

Case in Point

Organizing Pneumonia and Pneumothorax Associated With Daptomycin Use

James Prah, MD; Michael Tripp, MD; and Christopher Stafford, MD

This case examines the rare association between the administration of daptomycin and pulmonary toxicity.

Organizing pneumonia (OP) is a distinct lung injury pattern that may complicate a variety of collagen vascular diseases, bone marrow or heart-lung transplants, inflammatory bowel disease (IBD), inhalation of toxic gases, vasculitis, or medications. We report a case of OP complicated by a spontaneous tension pneumothorax that was temporally related to a prolonged course of daptomycin.



Figure 1. Chest radiograph showed mixed interstitial and airspace opacities with upper lobe predominance.

INITIAL PRESENTATION AND EXAMINATION

A 64-year-old man with a 40 pack-year smoking history was referred to the pulmonary service reporting cough, fever, and dyspnea. The patient had received 5 out of 6 weeks of treatment with daptomycin for a septic right shoulder joint following arthroscopic surgery. Respiratory symptoms began 3 weeks before presentation and had been progres-

sively worsening. At baseline, the patient was very active and walked regularly; however, on presentation he was unable to walk up a single flight of stairs without stopping due to significant dyspnea. He also reported a 14-pound unexplained weight loss over this same time.

Before his surgery he had been taking atenolol, atorvastatin, and escitalopram for many years without recent changes to this regimen. The patient seemed to be in mild respiratory distress and able to speak in only short

sentences. On room air he appeared cyanotic with clubbing of his upper digits. Initial vital signs revealed a pulse rate of 88, temperature of 100.8° F, respiratory rate of 30, and pulse oxygen saturation of 91% on 2 liters per minute of oxygen.

Pulmonary examination revealed diffuse coarse crackles and rhonchi bilaterally. Cardiac and abdominal examinations were normal. Examination of the extremities revealed clubbing and mild digital cyanosis while the patient was on room air. Complete blood count demonstrated anemia, thrombocytosis, and a leukocytosis of $12 \times 10^3/\mu\text{L}$ with a differ-

ential of 78% neutrophils, 20% lymphocytes, and 2% eosinophils. Serum creatine was normal, albumin was depressed, and the hepatic transaminases were mildly elevated. Arterial blood gas obtained while breathing room air demonstrated a respiratory alkalosis (pH of 7.51), hypoxia (partial pressure of oxygen in arterial blood [PaO_2] of 50 mm Hg), and hypocapnea (partial pressure of carbon dioxide in arterial blood [PaCO_2] of 30 mm Hg). The chest radiograph showed mixed interstitial and airspace

Drs. Prah, Tripp, and Stafford are physicians in the Department of Internal Medicine and Critical Care Medicine, U.S. Naval Hospital Guam in Agana Heights, Guam, and the Department of Pulmonary and Critical Care Medicine, Naval Medical Center San Diego in San Diego, California.

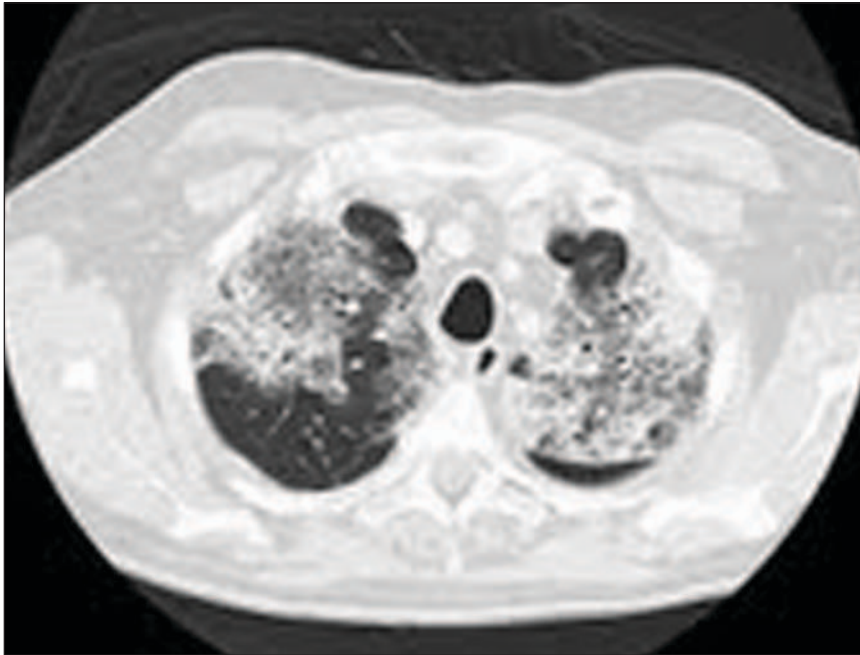


Figure 2. Chest CT demonstrating bilateral upper lobe mixed airspace consolidation with associated ground-glass opacities.

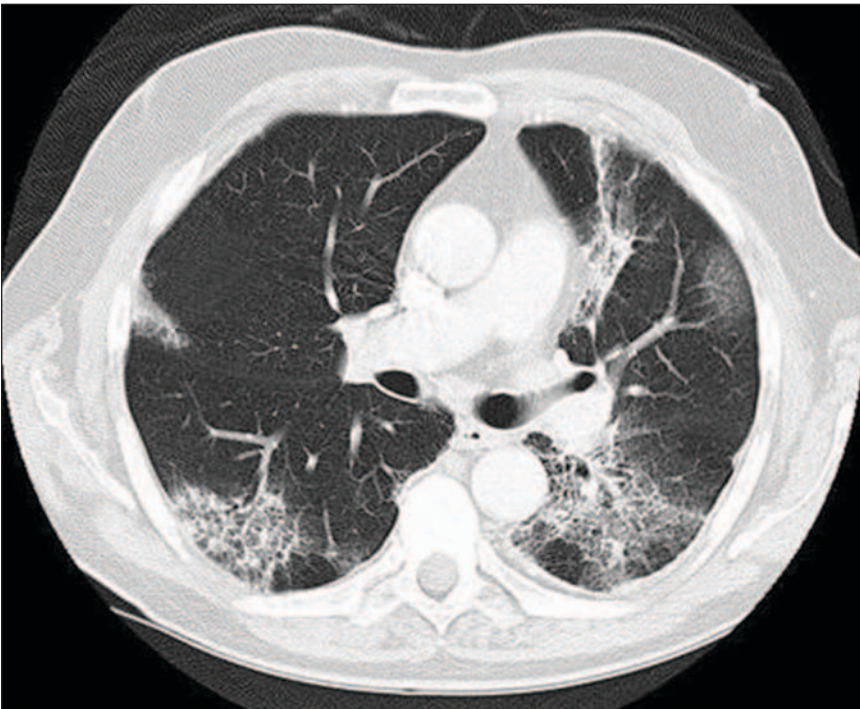


Figure 3. Chest CT again demonstrating mixed airspace and ground-glass opacities with no evidence of pleural effusions or lymphadenopathy.

opacities predominantly in the upper lobes (Figure 1). Computed tomography (CT) scan of the chest showed multifocal ground-glass opacities and areas of consolidation (Figures 2 and 3).

TREATMENT

Due to the patient's worsening respiratory status, he was admitted to the internal medicine service and treated with intravenous (IV) ciprofloxacin, piperacillin/tazobactam, and vancomycin for presumed pneumonia. Initial infectious disease workup included sputum and blood cultures, *Streptococcus pneumoniae* and *Legionella* urine antigens, and serology for endemic fungi, all negative. Failure to improve on hospital day 4 prompted a fiberoptic bronchoscopy with bronchoalveolar lavage (BAL), which revealed normal airways.

All bacterial, viral, and fungal cultures obtained from the BAL were negative. BAL showed 700 white blood cells of which 78% were neutrophils and 22% lymphocytes; no eosinophils were detected. Multiple transbronchial biopsies were obtained, and the histology showed an OP without infectious organisms (Figures 4 and 5). Daptomycin therapy was discontinued and 60 mg/d of prednisone and 250 mg/d of azithromycin were started, with rapid resolution of fever and improvement in hypoxemia.

The patient was subsequently discharged 2 days after therapy was initiated; however, 10 days later he presented to the Emergency Department hypotensive with acute left-side chest pain. A tension pneumothorax was diagnosed, and a tube thoracostomy was performed. Due to a persistent air leak, the patient underwent video-assisted thoracoscopic surgery. Biopsies were obtained, which confirmed the diagnosis of "OP." The

patient was discharged in good condition 5 days later. On outpatient follow-up, he had returned to his previous level of functioning, and radiographic abnormalities resolved after completing an 8-week tapering course of prednisone and azithromycin.

ABOUT OP

OP is a rare lung injury pattern that presents with signs and symptoms that mimic community-acquired pneumonia. The annual incidence is reported to be < 1 in 100,000.¹ OP is defined as an inflammatory process, characterized histologically by buds of granulation tissue that occlude the lumen of distal airways and inflammatory cells that surround the associated airways without disturbing the underlying normal lung architecture.^{2,3}

Clinically, patients present with subacute cough, fever, and malaise, which fail to resolve after multiple courses of antibiotics. Imaging studies may show multifocal airspace opacities, focal nodular opacities, or mixed interstitial and airspace lesions, all of which can be migratory. Spirometry can reveal a mild restrictive process.⁴ OP secondary to various etiologies, such as collagen vascular disease, infections, medications, neoplasm, foreign body aspiration, hypersensitivity, and fume inhalation, is known as secondary organizing pneumonia (SOP). Without a predisposing condition or insult, OP is known as cryptogenic organizing pneumonia (COP).

Traditionally, a lung biopsy obtained via video-assisted thoracoscopic surgery (VATS) has been the gold standard for diagnosis, but more recent literature suggests transbronchial lung biopsy may, in some cases, be adequate. One study using transbronchial lung biopsy showed a sensitivity of 64% and a specificity of 86% with a 94% positive predicted value in diagnosing COP.⁵ One limita-

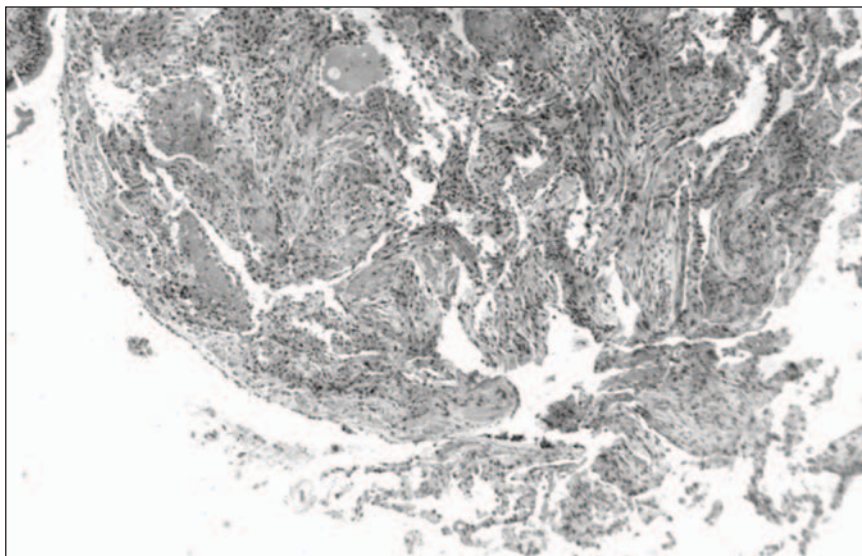


Figure 4. Low-power view of transbronchial lung biopsy, demonstrating alveoli with anastomosing plugs of connective tissue with preserved underlying lung architecture.

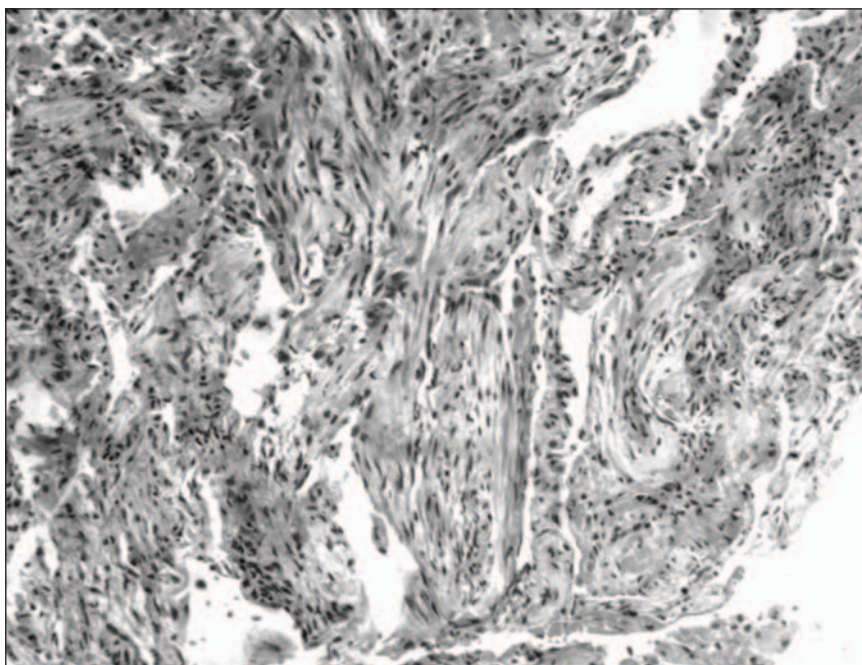


Figure 5. High-power view of lung biopsy, showing characteristic connective tissue plugs within airspaces with multiple surrounding inflammatory cells.

tion, however, is that areas of OP can occur in association with other interstitial lung diseases, such as eosinophilic pneumonia (EP), which may

be missed on a transbronchial lung biopsy; therefore, sampling errors are more likely with transbronchial lung biopsy.

Our patient had an open lung biopsy that confirmed the initial clinical and histological diagnosis of OP. Pneumothorax has been associated with OP, but this condition is not a major clinical feature.⁶ OP is generally treated with tapering doses of corticosteroids, although in the case of SOP, any suspected causes, such as radiation, environmental exposure, or infection, must be addressed first. The use of macrolides such as azithromycin has shown promise when added to the use of corticosteroids.⁷⁻¹⁰ Macrolides are believed to have anti-inflammatory effects and have been shown to suppress the release of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukins 1 and 8, and the expression of adhesion molecules necessary for neutrophil migration and activation.¹¹⁻¹⁵ The prognosis of patients who receive treatment with steroids is overall very good with complete recovery in up to 80% of patients within 3 months.⁴ Recurrence can be seen in up to 58% of cases and seems to occur equally in both secondary and cryptogenic cases.¹⁶

Antimicrobial Induced OP

SOP has been associated with various antimicrobial agents, including nitrofurantoin, minocycline, amphotericin, and several cephalosporins.² OP may occur months to years after a medication has been started and may recur when the medication is restarted.² Daptomycin is a novel lipopeptide derived from *Streptomyces* with the mechanism of action via depolarization of cell membranes of gram-positive bacteria. Daptomycin is not recommended for treatment of gram-positive pneumonia due to questions concerning different mechanisms in lung tissue.¹⁷ Some postulate that the drug's mechanism may

change secondary to inactivation of daptomycin by pulmonary surfactant.¹⁸

Daptomycin did not demonstrate significant pulmonary toxicity during the trials leading to its approved use; however, EP and 1 other case of OP have been subsequently reported with daptomycin.¹⁹ In July 2010, the U.S. Food and Drug Administration (FDA) issued safety information regarding the risk of developing EP during the use of daptomycin. The FDA reviewed 7 likely cases of EP. All of the reported cases occurred 2 to 4 weeks after therapy was initiated.²⁰ Although areas of OP may occur in EP, we were able to exclude this with an open lung biopsy.

Also, our patient was unlikely to have EP as he did not have eosinophils in his BAL or peripheral smear. Possible interaction of daptomycin with surfactant has been postulated to be the underlying pathophysiology behind the drug's pulmonary toxicity, allowing the accumulation of daptomycin in the alveolar spaces and subsequent injury to the epithelium and formation of OP.¹⁹ It is unknown at this time whether OP could be a dose-related complication of daptomycin or idiosyncratic. Our patient had extended therapy with daptomycin and improved following cessation of the medication, although he was also treated with oral corticosteroids and macrolide therapy.

Pneumothorax

Rarely, OP can present or be complicated by a pneumothorax. One case report describes a complication occurring due to "air leak syndrome."²¹ We hypothesize regional peripheral obstruction by fibrous plugs that secondarily led to a ball-valve effect and distal overinflation of airways. Severe coughing that causes overpressurization of the distal alveoli may be suffi-

cient to cause rupture.²¹ The incidence of pneumothorax following a bronchoscopic lung biopsy is reported to be between 1% and 6% in nonmechanically ventilated patients.^{22,23} Although we can't definitely rule out an iatrogenic pneumothorax from the patient's transbronchial biopsy, it seems unlikely as our patient's pneumothorax presented 10 days after his procedure. Review of the literature describes 5 days as the latest reported pneumothorax following a transbronchial biopsy.²⁴ We believe that the daptomycin initiated an OP that subsequently lead to a pneumothorax.

CONCLUSION

Daptomycin use has only rarely been associated with pulmonary toxicity, including OP. To our knowledge, this is the second case of OP associated with daptomycin and the first case complicated by a pneumothorax. It is unknown at this time whether OP is dose related or an idiosyncratic complication of daptomycin. Providers who use this antibiotic, particularly for prolonged courses of therapy, should be aware of potential lung toxicities. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, Quadrant HealthCom Inc., Naval Medical Center San Diego, the U.S. Navy, the Department of Defense, the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indica-

tions, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

REFERENCES

- Gudmundsson G, Sveinsson O, Isaksson HJ, Jonsson S, Frodadottir H, Aspelund T. Epidemiology of organising pneumonia in Iceland. *Thorax*. 2006;61(9):805-808.
- Epler GR. Drug-induced bronchiolitis obliterans organizing pneumonia. *Clin Chest Med*. 2004;25(1):89-94.
- Schlesinger C, Koss MN. The organizing pneumonias: An update and review. *Curr Opin Pulm Med*. 2005;11(5):422-430.
- Drakopanagiotakis F, Polychronopoulos V, Judson MA. Organizing pneumonia. *Am J Med Sci*. 2008;335(1):34-39.
- Poletti V, Cazzato S, Minicuci N, Zompatori M, Burzi M, Schiattone ML. The diagnostic value of bronchoalveolar lavage and transbronchial lung biopsy in cryptogenic organizing pneumonia. *Eur Respir J*. 1996;9(12):2513-2516.
- Lee PC, Lin JH, Lin CH, Chien ST, Hsu JY, Feng NH. Spontaneous pneumothorax after steroid treatment in a patient with bronchiolitis obliterans organizing pneumonia. *J Formos Med Assoc*. 2005;104(3):190-193.
- Stover DE, Mangino D. Macrolides: A treatment alternative for bronchiolitis obliterans organizing pneumonia? *Chest*. 2005;128(5):3611-3617.
- Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. *N Engl J Med*. 1985;312(3):152-158.
- Arbeter KR, Prakash UB, Tazelaar HD, Douglas WW. Radiation-induced pneumonitis in the "nonirradiated" lung. *Mayo Clin Proc*. 1999;74(1):27-36.
- Ichikawa Y, Ninomiya H, Katsuki M, Hotta M, Tanaka M, Oizumi K. Low-dose/long-term erythromycin for treatment of bronchiolitis obliterans organizing pneumonia (BOOP). *Kurume Med J*. 1993;40(2):65-67.
- Sakito O, Kadota J, Kohno S, Abe K, Shirai R, Hara K. Interleukin 1 beta, tumor necrosis factor alpha, and interleukin 8 in bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis: A potential mechanism of macrolide therapy. *Respiration*. 1996;63(1):42-48.
- Wales D, Woodhead M. The anti-inflammatory effects of macrolides. *Thorax*. 1999;54(suppl 2):S58-S62.
- Rubin BK, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest*. 2004;125(suppl 2):70S-78S.
- Labro MT, el Benna J, Abdelghaffar H. Modulation of human polymorphonuclear neutrophil function by macrolides: Preliminary data concerning dirithromycin. *J Antimicrob Chemother*. 1993;31(suppl C):51-64.
- Ianaro A, Ialenti A, Maffia P, et al. Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exp Ther*. 2000;292(1):156-163.
- Sveinsson OA, Isaksson HJ, Sigvaldason A, Yngvason F, Aspelund T, Gudmundsson G. Clinical features in secondary and cryptogenic organising pneumonia. *Int J Tuberc Lung Dis*. 2007;11(6):689-694.
- Cubicin [package insert]. Lexington, MA: Cubist Pharmaceuticals; 2010.
- Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: In vitro modeling and clinical impact. *J Infect Dis*. 2005;191(12):2149-2152.
- Cobb E, Kimbrough RC, Nugent KM, Phy MP. Organizing pneumonia and pulmonary eosinophilic infiltration associated with daptomycin. *Ann Pharmacother*. 2007;41(4):696-701.
- Federal Drug Administration. U.S. Food and Drug Administration website. FDA Drug Safety Communication: Eosinophilic pneumonia associated with the use of Cubicin (daptomycin). <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm220499.htm>. Updated July 29, 2010. Accessed June 28, 2012.
- Iwanaga T, Hirota T, Ikeda T. Air leak syndrome as one of the manifestations of bronchiolitis obliterans organizing pneumonia. *Intern Med*. 2000;39(2):163-165.
- Wang K-P, Mehta AC, Turner JF Jr, eds. *Flexible Bronchoscopy*. 2nd ed. Malden, MA: Blackwell Publishing, Inc; 2004.
- Izbicki G, Shitrit D, Yarmolovsky A, et al. Is routine chest radiography after transbronchial biopsy necessary?: A prospective study of 350 cases. *Chest*. 2006;129(6):1561-1564.
- Levy H, Kallenbach JM, Feldman C, Pincus P, Hurwitz M. Delayed pneumothorax after transbronchial lung biopsy. *Thorax*. 1986;41(8):647-648.