Spontaneous Bacterial Pericarditis with Tamponade due to *Ureaplasma* spp.

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Infectious pericardial effusion with tamponade is an uncommon but life threatening disease. We report an unusual case of spontaneous *Ureaplasma spp.* pericardial effusion with tamponade associated with pneumonia, pleural effusion, and urinary tract infection. All published cases of clinically invasive *Ureaplasma spp.* infections in the adult population are also reviewed.
A Hispanic female in her tenth decade of life with a past medical history of type 2 diabetes mellitus, hypertension, and colon cancer status-post hemicolecction performed nine years earlier presented to the emergency department (ED) of our tertiary care hospital with a chief complaint of shortness of breath, cough, and altered mental status. The patient’s symptoms began about one week prior to admission with a slow onset of generalized malaise and cough that had become increasingly more severe over the previous two days. The patient was limited to minimal exertion without having to stop due to shortness of breath. Upon arrival to the ED, she was confused and in respiratory distress. Vital signs were: blood pressure 111/52 mmHg, pulse 87/min, respiratory rate 18/min, temperature 97.4°F, and pulse oximetry 99% on 2 L of oxygen via nasal canula. 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. 1, A and B).

The patient was admitted with a diagnosis of pneumonia and altered mental status. Empirical antibiotic therapy was started immediately with ceftriaxone (1 g IV) and azithromycin (500 mg IV). Laboratory studies showed anemia of chronic disease (hemoglobin 11 g/dL [12-16], hematocrit 35.3% [37-47], MCV 97.8 fL [82-100], iron concentration 24 µg/dL [40-160], iron binding capacity 280 µg/dL [275-400], ferritin 97 ng/mL [38-384], and saturation 8.6% [15-38]). The peripheral blood smear showed a normal leukocyte count of 7.31 10³/µL [4.50 – 11.00] with mild neutrophilia (71%). Creatinine and beta-natriuretic peptide levels were within normal limits. On the fourth day of admission, the patient’s hemoglobin decreased to 10.1 g/dL and a red blood cell
transfusion was considered. The type and screen 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. Routine microbiological work-up was performed on 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. 1, C). An electrocardiogram revealed sinus tachycardia and low voltage on the precordial leads. A subsequent 2D echocardiogram confirmed the large circumferential pericardial effusion with right ventricular diastolic and right atrial systolic collapse (Fig. 1, D). The patient was started on methylprednisolone before placing a pericardial window based on a diagnosis of pericardial effusion with tamponade. Approximately 800 mL of bloody pericardial fluid were evacuated. The fluid was sent to pathology for Gram and acid fast bacteria stain, and anaerobic, aerobic, fungus, *Mycoplasma*, and *Nocardia* culture. The histopathological examination of the pericardial fluid (Fig. 1, E 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 Mycofast® US; (ELITech France SAS, France) culture method was also negative. Growth of *Ureaplasma* spp. was detected on A8 agar.
after 48-hours of incubation at 37°C in an atmosphere enriched with 7.5% CO₂. 

*Ureaplasma spp.* was distinguished from *M. hominis* on the A8 agar based on its round granular colony morphology. Bacterial colonies were not quantified. The isolate was not available for PCR testing, so species identification to discriminate *U. urealyticum* from *U. parvum* was not possible.

The patient had significant clinical improvement following placement of the pericardial window. When the *Ureaplasma. spp.* was reported on admission day 7, the patient was stable with mild clinical improvement but her neutrophil count remained elevated (85%). Immediately after the *Ureaplasma spp.* identification, she was switched to doxycyclin (100 mg q12 PO) from the two-day post-operative empirical antibacterial therapy that consisted of ceftriaxone (1 g IV), azithromycin (500 mg IV), and vancomycin (1g IV). Her clinical status and neurologic state returned to baseline two days later. Since *Ureaplasma spp.* are generally susceptible to azithromycin as well as 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 [12-16], hematocrit 34.8 % [37-47], MCV 98.3 fL [82-100], and WBC of 8.86 x 10³/µL [4.5-11] with 62% neutrophils [39-69]). This study was approved by the institutional review board.
Our 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 on 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. Identification of *Ureaplasma* spp. 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 (16), but it has been rarely associated with pericarditis (7). Likewise, bacterial pericarditis following pneumonia due to *Streptococcus pneumoniae* has been infrequently reported. *Ureaplasma spp.* infection was not suspected. Waites et al have postulated that expression of homologous virulence factors such as adhesions and IgA proteases that are expressed by *Ureaplasma spp.* may contribute significantly to pathogenesis of invasive infection, but well-controlled animal studies have yet to fully establish their contribution to disease (15).

*Ureaplasma spp.* is a weak pathogen that is frequently found in the urogenital tract of healthy asymptomatic adults. However, as demonstrated by the case presented herein, the organism may occasionally cause severe invasive disease. *Ureaplasma spp.* is a well-known agent of non-gonococcal urethritis, postpartum fever-abortion, chorioamnionitis, and neonatal sepsis (15). 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 post-operative mediastinitis with pericarditis and one case of post-transplant 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 spp.* pneumonia with direct extension into the pericardial space. Alternatively, she may have had a urinary tract infection with intermittent hematogenous dissemination of *Ureaplasma spp.* resulting in a purulent pericardial effusion and secondary pneumonia. Because *Ureaplasma spp.* 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 spp.* infections is limited. We suggest that that a prompt detection of invasive *Ureaplasma spp.* 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 spp.* 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 empiric antibiotic and anti-inflammatory treatment.

_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 (14). Colonies typically grow in 2-5 days, but cultures are not considered negative until 7 days of no growth (16). However, A8 agar has become the preferred growth media 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 24-48 hours 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 the resistance/susceptibility profile 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 species are resistant to Trimethoprim/Sulfamethoxazole). Published studies demonstrate the rapid culture techniques compare favorably to traditional culture in test performance, having relatively similar sensitivity, specificity, and positive predictive value (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 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 concentration of *Ureaplasma spp.* within the specimen. Samples with inoculums ≤ 10^3 color changing units (CCUs) yielded PCR sensitivities that ranged from 0-86% whereas those with > 10^3 CCUs produced PCR sensitivities ranging from 97-100%. 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 24-48 hr from the 2-5 day expected turn around time for culture (1, 5).

Importantly, Cheah et al demonstrated a 96% agreement between the Mycoplasma Duo® Test and PCR for *Ureaplasma spp.* detection in endotracheal aspirates from sixty-eight premature infants (3).

As with all diagnostic testing in the clinical laboratory, multiple factors must be considered before implementation, including 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 is important. The potentially rapid turnaround times offered by 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. As such, we recommend that laboratories utilize a
combination of rapid and conventional techniques for *Ureaplasma spp.* isolation, particularly when suspicion for an invasive infection is high.
CONCLUDING COMMENT

This case is remarkable for three reasons. (i) *Ureaplasma spp.* 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 a valuable tool to supplement conventional culture in the clinical laboratory, rapid diagnostic techniques may still not allow *Ureaplasma spp.* to be diagnosed.
REFERENCES


FIGURE LEGEND

Fig. 1 A and B: Anterior-posterior and lateral chest x-ray demonstrating enlarged cardiac silhouette and mild left lower lobe infiltrates. C. CT scan showing pericardial effusion with bilateral mild pleural effusion and left lower lobe pneumonia. D. Two-dimensional echocardiogram (apical, left chambers view) showing pericardial effusion. E. Fibrinoid pericarditis with chronic inflammation was identified in tissue sections from the pericardium (hematoxylin and eosin stain, original magnification 10X). F. Lymphocytes and hemosiderin-laden histiocytes were identified in the pericardial effusion cytospin preparations (Papanicolaou stain, original magnification 60X).
Table 1: Review of published cases of invasive *Ureaplasma spp.* infection.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Clinical presentation</th>
<th>Predisposing condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(11)</td>
<td>55</td>
<td><em>Ureaplasma urealyticum</em> pericarditis</td>
<td>Heart transplant, immunosuppressors</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>(9)</td>
<td>38</td>
<td><em>Ureaplasma urealyticum</em> meningitis</td>
<td>Kidney transplant, infected retroperitoneal hematoma, immunosuppressors, lympholiferative disorder</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>(6)</td>
<td>19</td>
<td>Intrarenal abscesses in transplanted kidney</td>
<td>Kidney transplant, immunosuppressors, history of B cell lymphoma</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>(13)</td>
<td>48</td>
<td><em>Ureaplasma urealyticum</em> in mediastinum and pleural</td>
<td>Heart and lung transplant, immunosuppressors</td>
<td>Resolved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluid</td>
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<td>---</td>
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</tr>
<tr>
<td>(13)</td>
<td>63</td>
<td><em>Ureaplasma urealyticum</em> in sternum wound specimen</td>
<td>Coronary artery bypass surgery, diabetes</td>
<td>Resolved</td>
</tr>
<tr>
<td>(8)</td>
<td>77</td>
<td>Post-operative mediastinitis</td>
<td>Aortic valve replacement, chronic obstructive pulmonary disease</td>
<td>Fatal</td>
</tr>
</tbody>
</table>
Table 2. Methods to detect *Ureaplasma* spp.

<table>
<thead>
<tr>
<th>TEST</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
<th>POSITIVE PREDICTIVE VALUE</th>
<th>TURN AROUND 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 hr</td>
</tr>
<tr>
<td><em>Ureaplasma</em> spp. culture (1, 4, 5)</td>
<td>86-93%</td>
<td>89-91%</td>
<td>97%</td>
<td>2-5 d</td>
</tr>
<tr>
<td>PCR for <em>Ureaplasma</em> spp. (2, 3, 5)</td>
<td>64-95%</td>
<td>95-98%</td>
<td>91-99%</td>
<td>24-48 hr</td>
</tr>
</tbody>
</table>