Spontaneous Bacterial Pericarditis with Tamponade Due to \textit{Ureaplasma} \textit{spp.}\textsuperscript{\textdagger}

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Infectious pericardial effusion with tamponade is an uncommon but life-threatening disease. We report an unusual case of spontaneous \textit{Ureaplasma} pericardial effusion with tamponade associated with pneumonia, pleural effusion, and urinary tract infection. All published cases of clinically invasive \textit{Ureaplasma} infections in the adult population are also reviewed.

CASE REPORT

A Hispanic female in her 10th decade of life, with a past medical history of type 2 diabetes mellitus, hypertension, and colon cancer status post hemicolectomy performed 9 years earlier, presented to the emergency department of our tertiary care hospital with chief complaints of shortness of breath, cough, and altered mental status. The patient’s symptoms began about 1 week prior to admission, with a slow onset of generalized malaise and cough that had become increasingly more severe over the previous 2 days. The patient was limited to minimal exertion without having to stop due to shortness of breath. Upon arrival at the emergency department, she was confused and in respiratory distress. Her vital signs were as follows: blood pressure, 111/52 mmHg; pulse, 87 beats/min; respiratory rate, 18 breaths/min; temperature, 97.4°F; and pulse oximetry, 99% on 2 liters of oxygen via nasal cannula. Physical exam was notable for rales bilaterally in the lower lobes, distant heart sounds, and jugular venous pressure of 9 cm/H2O. A left lower lobe infiltrate and an enlarged cardiac silhouette were noted on the initial chest radiograph (Fig. 1A and B).

The patient was admitted with a diagnosis of pneumonia and altered mental status. Empirical antibiotic therapy was started immediately, using ceftriaxone (1 g intravenously [IV]) and azithromycin (500 mg IV). Laboratory studies showed anemia of chronic disease (hemoglobin, 11 g/dl [normal reference range, 12 to 16 g/dl]); hematocrit, 35.3% [37 to 47%]; mean corpuscular volume, 97.8 fl [82 to 100 fl]; iron concentration, 24 \mu g/dl [40 to 160 \mu g/dl]; iron binding capacity, 280 \mu g/dl [275 to 400 \mu g/dl]; ferritin, 97 ng/ml [38 to 384 ng/ml]; and saturation, 8.6% [15 to 38%]). The peripheral blood smear showed a normal leukocyte count of 7.31 \times 10^{3} cells/\mu l (4.50 \times 10^{3} to 11.00 \times 10^{3} cells/\mu l), with mild neutrophilia (71%). Creatinine and beta-natriuretic peptide levels were within the normal limits. On the fourth day of admission, the patient’s hemoglobin level decreased to 10.1 g/dl, and a red blood cell transfusion was considered. The typing and screening revealed no blood antigen group antibodies, and no cryoglobulins were found using a direct agglutination test. After a 24-hour follow-up observation, the anemia was determined to be stable, so no transfusion was performed. A routine microbiological workup was performed on her urine and blood. Urinalysis demonstrated cloudy urine, with many bacteria on the Gram stain; however, no organisms were isolated by the urine culture. There was no growth in the blood cultures, and no microorganisms were seen on the direct Gram stain or Kinyoun acid-fast stain.

Further evaluation included a detailed radiology study of the chest and abdomen that showed a moderate right and a small left pleural effusion, with atelectasis in the bilateral lower lobes and a moderate pericardial effusion (Fig. 1C). An electrocardiogram revealed sinus tachycardia and low voltage on the precordial leads. A subsequent two-dimensional echocardiogram confirmed the large circumferential pericardial effusion, with right ventricular diastolic and right atrial systolic collapse (Fig. 1D). The patient was started on methylprednisolone before receiving a pericardial window, based on a diagnosis of pericardial effusion with tamponade. Approximately 800 ml of bloody pericardial fluid was evacuated. The fluid was sent to pathology for Gram and acid-fast bacteria staining and anaerobic, aerobic, fungus, \textit{Mycoplasma}, and \textit{Nocardia} culturing. Histopathological examination of the pericardial fluid (Fig. 1E and F) showed small lymphocytes, acute inflammatory cells, mesothelial cells, and hemosiderin-laden histiocytes. No malignant cells were seen. All microbiology stains and cultures performed in our laboratory were negative. Mycoplasma testing (performed at the ARUP National Reference Laboratory) by the Mycofast US (ELITech France SAS, France) culture method was also negative. Growth of \textit{Ureaplasma} sp. was detected on A8 agar after 48 hours of incubation at 37°C in an atmosphere enriched with 7.5% CO₂. \textit{Ureaplasma} sp. were distinguished from \textit{Mycoplasma hominis} on the A8 agar based on their round granular colony morphology. Bacterial colonies were not quantified. The isolate was not available for molecular testing, so species identification to discriminate \textit{Ureaplasma urealyticum} from \textit{Ureaplasma parvum} was not possible.

The patient had significant clinical improvement following placement of the pericardial window. When the \textit{Ureaplasma} sp.

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was reported on admission day 7, the patient was stable, with mild clinical improvement, but her neutrophil count remained elevated (85%). Immediately after the identification of the *Ureaplasma* sp., she was switched to doxycycline (100 mg every 12 h orally) from the 2-day postoperative empirical antibacterial therapy that consisted of ceftriaxone (1 g IV), azithromycin (500 mg IV), and vancomycin (1 g IV). Her clinical status and neurologic state returned to baseline 2 days later. Since *Ureaplasma* spp. are generally susceptible to azithromycin and doxycycline, it was unclear whether the antibiotic change played a significant role in her recovery following placement of the pericardial window. She was discharged on day 18, with resolution of the neutrophilia (hemoglobin, 10.9 g/dl [normal reference range, 12 to 16 g/dl]; hematocrit, 34.8% [37 to 47%]; mean corpuscular volume, 98.3 fl [82 to 100 fl]; and leukocyte count, $8.86 \times 10^3$ cells/μl [$4.5 \times 10^3$ to $11 \times 10^3$ cells/μl], with 62% neutrophils [39 to 69%]). This study was approved by the Institutional Review Board.

**Discussion.** This patient’s pericardial effusion was diagnosed only after the imaging studies were performed, following an initial evaluation for dyspnea. Although clinical signs of cardiac tamponade developed while she was in the hospital, the clinical picture upon admission was atypical community-acquired pneumonia with anemia and altered mental status. The possibility of congestive heart failure was thought to be low, especially considering the normal level of serum beta-natriuretic peptide. The identification of the *Ureaplasma* sp. in the pericardial fluid was an unanticipated but significant finding. The underlying clinical concern was an atypical pneumonia with anemia of chronic disease and secondary pericardial effusion. In this clinical context, *Mycoplasma pneumoniae* is among the most common pathogens (17), but it has rarely been associated with pericarditis (7). Likewise, bacterial pericarditis following pneumonia due to *Streptococcus pneumoniae* has been infrequently reported. *Ureaplasma* infection was not suspected. Waites et al. have postulated that expression of homologous virulence factors such as adhesins and immunoglobulin A proteases that are expressed by *Ureaplasma* spp. may contribute significantly to the pathogenesis of invasive infection, but well-controlled animal studies have yet to fully establish their contribution to disease (16).
Ureaplasma spp. are weak pathogens that are frequently found in the urogenital tract of healthy asymptomatic adults. However, as demonstrated by the case presented herein, these organisms may occasionally cause severe invasive disease. Infection with Ureaplasma spp. in anatomical sites outside the urogenital tract is extremely rare in the adult population (Table 1) (6, 8, 9, 12, 13). Notably, published cases include infection of the pleura and meninges. Each of these patients had well-defined predisposing conditions and a plausible source of infectious inoculation (Table 1). Although several cases of postoperative mediastinitis with pericarditis and one case of posttransplant pericarditis have also been described (Table 1) (8, 11, 12, 13), no cases of spontaneous pericarditis have been previously reported with this pathogen. Even though the patient reported herein has several immunosuppressing conditions that may have contributed to infection susceptibility, she had no recent history of surgery or instrumentation that would have introduced the pathogen into her thorax or vascular system. As such, the exact etiology of her pericardial effusion remains uncertain. She may have had a primary Ureaplasma pneumonia, with direct extension into the pericardial space. Alternatively, she may have had a urinary tract infection with intermittent hemogenous dissemination of Ureaplasma sp., resulting in a purulent pericardial effusion and secondary pneumonia. Because the Ureaplasma sp. was isolated only from the pericardial fluid, it is impossible to determine the primary source of infection. Either scenario is feasible, given a recent history of cloudy urine and cough. Regardless of the source, the occurrence of this pathogen in her pericardial space resulted in a life-threatening infection. Experience in treating invasive Ureaplasma infections is limited. We suggest that that a prompt detection of invasive Ureaplasma infections is crucial for directing appropriate antibiotic coverage and achieving an optimal clinical outcome. As such, this case demonstrates that difficult identification and infrequent occurrence may cause invasive Ureaplasma infections to be overlooked by physicians and laboratory personnel. A heightened clinical suspicion is necessary when routine culture and histopathology findings do not readily isolate an organism or when the patient does not respond to empirical antibiotic and anti-inflammatory treatments.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Predisposing conditions</th>
<th>Age (yr)</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureaplasma urealyticum pericarditis</td>
<td>Heart transplant, immunosuppressors</td>
<td>55</td>
<td>Complete recovery</td>
<td>11</td>
</tr>
<tr>
<td>Ureaplasma urealyticum meningitis</td>
<td>Kidney transplant, infected retroperitoneal hematoma, immunosuppressors, lympholiferative disorder</td>
<td>38</td>
<td>Complete recovery</td>
<td>9</td>
</tr>
<tr>
<td>Intrarenal abscesses in transplanted kidney</td>
<td>Kidney transplant, immunosuppressors, history of B-cell lymphoma</td>
<td>19</td>
<td>Complete recovery</td>
<td>6</td>
</tr>
<tr>
<td>Ureaplasma urealyticum in mediastinum and pleural fluid</td>
<td>Heart and lung transplants, immunosuppressors</td>
<td>48</td>
<td>Resolved</td>
<td>13</td>
</tr>
<tr>
<td>Ureaplasma urealyticum in sternum wound specimen</td>
<td>Coronary artery bypass surgery, diabetes</td>
<td>63</td>
<td>Resolved</td>
<td>13</td>
</tr>
<tr>
<td>Post-operative mediastinitis</td>
<td>Aortic valve replacement, chronic obstructive pulmonary disease</td>
<td>77</td>
<td>Fatal</td>
<td>8</td>
</tr>
</tbody>
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Ureaplasma spp. can be detected by several laboratory methods (Table 2). Isolation traditionally relied on growth on A7 agar, followed by microscopic examination of the colonies (15). Colonies typically grow in 2 to 5 days, but cultures are not considered negative until 7 days of no growth (17). However, A8 agar has become the preferred growth medium in many microbiology laboratories since it does not contain manganese salts that inhibit some Ureaplasma serotypes. Commercially available diagnostic kits such as Mycofast US (ELITEch France SAS, France) and Mycoplasma Duo (Sanofi Diagnostics Pasteur, France) offer simplified alternatives to conventional culture. These rapid diagnostic kits use biochemical phenotyping of organisms grown in a selective and differential liquid media following 24 to 48 h of incubation. Specifically, they test for urea or arginine hydrolysis via a phenol red pH indicator that detects ammonia liberation. Ureaplasma spp. are then identified based on their resistance/susceptibility profiles to a panel of three antibiotics (Ureaplasma spp. are resistant to lincomycin but susceptible to erythromycin, whereas M. hominis is susceptible to lincomycin but resistant to erythromycin; both are resistant to trimethoprim-sulfamethoxazole). Published studies demonstrate that the rapid culture techniques compare favorably to traditional culture in test performance, having relatively similar sensitivities, specificities, and positive predictive values (Table 2). Nucleic acid amplification-based modalities have also been developed for Ureaplasma spp. PCR has detected the organisms from a variety of clinical specimens, including the adult urogenital tract, amniotic fluid, and neonatal endotracheal aspirates (2, 3, 5). Reports comparing PCR and traditional culture techniques have shown sensitivities and specificities to favor PCR (Table 2). However, Povlsen et al. demonstrated that the sensitivity of PCR was dependent on the

<table>
<thead>
<tr>
<th>Method (reference[s])</th>
<th>Sensitivities (%)</th>
<th>Specificities (%)</th>
<th>Positive predictive value(s) (%)</th>
<th>Turnaround time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycofast US (10)</td>
<td>86–98</td>
<td>73–100</td>
<td>93</td>
<td>24–48 h</td>
</tr>
<tr>
<td>Ureaplasma culture</td>
<td>86–93</td>
<td>89–91</td>
<td>97</td>
<td>2–5 days</td>
</tr>
<tr>
<td>PCR for Ureaplasma spp. (2, 3, 5)</td>
<td>64–95</td>
<td>95–98</td>
<td>91–99</td>
<td>24–48 h</td>
</tr>
</tbody>
</table>
concentration of *Ureaplasma* spp. within the specimen (14). Samples of inocula with \( \leq 10^3 \) color-changing units yielded PCR sensitivities that ranged from 0 to 86%, whereas those with \( > 10^3 \) color-changing units produced PCR sensitivities ranging from 97 to 100%. PCR also enables isolate identification to the species level using the newly derived serovar classification system. Although some evidence suggests that *U. urealyticum* is more pathogenic than *U. parvum*, the clinical/pathological significance of this new nomenclature remains uncertain. In addition, turnaround times for in-house PCR testing are reduced to 24 to 48 h from the 2- to 5-day expected turnaround time for culture (1, 5). Importantly, Cheah et al. demonstrated a 96% agreement between the Mycoplasma Duo test and PCR for *Ureaplasma* detection in endotracheal aspirates from 68 premature infants (3).

As with all diagnostic testing in the clinical laboratory, multiple factors must be considered before implementation, including the patient population served, demand by ordering physicians, cost and reimbursement, laboratory personnel and technology availability, and turnaround times. The fragility of *Ureaplasma* spp. can pose a challenge to traditional culture techniques. Likewise, transport and storage of specimens prior to processing are important. The potentially rapid turnaround times offered by the use of molecular techniques is appealing, but the associated cost and personnel requirements may not make in-house PCR testing feasible. Similarly, the rapid culture kits may facilitate pathogen identification; however, as in our case presented herein, conventional culture offers the highest recovery rate. As such, we recommend that laboratories utilize a combination of rapid and conventional techniques for *Ureaplasma* isolation, particularly when suspicion of an invasive infection is high.

**Concluding comment.** This case is remarkable for the following three reasons. (i) A *Ureaplasma* sp. has not been reported previously as a cause of spontaneous bacterial pericardial effusion. (ii) *Mycoplasma* spp. and *Ureaplasma* spp. must be included on the differential diagnosis of primary pericardial effusion and other invasive infections, or it may be easily missed. (iii) Though they are valuable tools to supplement conventional culture in the clinical laboratory, rapid diagnostic techniques still may not allow *Ureaplasma* spp. to be diagnosed.

REFERENCES