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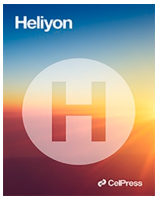

First case of *Cutibacterium avidum*-infected pelvic lymphocele post-lymphadenectomy for endometrial cancer: A case report

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ABSTRACT

Background: Pelvic lymphocele (lymphocyst) infection after lymphadenectomy is a rare complication that can cause the spread of inflammation to neighboring organs whose microbiology is not well known. *Cutibacterium avidum* causes various infections. However, no case reports of *C. avidum* pelvic lymphocele infection are available; therefore, its clinical characteristics in pelvic lymphocele infections remain unknown.

Case presentation: A 38-year-old woman with obesity (body mass index: 38.1 kg/m^2) and a history of pelvic lymphadenectomy and chemotherapy for endometrial cancer presented with worsening left lower quadrant (LLQ) pain with fever. Physical examination revealed decreased abdominal bowel sounds and tenderness on LLQ palpation with no signs of peritonitis. Computed tomography (CT) revealed an infected left pelvic lymphocele with inflammation spreading to the adjacent sigmoid colon. Following blood culture, ampicillin/sulbactam (2 g/1 g every 6 h) was administered intravenously. Anaerobic culture bottles revealed gram-positive rods on day 4 of incubation at 37 °C. No other disseminated foci were observed in enhanced whole-body CT and upon transthoracic echocardiography. The isolates grew aerobically and anaerobically on blood agar plates with strong hemolysis. The bacterium was identified as *C. avidum* using a combination of characteristic peak analysis with matrix-assisted laser desorption ionization (MALDI) and 16S rRNA gene sequencing. The patient was diagnosed with *C. avidum* pelvic lymphocele infection. Based on penicillin susceptibility, the patient was successfully treated with intravenous ampicillin/sulbactam and de-escalated with intravenous ampicillin (2 g every 6 h) for 10 days, followed by oral amoxicillin (2000 mg/day) for an additional 11 days without drainage.

Conclusions: C. avidum should be considered a causative microorganism of pelvic lymphocele infection. Peak analysis using MALDI and distinctive growth on blood agar plates are suitable for identifying *C. avidum*. Mild pelvic lymphocele caused by *C. avidum* can be treated with a short course of appropriate antimicrobial treatment without surgical intervention.

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1. Introduction

Bacteria of the genus *Cutibacterium* are skin commensal gram-positive rods that have been divided into five species: *Cutibacterium acnes, Cutibacterium granulosum, Cutibacterium modestum, Cutibacterium namnetense,* and *Cutibacterium avidum* [1,2]. *C. acnes*, the most predominant of these species, is a well-known causative microorganism of device/implant-related infections [2]. *C. avidum* was first described in 1935 [3] and has been recognized as a skin commensal characterized as an anaerobic and aerotolerant gram-positive rod [1]. In recent years, *C. avidum* has been recognized as causing various superficial or deep invasive infections in addition to device-related infections [1]. Pelvic lymphocele (lymphocyst) infection after lymphadenectomy for gynecological or urological cancers is a rare complication; however, it can cause problems in neighboring organs (e.g., hydronephrosis, inflammatory spread to neighboring organs) [4]. No case reports of infected pelvic lymphoceles caused by *C. avidum* have been described to date. Therefore, pathogenicity, optimal identification methods, and appropriate clinical management still need to be determined. Herein, we report the first case of *C. avidum* pelvic lymphocele infection after lymphadenectomy for endometrial cancer.

2. Case Presentation

A 38-year-old Japanese woman was admitted to our hospital with worsening left lower quadrant (LLQ) pain and fever for 10 days. Two years prior, she had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy for endometrial cancer, followed by six courses of chemotherapy (paclitaxel and carboplatin; TC therapy) because of the high risk of recurrence based on lymphovascular space invasion, myometrial invasion of ≥50 %, and cervical stromal invasion despite having tumor grade 1. The last chemotherapy regimen was administered 19 months before the current admission. At a follow-up outpatient visit 5 months before the admission, she was diagnosed with postoperative left pelvic lymphocele of the external iliac area without endometrial cancer recurrence. However, the patient had no other history of lymphocele (Fig. 1A).

On admission, she was alert; vital signs were as follows: body temperature, 38.9 °C; blood pressure, 141/82 mmHg; heart rate, 107 beats/min; respiratory rate, 18 breaths/min; and oxygen saturation, 99 % with ambient air. Her height and weight were 162 cm and 100 kg, respectively; her body mass index was 38.1 kg/m^2. Physical examination revealed decreased abdominal bowel sounds and tenderness on palpation of the LLQ, with no signs of peritonitis. No other abnormalities, including asymptomatic lower-limb abrasion, were observed. The laboratory findings included: C-reactive protein, 176.4 mg/L (reference range, 0.0–1.0 mg/L); and white blood cell count, 15,400/μL (reference range, 3800–9000/μL) with 78.9 % neutrophils. Abdominal computed tomography (CT) on admission showed evidence of infection of the postoperative left pelvic lymphocele, with inflammation spreading to the adjacent sigmoid colon (Fig. 1B and C).

After two sets of blood cultures (aerobic and anaerobic) were obtained, intravenous ampicillin/sulbactam (2 g/1 g every 6 h) was administered since she had normal renal function. Planned CT-guided drainage on day 4 was canceled because the pain gradually reduced with the alleviation of fever; CT showed that the infected lymphocele was shrinking following intravenous ampicillin/sulbactam administration (Fig. 1D). Anaerobic culture bottles were found to be positive on day 4 of incubation at 37 °C, and gram-positive rods were observed (Fig. 2A). The isolates were cultured on trypticase soy agar with 5 % sheep blood (Nihon Becton-Dickinson, Tokyo,

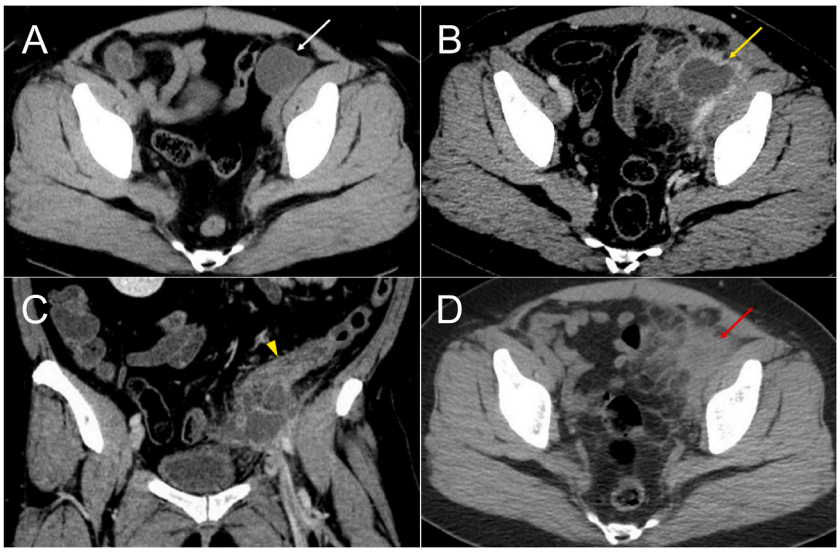

Fig. 1. Radiological findings. (A) In the postoperative follow-up CT, the patient exhibited a left pelvic lymphocele of the external iliac area without infection (white arrow). (B) CT on day 0 showed severe inflammation around the lymphocele (yellow arrow). (C) The inflammation spread to the adjacent sigmoid colon (yellow arrowhead) in the coronal section. (D) CT image in planned CT-guided drainage on day 4 revealed that the infected lymphocele was shrinking (red arrow). CT, computed tomography.

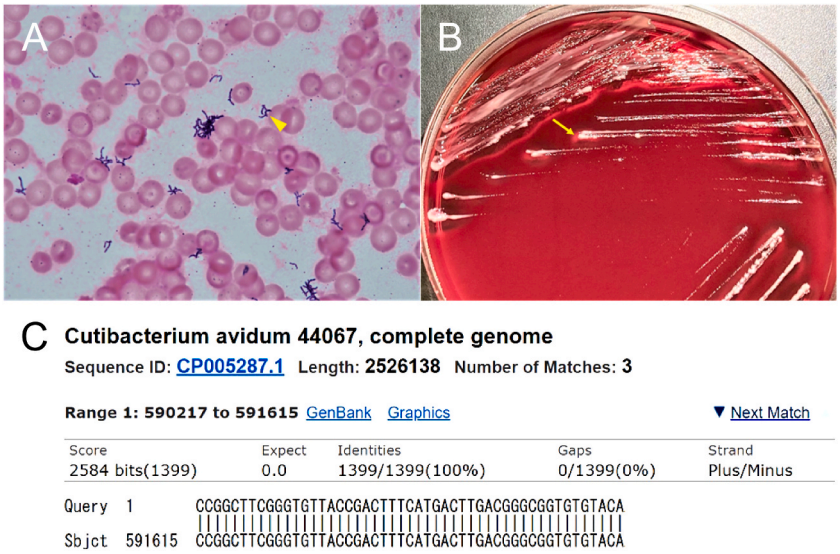

Fig. 2. Microbiological findings. (A) Gram staining (1000 ×) revealed coryneform gram-positive rods (yellow arrowhead). (B) Circular, shiny, white colonies with beta-hemolysis (yellow arrow) were observed after culturing on trypticase soy agar with 5 % sheep blood (Nihon Becton-Dickinson) for 2 days at 37 °C under anaerobic conditions. (C) The isolate was identified as *Cutibacterium avidum* using 16S rRNA gene sequencing and analysis using the GenBank Basic Local Alignment Search Tool, which indicated 100 % similarity to *C. avidum* (GenBank accession no. CP005287.1).

Japan) for 2 days at 37 °C under aerobic and anaerobic conditions; they formed hemolytic and circular, white, shiny colonies under both conditions (Fig. 2B). Using a Vitek® 2 automated microbial identification system (bioMérieux, Marcy l'Etoile, France), the isolates were identified as *C. granulosum*. In contrast, a matrix-assisted laser desorption ionization (MALDI) Biotyper® (Bruker Daltonik GmbH, Bremen, Germany) identified them as *C. avidum* with a high score of >2.0. The isolate from anaerobic culture was further identified as *C. avidum* using 16S rRNA gene sequencing and analysis using the GenBank Basic Local Alignment Search Tool, which indicated 100 % (with identities 1399/1399, gaps 0/1399) similarity to *C. avidum* (GenBank accession no. CP005287.1) (Fig. 2C). Antimicrobial susceptibility testing was performed using E-test® (bioMérieux) after 48 h of incubation at 37 °C under anaerobic conditions, indicating that these isolates were susceptible to various antimicrobials, including ampicillin, with a minimum inhibitory concentration of 0.125 μg/mL, according to the Clinical and Laboratory Standards Institute criteria (M100-S32; Table 1) [5].

The patient was diagnosed with pelvic lymphocele infection caused by *C. avidum*, and ampicillin/sulbactam was de-escalated to intravenous ampicillin (2 g every 6 h) on day 7 in accordance with the susceptibility test results. There was no evidence of disseminated foci in enhanced whole-body CT and infective endocarditis upon transthoracic echocardiography. The patient was discharged with oral amoxicillin (2000 mg/day) on day 10 and was followed up as an outpatient. Oral amoxicillin was discontinued on day 21 after admission, and the patient remained disease-free without recurrence at the postoperative follow-up for endometrial cancer three months after discharge.

3. Discussion

This case highlights the potential of *C. avidum* to cause pelvic lymphocele in patients with obesity and a history of surgery and

Table 1
Antimicrobial susceptibility test results.

Cutibacterium avidum		
Antimicrobial agent	MIC (μg/mL)	
Benzylpenicillin	0.094	S
Ampicillin	0.125	S
Amoxicillin	0.19	S
Ampicillin/sulbactam	0.094	S
Amoxicillin/clavulanate	0.125	S
Cefotaxime	0.25	S
Ceftriaxone	0.25	S
Meropenem	0.125	S
Tetracycline	0.75	S
Clindamycin	0.032	S

MIC, minimal inhibitory concentration; S, susceptible.

chemotherapy for endometrial cancer. There are three clinical issues to address: 1) the clinical characteristics of *C. avidum*, 2) reasonable methods to identify *C. avidum*, and 3) therapeutic strategies for lymphoceles caused by *C. avidum*.

Of the five Cutibacterium species, C. avidum is microbiologically different from the predominant Cutibacterium species, including C. acnes, with respect to its habitat and nutritional requirements [1,2]. *C. acnes* and *C. granulosum* reside in oil-rich areas in humans, whereas *C. avidum* is distributed in moist areas (e.g., the anterior nares, axilla, groin, and rectum) and requires less nutrition to grow compared with other *Cutibacterium species* [1,2]. These characteristics indicate that *C. avidum* may be clinically different from *C. acnes* and *C. granulosum* [1,2]. Over the last two decades, *C. avidum* has gained recognition for causing various superficial or deep, invasive infections. These include device/implant-related infections [6,7], bone and joint infections [8,9], infective endocarditis [10], and skin [11–16], perianal [17], splenic [18,19], and intraperitoneal [20,21] abscesses. *C. avidum* is associated with implanted foreign bodies, trauma, diabetes, previous surgery, malignancy, immunosuppression, and obesity [11,22]. In particular, immunosuppressed patients with obesity and malignancies who undergo surgery and chemotherapy/radiotherapy can be predisposed to *C. avidum* infections despite the absence of an implanted foreign body [1]. Therefore, our patient was susceptible to *C. avidum* infection.

C. avidum resides not only in moist skin areas but also in the intestinal tract, including the rectum, which is populated with enteric gram-negative bacteria [1]. In our patient, the source of the left pelvic lymphocele was unclear, as there were no visible skin abnormalities (e.g., wounds and abrasion) of the limbs at admission. However, we believe that the most plausible entry site of *C. avidum* was a preceding microinjury of the left lower limb, since a postoperative left pelvic lymphocele of the external iliac area without inflammation has previously been observed in an outpatient setting. Additionally, our patient with a pelvic lymphocele and inflammation spreading to the adjacent sigmoid colon recovered following de-escalation with intravenous ampicillin and oral amoxicillin. This antimicrobial treatment should not affect the intestinal/colon microbiota as it is populated with *Bacteroides fragilis*, a β-lactamase-producing intestinal bacterium.

In clinical settings, diagnosing *Cutibacterium* infections is difficult because the anaerobic incubation period required for the isolates to grow is >7 days [1]. Additionally, identifying *C. avidum* at the species level is difficult because of its similarity to other *Cutibacterium* species [1]. However, *C. avidum* has three features that differentiate it from other *Cutibacterium* species. First, *C. avidum* grows faster than other *Cutibacterium species*, particularly *C. acnes* [1]. In our case, the anaerobic culture bottles were positive on day 4 of incubation, and the isolates grew anaerobically on trypticase soy agar with 5 % sheep blood for 2 days at 37 °C; this contributed to prompt and appropriate antimicrobial de-escalation. Second, environmental oxygen concentrations affect the growth of *Cutibacterium* species [23]. *C. avidum* exhibits a remarkable ability to thrive under aerobic conditions because it is an aerobically tolerant microorganism [23]. In our case, the isolates grew with β-hemolysis on trypticase soy agar with 5 % sheep blood (Nihon Becton–Dickinson) for 2 days at 37 °C under not only anaerobic but also aerobic conditions. Third, colonies of *C. avidum*, which produce hemolysins, grow on blood agar plates with stronger hemolysis than does *C. acnes* [1,2,6]. Considering the strong hemolysis, we suspected *C. avidum* despite the result of "*C. granulosum*" given by Vitek 2®, as it is a conventional microbial identification system that does not have the spectra of *C. avidum* within its database (ver. 9.02) and because *C. granulosum* does not yield colonies with hemolysis. These features should aid clinicians in identifying *C. avidum*.

Over the last two decades, MALDI-time-of-flight mass spectrometry has enabled clinicians to identify the causative microorganisms of infections quickly and accurately. Corvec reported that, using Vitek MS®, the eight dominant peaks in the MALDI spectrum of *C. avidum* are present at 3685.4, 4,762, 5125.9, 6526.4, 6776.6, 6818.7, 7,369, and 1,3045 *m/z* with excellent discriminatory power and intensity, which are absent for other *Cutibacterium* species [1]. The MALDI Biotyper® has four *C. avidum* spectra in version 8.0 of the database (Table S1). In our case, the MALDI Biotyper® (Bruker Daltonik GmbH) accurately identified the isolates as *C. avidum* VA7144_11 ERL, which coincided with the result of 16S rRNA gene sequencing, with a high score value.

The optimal therapeutic strategy to treat lymphoceles caused by *C. avidum* remains uncertain. The microbiota of infected lymphoceles consisted of 73.9 % gram-positive bacteria, 22.2 % gram-negative bacteria, and 3.9 % others [4]. Notably, gram-positive rods accounted for less than 1.8 % of the gram-positive bacteria [4]. *C. avidum* has been recognized as generally susceptible to β-lactams (such as penicillins), fluoroquinolones, and macrolides, whereas it is resistant to clindamycin [1,24]. However, two recent studies have reported the antimicrobial resistance of *C. avidum*. One study reported that erm(X) can be transmitted between *C. acnes* and *C. avidum* via Tn5432, which leads to both macrolide and clindamycin resistance [25]. Another study reported that a *C. avidum* strain acquired resistance to rifampin and levofloxacin during the treatment of orthopedic device-related infection [26]. These results suggest that penicillins can be reasonable antimicrobial agents for infected lymphocele cases presenting with coryneform gram-positive rods that can grow aerobically and anaerobically on blood agar plates with strong hemolysis and negative indole spots.

Early drainage of infected lymphoceles (by day 5) contributes to a reduced total antimicrobial treatment period [27]; it is performed in cases of prolonged fever, complications (e.g., hydronephrosis), and for the identification of causative bacteria [4,27]. Our patient was scheduled to undergo early drainage on day 4 for the left pelvic lymphocele as the inflammation had spread to the adjacent sigmoid colon and to identify the pathogen. However, the procedure was canceled when the fever subsided, the infected lymphocele shrunk, and *C. avidum* was identified in blood cultures.

The optimal duration of antimicrobial treatment for infected pelvic lymphocele has not yet been established. Yamamoto et al. reported that they administered antimicrobials for 4–6 weeks with drainage for infected pelvic lymphoceles in 70 % of cases in accordance with the therapeutic strategy for abdominal abscesses [4]. In contrast, Hiramatsu et al. reported that the average duration of antimicrobial therapy was 14 days, with drainage in 74 % of cases [27]. Additionally, a literature review of *C. avidum* infections revealed that most cases (95.8 %) required surgical intervention, including drainage, debridement, or other surgery; approximately one third of cases (30.8 %) resulted in unfavorable outcomes [1]. In our case, the patient was treated with intravenous ampicillin/sulbactam and de-escalated with intravenous ampicillin for 10 days, followed by oral amoxicillin for 11 days without drainage.

This study has two limitations. First, a drainage sample was not obtained to determine mono-bacterial infections caused by

C. avidum. Second, the isolates were tested using a MALDI Biotyper® but not by Vitek MS®; therefore, we could not compare the accuracy of both MALDI-based analysis techniques.

4. Conclusion

In conclusion, an unrecognized microorganism, which was found to be *C. avidum*, caused pelvic lymphocele infection in an individual with obesity who had undergone lymphadenectomy followed by chemotherapy/radiotherapy for endometrial cancer. Peak analysis using MALDI is acceptable for identifying *C. avidum* in addition to its distinctive growth on blood agar plates. Mild pelvic lymphocele caused by *C. avidum* can be treated with a short course of appropriate antimicrobial treatment without surgical intervention.

Ethics statement

This study was reviewed and approved by the Institutional Review Board and Ethics Committee of the Japanese Red Cross Ise Hospital (approval number: ER2023-4). The patient provided informed consent to participate in the study.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the written consent form is available for review by the Editor-in-Chief of this journal upon request.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are included in the manuscript.

CRediT authorship contribution statement

Hirokazu Toyoshima: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Motoaki Tanigawa:** Writing – review & editing, Writing – original draft, Supervision. **Kanako Nakamura:** Formal analysis, Data curation. **Chiaki Ishiguro:** Formal analysis, Data curation. **Hiroyuki Tanaka:** Conceptualization. **Yuki Nakanishi:** Conceptualization. **Shigetoshi Sakabe:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21396.

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