Pneumonitis Associated with *Ureaplasma urealyticum* in Children with Cancer

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We describe 3 pediatric patients with cancer who had clinical and radiographic evidence of pneumonitis and for whom cultures of bronchoalveolar lavage fluid specimens yielded *Ureaplasma urealyticum*. Two of the patients died; for the surviving patient, clinical improvement coincided temporally with administration of erythromycin. Immune compromised patients with pneumonitis of unclear etiology should have respiratory secretions cultured for mycoplasmas and should receive empiric therapy that includes a macrolide antibiotic.

The scope of respiratory disease attributable to infection with *Ureaplasma urealyticum* has been increasingly recognized in recent years. In preterm neonates, this organism causes pneumonia and may contribute to the development of chronic lung disease of prematurity [1, 2]. *U. urealyticum* has been recovered in cultures of respiratory secretions obtained from infants presenting with lower respiratory tract infections after the neonatal period, usually in combination with other respiratory pathogens [3–7]. This organism has also been implicated as a possible cause of pneumonitis in immunocompromised patients [8], including adults and children with hypogammaglobulinemia [9] or AIDS [4, 10]. Whether *U. urealyticum* causes lower respiratory tract infections in children undergoing treatment for malignancies has not been adequately investigated. In the present report, we describe 3 children with cancer who had clinical and radiographic evidence of interstitial pneumonitis and in whom *U. urealyticum* was detected by culture of bronchoalveolar lavage (BAL) fluid specimens.

**Methods.** During the time when these patients were hospitalized, all BAL fluid specimens obtained at this center routinely underwent the following microbiologic tests: Gram stain, silver stain, bacterial culture (with the use of blood, chocolate, and MacConkey agar plates and with the use of thioglycollate broth), fungal culture (with the use of brain-heart infusion agar with and without gentamicin), acid-fast stain and culture for mycobacteria, cultures and direct fluorescent antibody (DFA) tests for *Chlamydia* and *Legionella* species (performed at a local reference laboratory), DFA tests for viruses (cytomegalovirus, herpes simplex viruses 1 and 2, varicella-zoster virus, respiratory syncytial virus, influenza viruses A and B, adenovirus, and parainfluenza viruses 1–3), viral culture (with the use of MRC5, A549, rhesus monkey kidney, and HEP-2 cells), and culture for mycoplasmas (with the use of Shepard 10B broth and A8 plates). *U. urealyticum* colonies were identified on A8 plates by their typical morphologic characteristics and precipitation of ammonium chloride, which makes colonies appear to be dark brown when viewed microscopically. Blood cultures were performed with Wampole isolator tubes (Wampole Laboratories).

**Patient 1.** A 2-year-old white boy with acute nonlymphocytic leukemia received an allogeneic bone marrow transplant from a mismatched, unrelated donor after following a conditioning regimen that consisted of cytarabine, cyclophosphamide, antithymocyte globulin, and total-body irradiation. On day 8 after bone marrow transplantation (BMT), while the patient was receiving therapy with vancomycin, ceftazidime, and intravenous immunoglobulin (IVIG; 250 mg/kg given once weekly), he became febrile without localizing signs. The absolute neutrophil count (ANC; defined as the sum of the number of polymorphonuclear leukocytes per microliter and the number of band forms per microliter) was zero, and a blood culture was sterile. Fever persisted despite the addition of amphotericin B and meropenem to therapy; ceftazidime therapy was discontinued. On day 11, the patient developed tachypnea, nasal flaring, and hypoxemia; the ANC was 50 cells/μL. Supplemental oxygen was administered, and a BAL fluid specimen was obtained. Erythromycin and tobramycin were added to therapy. The patient’s fever resolved, and his respiratory status improved during the ensuing 48 h.

By day 14, the patient’s respiratory symptoms had completely resolved, and his ANC was >500 cells/μL; supplemental oxygen...
and antibiotics were discontinued. On day 21, the BAL fluid culture for mycoplasmas was reported to be positive for *U. urealyticum*. Results of all other BAL fluid cultures, stains, and DFA tests were negative. Azithromycin (10 mg/kg per day) was administered orally for the next 7 days. The patient subsequently recovered without experiencing additional respiratory complications.

**Patient 2.** A 16-year-old black girl with metastatic alveolar rhabdomyosarcoma was hospitalized with fever, hematemesis, tachypnea, and hypoxemia 8 weeks after receiving radiation therapy to the thorax and mediastinum. Her ANC was >500 cells/μL and remained at that level throughout her hospital stay. She received methylprednisolone, supplemental oxygen, and empiric antimicrobial therapy with oxacillin, ceftazidime, and amphotericin B. Because of progressive deterioration of her respiratory status, she began receiving mechanical ventilation on day 20 of hospitalization.

Pathological examination of a lung biopsy specimen obtained on day 24 demonstrated findings consistent with radiation-induced pneumonitis. Cultures of lung tissue were negative for bacteria, fungi, viruses, and mycobacteria; culture for mycoplasmas was not performed. On day 30 of hospitalization, a new fever (temperature, 40.2°C) was noted. The next day, her ventilatory requirements increased, and a BAL fluid specimen was obtained. Her clinical course worsened and was complicated by multiple pneumothoraces and refractory hypotension, despite the addition of erythromycin, tobramycin, and vancomycin to therapy.

The patient died on day 36 of hospitalization. Cultures of BAL fluid eventually yielded *U. urealyticum* and viridans streptococci; the results of other cultures, stains, and DFA tests of the BAL fluid specimen were negative. Postmortem examination of the lungs revealed residual rhabdomyosarcoma and changes consistent with severe radiation pneumonitis with superimposed acute diffuse alveolar damage. The lung tissue obtained at autopsy was not cultured for mycoplasmas.

**Patient 3.** A 16-year-old white girl with mixed phenotypic leukemia received an allogeneic bone marrow transplant from a human leukocyte antigen–matched unrelated donor after following a conditioning regimen that consisted of cytarabine, antithymocyte globulin, cyclophosphamide, and total-body irradiation. The posttransplantation period was complicated by severe veno-occlusive disease of the liver, renal insufficiency, osteomyelitis of the left distal ulna caused by *Aspergillus flavus*, intermittent febrile episodes, and a persistent supplemental oxygen requirement. The ANC was >1000 cells/μL on day 13 after transplantation and subsequently remained >2000 cells/μL. Weekly infusions of IVIG (250 mg/kg) were begun at the time of marrow infusion. Prophylactic therapy with trimethoprim-sulfamethoxazole and ganciclovir was initiated on day 18.

On day 10 after BMT, a chest radiograph revealed a right-side pleural effusion. Despite therapy with various combinations of vancomycin, ceftazidime, meropenem, clindamycin, tobramycin, amphotericin B, and 5-fluorocytosine, there was no change in the size of the pleural effusion as measured on radiographs and CT scans. On day 42, a chest CT scan revealed an increase in the size of the pleural effusion. On day 45, dyspnea and hypoxemia worsened, and mechanical ventilation was initiated. Cultures of pleural fluid samples obtained by thoracentesis were negative for bacteria, fungi, viruses, and mycobacteria. A BAL fluid specimen was obtained on day 46; a chest radiograph obtained on that day is shown in figure 1.

The patient subsequently experienced worsening hypoxemia, persistent bleeding, and refractory hypotension, and she died on day 48 after BMT. *U. urealyticum* was isolated from the BAL fluid mycoplasma culture; the results of all other BAL fluid cultures, stains, and DFA tests were negative. Postmortem microscopic examination of the lungs revealed scattered foci of acute inflammation in the alveolar spaces and terminal bronchiolar lumens and foci of hemorrhage and proteinaceous exudate within the alveolar spaces. Cultures of lung tissue obtained at autopsy were negative for bacteria and mycoplasmas.

**Discussion.** Although pneumonia caused by *U. urealyticum* is well documented in neonates [11], the role of this or-
ganism as a pulmonary pathogen in other human populations has been incompletely evaluated. Ureaplasmas definitely cause pulmonary disease in animals: *Ureaplasma diversum* causes naturally occurring pneumonia in cows [12–14], and *U. urealyticum* can cause experimentally induced pneumonia in mice [15]. Previous reports have suggested that *U. urealyticum* is associated with lower respiratory tract infections in immunocompromised children and adults [4, 8–10]. Our report extends this association to include children receiving therapy for malignancies.

Several lines of evidence support the assertion that *U. urealyticum* was responsible for the lower respiratory tract infections in our patients. First, *U. urealyticum* was isolated from the BAL fluid specimens obtained from each patient during a period of acute respiratory deterioration marked by fever, hypoxemia, and pulmonary infiltrates. Second, *U. urealyticum* was the only potential respiratory pathogen recovered from BAL fluid in 2 of our 3 patients; in the remaining patient, it was recovered in combination with viridans streptococci, an unlikely lower respiratory tract pathogen. Third, evidence of a treatment effect was apparent in the surviving patient, whose recovery temporally coincided with the administration of erythromycin. In contrast, of the 2 patients who died, one did not receive erythromycin until late in the clinical course of the disease, and, before her death, the other patient did not receive any antimicrobial drugs active against ureaplasmas. Fourth, it is unlikely that these positive results of BAL fluid cultures resulted from contamination by oropharyngeal flora, because available data suggest that oropharyngeal carriage of *U. urealyticum* after infancy is distinctly unusual [16, 17]. Moreover, the absence of typical oropharyngeal flora in the BAL fluid cultures (in 2 of our 3 patients) argues against upper respiratory tract contamination of the BAL fluid. Finally, environmental contamination is exceedingly unlikely, because ureaplasmas were not isolated from other laboratory specimens cultured concomitantly with those of our patients. Our patients were hospitalized in different wards during different months, minimizing the possibility that they were infected or that their specimens were contaminated by a common source.

In 2 of our patients, pneumonitis developed in the first 2 months after BMT. Whether *U. urealyticum* or other related mycoplasmas might play a role in interstitial pneumonitis that occurs after BMT has not been investigated. Interstitial pneumonitis ranks among the most frequent and fatal complications of allogeneic BMT, although it appears to occur less frequently in children than in adults [18–20]. In 30%–50% of patients with interstitial pneumonitis, no infectious etiology is identified, despite the performance of microbiologic investigations for bacteria, viruses, and fungi [21–24]. Our findings raise the possibility that *U. urealyticum* might contribute to the development of at least some of these cases of “idiopathic” pneumonitis in bone marrow transplant recipients. This possibility could be further investigated in prospective studies of bone marrow transplant recipients with pneumonitis by routinely culturing respiratory secretions for mycoplasmas.

The mechanisms underlying host defense against mycoplasmas have not been fully elucidated. Previous reports, which are summarized elsewhere [25], indicate that patients with antibody deficiency have a significantly higher risk for mycoplasmal infections, including those caused by *U. urealyticum*. Invasive infections, including septic arthritis, pneumonia, sinusitis, cellulitis, and osteomyelitis, have been described, even in patients receiving scheduled γ-globulin replacement therapy. It is likely that our patients had deficient antibody production as a consequence of their intensive treatments for malignancy. Moreover, it is noteworthy that weekly infusions of IVIG failed to prevent *Ureaplasma* infections in our 2 bone marrow transplant recipients; presumably, this is because most IVIG preparations contain low titers of antibodies to mycoplasmas [25]. Although the reasons for the unique susceptibility of antibody-deficient patients to mycoplasmal infections are unknown, studies of animals may provide insights. In mice infected with *Mycoplasma pulmonis*, innate and humoral defenses were shown to be important in protecting against pulmonary infection and systemic dissemination, whereas cellular immune responses were associated with exacerbation of lung disease [26].

In addition to *U. urealyticum*, other mycoplasmas are capable of causing severe infections in immunocompromised humans. *Mycoplasma pneumoniae* has been associated with pneumonia and polyarthritis in patients with hypogammaglobulinemia [9]. *Mycoplasma hominis*, *Mycoplasma fermentans*, *Mycoplasma salivarium*, and *M. pneumoniae* have been isolated from HIV-infected adults with acute respiratory tract infections [10]. *M. hominis* has been associated with pneumonia in solid-organ transplant recipients [27], sternal wound infections in heart-lung transplant recipients [28], and diffuse alveolar hemorrhage in a bone marrow transplant recipient [29]. It should be noted that *M. hominis* is intrinsically resistant to macrolides; therapeutic options for this pathogen include tetracyclines and fluoroquinolones [30].

In summary, we report the cases of 3 pediatric patients who developed pneumonitis putatively caused by *U. urealyticum* while they were undergoing therapy for malignancies. These cases add to a growing body of evidence suggesting that *U. urealyticum* is a pulmonary pathogen in compromised humans, including young infants and immunosuppressed patients. Culture of respiratory secretions (preferably those obtained from the lower respiratory tract) for mycoplasmas should be included in the evaluation of immunosuppressed patients with pneumonitis. Furthermore, in such cases, early empiric therapy with a macrolide antibiotic should be considered to provide activity against *U. urealyticum* and other atypical pulmonary pathogens.
References


