 years). Seven patients (70 %) were on continuous ambulatory peritoneal dialysis (CAPD), with *Ureaplasma* likely gaining access to the peritoneum through the fallopian tubes [14]. The remaining infections, including our case, mainly occurred following surgery and/or manipulation of the urogenital tract in cases of oocyte retrieval for in vitro fertilization, or IUD insertion. We excluded one case of *U. parvum* ventriculitis related to ovarian cyst marsupialization, adhesiolysis and ventricular peritoneal drainage repositioning weeks after a polymicrobial peritonitis due to bladder rupture treated with laparotomy and I.V. vancomycin in a 18-year-old female with congenital myelomeningocele and hydrocephalus [16]. In fact, even if the abdominal clinical picture might be compatible with *Ureaplasma* infection, there was no direct isolation from peritoneal fluid of *Ureaplasma* spp. with conventional or molecular microbiological techniques and the authors stated that the source of ventriculitis was uncertain.

All patients presented with clinical features suggestive of acute peritonitis, such as fever, varying degrees of abdominal tenderness and pain, purulent drainage, ascites, high leukocyte and CRP levels, and abnormal peritoneal fluid analysis. Some cases (cases 2, 3, 4, and 5) developed recurrence of symptoms, and many required multiple invasive procedures before establishing a microbiological diagnosis, emphasizing the stubborn and elusive nature of these infections. The majority of patients had chronic renal diseases requiring renal replacement therapy. Specifically, lupus nephritis in young women was the primary indication for CAPD in 3 out of 7 patients (42.8 %) (cases 4, 5, 8). Only two patients were immunocompromised (20 %) (cases 2 and 10), highlighting that, unlike other forms of extragenital manifestations, the main risk factor for *Ureaplasma* spp peritonitis appears to be urogenital manipulation or bacterial translocation in colonized female patients.

Of the ten cases, *U. parvum* was isolated in six (60 %) (cases 1, 6, 7, 8,

Table 1
Ten cases of peritonitis caused by *Ureaplasma* spp.

Case number	Age/ ASAB	Clinical presentation	Underlying condition/ risk factors	Organism	Source	Peritoneal fluid analysis	Identification method	Susceptibility testing	Concurrent organisms	Treatment	Duration	Outcome	Ref.
1	34/F	Peritonitis No improvement on empiric cefixime	Ultrasound guided oocyte retrieval for in vitro fertilization	*Ureaplasma parvum*	Fluid from retrouterine pelvic collection	NR	Culture, real-time PCR	Susceptible to tetracyclines and fluoroquinolones	None	Surgical drainage of the abscess Ticarcillin/ clavulanic acid I. V. and ciprofloxacin I.V. Transitioned to a P.O. regimen	3 weeks	Complete resolution of symptoms	[11]
2	45/F	Peritonitis Purulent abdominal wall drainage at the laparotomy site	Emergency liver transplantation due to fulminant hepatic failure	*Ureaplasma urealyticum* *Mycoplasma hominis*	Swabs from the abdominal cavity and abdominal wall	NR	Culture	NR	None	Multiple laparotomies Ciprofloxacin I. V.	3 days*	Resolution of the peritonitis	[12]
3	50/F	Recurrent peritonitis Clinical response to empiric IP tobramycin and oral ciprofloxacin followed by relapse	PKD ESRD on CAPD Sexual intercourse 10 h prior to most recent peritonitis episode	*Ureaplasma urealyticum*	Peritoneal fluid Vaginal canal swab	NR	Culture	NR	None	I.P. erythromycin Doxycycline P.O. Vaginal demeclocycline	10 days	Resolution of the peritonitis with no relapse	[13]
4	28/F	Recurrent peritonitis No improvement with IP vancomycin	Lupus nephritis ESRD on CAPD	*Ureaplasma urealyticum*	Peritoneal fluid	1611 WBC/ μL (76 % N)	16 S rRNA PCR	NR	None	Removal of the CAPD catheter Doxycycline P.O.	2 weeks	Resolution of the peritonitis with no relapse	[14]
5	32/F	Recurrent peritonitis Clinical response to empiric ciprofloxacin therapy followed by relapse	Lupus nephritis ESRD on CAPD Menorrhagia, prompting IUD insertion	*Ureaplasma urealyticum*	Peritoneal fluid	NR	16 S rRNA PCR	NR	None	Removal of the CAPD catheter Removal of the IUD followed by Doxycycline P.O.	10 days	Multiple relapses following empiric ciprofloxacin Resolution of the peritonitis after IUD removal and P. O. doxycycline	[17]
6	50/F	Peritoneal dialysis-associated peritonitis treated with I.V. ceftazidime and cefazolin, then vancomycin and levofloxacin.	Proliferative sclerosing glomerulonephritis ESRD on CAPD	*Ureaplasma parvum*	Peritoneal fluid	1425 WBC/ μL on admission, then 37μLbefore targeted antibiotic	mNGS	Not reported	None	Clarithromycin P.O.	2 weeks	Complete symptom resolution	[18]
7	35/F	Peritoneal dialysis-associated peritonitis treated with IP cefazolin, vancomycin,	Immunoglobulin A nephropathy ESRD on CAPD	*Ureaplasma parvum*	Peritoneal fluid	NR	mNGS Culture of vaginal secretions^	Not reported	None	IP and P.O. azithromycin, IP tigecycline	14 days	Complete symptom resolution	[19]

(*continued on next page*)

Table 1 (*continued*)

Case number	Age/ ASAB	Clinical presentation	Underlying condition/ risk factors	Organism	Source	Peritoneal fluid analysis	Identification method	Susceptibility testing	Concurrent organisms	Treatment	Duration	Outcome	Ref.
		meropenem, tigecycline											
8	35/F	Peritoneal dialysis-associated peritonitis treated with IP cefazolin, vancomycin, meropenem	Lupus nephritis ESRD on CAPD	*Ureaplasma parvum*	Peritoneal fluid	NR	mNGS	Not reported	None	IP and oral azithromycin	11 days	Complete symptom resolution	[19]
9	42/F	Peritoneal dialysis-associated peritonitis treated with IP cefazolin, vancomycin, meropenem, tigecycline	Chronic renal failure ESRD on CAPD	*Ureaplasma parvum*	Peritoneal fluid	NR	mNGS Culture of vaginal secretions^	Not reported	None	IP tigecycline and oral minocycline (stopped for adverse event)	2 weeks	Complete symptom resolution	[19]
10	36/F	Postoperative peritonitis treated with no improvement on vancomycin, piperacillin-tazobactam and caspofungin	Sigmoid colon adenocarcinoma with distant metastasis to liver, omentum, spleen and bilateral ovaries. Liver wedge resection, left colectomy with primary anastomosis, splenectomy, hysterectomy with bilateral salpingo-oophorectomy, intra-abdominal debulking, and bilateral ureteral stent placement.	*Ureaplasma parvum*	Peritoneal and perihepatic fluids Urine	6809 WBC µL, 83 % N	16 s rRNA PCR and in-house PCR	Unsuccessful growth on cultures	None	Drainage of abdominal fluid collection Doxycycline PO	8 weeks	Complete symptom resolution	PR

^ The authors specified that *Mycoplasma* culture of vaginal secretions does not distinguish *U. urealyticum* from *U. parvum.*

Abbreviations: 16 s rRNA PCR, 16 s ribosomal RNA polymerase chain reaction; ASAB, assigned sex at birth; CSF, cerebrospinal fluid; CAPD, continuous ambulatory peritoneal dialysis; ESRD, end-stage renal disease; F, female; IP, intraperitoneal; IUD, intrauterine device; M, male; mNGS, metagenomic next-generation sequencing; N, neutrophils; NR, not reported; PCR, polymerase chain reaction; PKD, polycystic kidney disease; P.O., oral; PR, present report; WBC, white blood cells.

* The total duration of therapy is unclear. Pathogens were eliminated based on serial cultures after 3 days of treatment.

9, 10), while *U. urealyticum* in three (30 %) (cases 3, 4, and 5). In one patient, *Mycoplasma hominis* and *U. urealyticum* coinfection were observed (case 2). Diagnosis was made using conventional cultures alone in two patients (cases 2 and 3), while molecular testing was positive as a standalone test in five patients (cases 4, 5, 6, 8, 10). Specifically, 16 S rRNA PCR was used in three cases (cases 4, 5, and 10), whereas metagenomic next-generation sequencing (mNGS) was used in two patients (cases 6 and 8). Three patients had a concomitant diagnosis using culture and molecular methods (cases 1, 7 and 9).

The median duration of antibiotic therapy in the reported cases was 14 days (range 3 – 56 days). In our patient, doxycycline was continued concurrently with chemotherapy to minimize the risk of relapse or treatment failure, accounting for the prolonged course. Oral tetracyclines were the most commonly used drugs (4/10, 40 %), followed by macrolides (3/10, 30 %), fluoroquinolones (2/10, 20 %), and minocycline (1/10, 10 %). Procedures aimed at source control were performed in 5/10 (50 %) patients, with catheter removal in patients with CAPD being the most common. The overall outcome was positive for all patients, with no recurrences observed after definitive treatment.

Complicated intra-abdominal infections are a significant cause of infection-related mortality in the intensive care unit, with mortality rates ranging from 22 % to 55 % in cases of generalized post-operative peritonitis [20,21]. Management typically involves achieving adequate source control through the drainage of infected foci, surgical management of peritoneal contamination, and the administration of broad-spectrum antimicrobial therapy, often targeting enteric organisms [20]. In hospitalized patients with peritonitis, fluoroquinolones, tetracyclines, and macrolides — the agents of choice for treating infections caused by *Ureaplasma* spp — are rarely used as empirical regimens [14]. This underscores the importance of maintaining a high index of clinical suspicion, particularly in patients with culture-negative peritonitis who do not respond to broad-spectrum antibiotics and in patients with a history of recent urogenital manipulations or intra-abdominal surgical interventions.

Antimicrobial susceptibility testing (AST) was not performed in our case due to the failure to isolate the organism by conventional cultures. Data regarding the antimicrobial susceptibility of *Ureaplasma* spp., is limited. Inconsistencies arise from variability in interpretative criteria, coupled with challenges in the cultivation and performance of broth microdilution [5,22]. In some regions, such as South Africa, resistance rates of *Ureaplasma* spp to first-line drugs are high, significantly limiting treatment options [23]. In the United States, recent reports have identified levofloxacin resistance rates of 6.4 % and 5.2 % and a proportion of isolates showing ciprofloxacin MICs of ≥ 4 μg/mL for 27.2 % and 68.8 % in *U. parvum* and *U. urealyticum*, respectively, with no detected macrolide resistance. Only a single *U. parvum* isolate was resistant to tetracyclines, supporting the use of doxycycline in this context [5]. Variable resistance patterns to fluoroquinolones, macrolides, and tetracyclines have been reported in France, the UK, and Italy [24–26]. Therefore, when *Ureaplasma* spp. infection is suspected, clinicians should initially send specimens for molecular testing to establish a rapid diagnosis. This should ideally be followed by sending specimens to a especialized referral center for cultures and AST. When isolation of the organism is not possible, empiric mono- or combination therapy can be considered, depending on the local epidemiology, the clinical syndrome, and the overall status of the patient.

In conclusion, *Ureaplasma* spp infection should be considered in patients with culture-negative peritonitis who do not improve with broad-spectrum antibiotics, particularly young women following invasive urogenital procedures. Understanding local resistance patterns and isolating the organism for susceptibility testing, along with interventions aimed at source control are essential for successful treatment. The difficulty in cultivating *Ureaplasma* spp. highlights the importance of molecular diagnostics, such as 16 S rRNA PCR, in identifying these pathogens.

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Ethical Statement

A research authorization was signed by the patient allowing for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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