Bronchiolitis Obliterans Organizing Pneumonia: A Late Complication of Stem Cell Transplantation

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Improvements in antibiotic and antifungal therapy, immunosuppressive medications, and hematopoietic stem cell collection have made survival beyond 100 days common for patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Because of longer disease-free survival, allogeneic HSCT recipients may encounter a wider variety of late or chronic complications, including chronic graft-versus-host disease (cGVHD), graft failure or marrow dysfunction, and pulmonary, integumentary, gastrointestinal, and ocular complications.

Pulmonary complications are a significant source of nonrelapse morbidity and mortality in early and late phases of stem cell transplantation. Common pulmonary problems after HSCT include cytomegalovirus (CMV) pneumonia, bacterial pneumonias, and toxicity from drug regimens. A specific pulmonary syndrome that requires early recognition is bronchiolitis obliterans organizing pneumonia (BOOP). “Organizing” refers to unresolved pneumonia in which the alveolar exudate persists and forms fibrous tissue in the alveoli. Patients with BOOP present with common and vague symptoms that can be associated with other pulmonary complications. Undiagnosed, it can progress to respiratory failure. However, initiation of appropriate treatment may result in almost complete recovery over time. This article describes BOOP, a late complication associated with allogeneic stem cell transplantation, and reviews its symptoms, diagnosis, and treatment. The role of community oncology nurses also is discussed.

Etiology

BOOP is an inflammatory lung disease that is characterized by the formation of granulation tissue plugs in the alveoli that can extend into the bronchioles. The association with cGVHD suggests that BOOP may represent the rejection of the lungs by transplanted stem cells (Afessa, Litzow, & Tefferi, 2001). Inflammatory cells, such as neutrophils, lymphocytes, and plasma cells, sometimes are seen at the center of intraluminal myxoid polyps (newly formed connective tissue that participates in remodeling and destruction of the interstitium) (Mokhtari, Bach, Tietjen, & Stover, 2002).

Several known causes of BOOP exist, and the most common is idiopathic (Epler, 2001). Other causes include infection, medications, and stem cell transplantation, which is the second most common cause. Many medications used with stem cell transplantation reportedly interact with radiation used as a conditioning regimen and potentially can increase damage to normal lung tissue. Figure 1 lists risk factors for BOOP related to allogeneic HSCT. Although no direct correlation between BOOP and cGVHD exists, blood chemistries performed on patients with respiratory symptoms show decreased immunoglobulin A and G antibody levels. This suggests that immunosuppression plays an important role in this condition (Buchsel, Leun, & Randolph, 1996).

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BOOP occurs in 10%–20% of long-term survivors of allogeneic stem cell transplants (Buchsel et al., 1996). These survivors experience an obstructive, inflammatory lung process with symptoms such as cough, fever, dyspnea, bronchospasms, and wheezing (Curtis, Smale, Thien, Schwarz, & Szer, 1995). Because these symptoms are common to most pathologic pulmonary processes, BOOP should be included in differential diagnoses when respiratory symptoms do not respond to antibiotic therapy. A complete medical history and physical examination may be used to identify additional risk factors for BOOP.

Patients who experience GVHD as a complication of transplantation are predisposed to lung infections because of the immunosuppression that accompanies treatment. The sicca syndrome of cGVHD (dry mucous membranes) also can target the lungs. This syndrome is a result of a reduced local humoral immunity caused by the decrease in the production of immunoglobulin A. The death of epithelial cells causes a decrease in ciliary function and bronchial secretions, which results in a loss of normal protective functions (Wikle, 1991). This pulmonary syndrome also is seen in solid organ transplant recipients, which suggests a link among BOOP, immunosuppression, and the use of corticosteroids (Deeg, 1999).

Inflammatory processes secondary to lung injury cause fibrotic obliteration of bronchiolar lumens. This is a common histologic tissue reaction at the level of small airways (see Figure 2). Histopathologic lesions can develop, which consist of organized exudates that plug the lumens of terminal and respiratory bronchioles (Quabeck, 1994). Cellular bronchitis often is present. Mucosal necrosis and ulceration also may be present and inflammatory changes may exist in the surrounding alveolar walls in addition to foam macrophages in the alveoli. Despite the intraluminal changes, the lung architecture is maintained (Epler, Colby, McLoud, Carrington, & Gaensler, 1985).

**Presentation and Diagnosis**

The most common presenting symptoms of BOOP are vague respiratory complaints with a rapid onset of one to three days. Patients may have a fever, cough, dyspnea, bronchospasms, wheezing, and general fatigue. Patients rarely have hemoptysis (Mokhtari et al., 2002).

Pulmonary function tests (PFTs) in patients with BOOP will be abnormal. A small but consistent decline may exist in the forced vital capacity, but no significant difference should be found in forced expiratory volume or single-breath carbon monoxide diffusion capacity (Mokhtari et al., 2002). High-resolution computed tomography (CT) scans are consistent with patchy consolidation or “ground glass” attenuation with subpleural or peribronchial distribution, which usually is random (Worthy, Flint, & Muller, 1997).

Although PFT and CT scan findings with clinical features suggest the diagnosis, definitive confirmation requires surgical or transbronchial lung biopsy (Afessa et al., 2001). Lung biopsy continues to be the preferred method for establishing a diagnosis (Epler, 2001). Histopathologic analysis of open lung biopsy specimens allows accurate diagnosis but is a risky procedure that may not improve patients’ overall outcomes (Hayes-Jordan et al., 2002). The seriousness and course of the illness help to determine whether a “wait and see” attitude will suffice with empiric treatment or whether an invasive procedure should be performed immediately. Clinical diagnoses alone or diagnoses without pathologic confirmation carry a risk because corticosteroids are contraindicated in some of the diseases that are considered in the differential diagnosis of BOOP (Agusti & Xaubet, 2000). Bacterial, viral, or fungal pneumonia are not treated with steroids and would place patients at risk for additional immunosuppression. Therefore, tissue confirmation is warranted. Figure 3 lists the tests used to diagnose BOOP.

**Treatment**

Prompt treatment with corticosteroids often brings swift resolution of BOOP symptoms. Prednisone is the treatment of choice with 1 mg/kg for one to three months as the initial starting dose. After the initial response, patients are put on a gradual steroid taper, such as 40 mg per day for three months, then 10–20 mg per day or every other day for a total of one year (Epler, 2001).

Some patients may have to continue low-dose steroid therapy indefinitely. Compliance with the treatment regimen is vital to prevent the relapse of BOOP. Corticosteroid therapy may cause weight gain, fluid retention, hyperglycemia, altered skin integrity, insomnia, and mood swings. Side effects should be monitored closely. Patients undergoing immunosuppression therapy also should receive prophylactic antibiotic, antifungal, and antiviral treatment for as long as they are on steroids or other immunosuppressive therapy.

The symptoms’ dramatic response to therapy, often with complete clinical resolution, is strong evidence that the fibrous tissue in the airways is associated with an inflammatory response (Epler et al., 1985). A particular challenge for allogeneic HSCT recipients is limited response or no response because of their immunosuppression. Respiratory failure leading to death occurs in 5% of these patients (Epler, 1995).

**Nursing Care in the Community**

Community oncology nurses who participate in the ongoing care of post-HSCT recipients need to be able to recognize treatment-related complications. First, nurses should know which previous treatment patients have received and which conditioning

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**Figure 1. Allogeneic Hematopoietic Stem Cell Transplantation Risk Factors for Bronchiolitis Obliterans Organizing Pneumonia**

Note. Based on information from Buchsel et al., 1996.

- Cytomegalovirus pneumonia
- Bacterial infections
- Fungal infections
- History of smoking
- Borderline pulmonary functions at baseline
- Total body irradiation
- Chemotherapeutic agents used in conditioning: diagnosis (incidence)
  - Carmustine: pulmonary fibrosis (20%–30%)
  - Busulfan: interstitial pulmonary fibrosis (rare)
  - Cyclophosphamide: pulmonary toxicity (rare)
  - Melphalan: bronchopulmonary dysplasia (rare)
  - Methotrexate: pneumonitis (rare)

**Figure 2. Fibrotic Obliteration of Bronchiolar Lumens in Patient With Bronchiolitis Obliterans Organizing Pneumonia**

Note. Slide depicts open lung biopsy tissue sample.
regimen was used. This gives nurses an idea of the various pulmonary toxicities that could result. Each time patients are seen, the following should be reviewed.

- Complete medication list
- Weight
- Systems
- Performance status (e.g., Karnofsky scale)
- Routine laboratory work (i.e., complete blood cell count, platelet count, differential, complete metabolic panel, and immunoglobulin G level)

If patients present with pulmonary symptoms, a chest x-ray or a high-resolution CT scan should be obtained. Nurses or physicians should not hesitate to contact the transplant center to relate these findings and receive direction on providing treatment if BOOP or other HSCT-related complications are suspected. Patients may need to return to the transplant center.

Reinforcement of patient and family education regarding early recognition of transplant complications by community oncology nurses complements the information given by the transplant team. When patients are diagnosed with BOOP, community oncology nurses also must monitor medication adherence and manage symptoms, such as fatigue, dyspnea, and steroid-induced myopathy. Preventing pulmonary complications in transplant recipients is not always possible, but patient and family education and early recognition of complications by community oncology nurses can be crucial in reducing the morbidity associated with HSCT.

**Conclusion**

In the transplant population, patients with BOOP who require long-term therapy with steroids are at risk for developing infections. Because of the immunosuppressive nature of steroids, monitoring graft function and regular viral surveillance is important. A balance must be maintained to prevent other complications. As long as patients are receiving immunosuppressive therapy, they also should undergo prophylactic infection treatment. Because many patients are living longer and experiencing delayed complications, these patients are being seen and treated in the community setting away from the transplant center. Regular and frequent communication between the transplant center and referring physician is important for continued patient well-being and early recognition of late-onset complications.

**Case Study 1**

Mr. H is a 41-year-old man who is 123 days past allogeneic bone marrow transplant for refractory T cell non-Hodgkin’s lymphoma. On admission to the community hospital, his signs and symptoms included fever, worsening productive cough, and severe shortness of breath. Mr. H reported having the cough for three to four weeks prior to this admission. Past medical history includes GVHD of the skin, and he takes cyclosporine and methylprednisolone.

Chest radiography showed bilateral interstitial pneumonia of uncertain etiology. Differential diagnosis included community-acquired pneumonia, pneumocystis carinii pneumonia, Legionella, mycoplasma pneumonia, aspergillosis, actinomyces, CMV pneumonia, herpes simplex virus, and enterococcus infection.

Mr. H was started on broad-spectrum IV antibiotics. Blood, urine, and sputum cultures were taken and all returned with negative results. Bronchoscopy was performed with biopsies, and the results were consistent with viral pneumonia. However, CMV and gram stains were negative.

Mr. H’s respiratory condition continued to worsen, and he remained febrile despite the IV antibiotics. Several days later, the patient required intubation with mechanical ventilation. A fluoroscopy-guided lung biopsy was obtained, and the pathology was consistent with BOOP. Respiratory status improved following the addition of steroids at 1 mg/kg to his treatment regimen, and he was extubated successfully four days later. He eventually was discharged from the hospital and continued taking oral steroids. He has done well on maintenance steroids, although he has had intermittent bouts of pneumonia.

Prior to this admission, he had been hospitalized for bronchitis. He complained of increased, relentless cough and stated that the cough was nonproductive. He also reported shortness of breath at rest and severe dyspnea with exertion.

Chest radiography showed multifocal, predominately bilateral, interstitial infiltrates and a nodular component to some of the infiltrates that suggested a granulomatous process. A bronchoscopy was performed, and a transbronchial biopsy showed focal area interstitial fibrosis, suggestive of BOOP.

Mr. G reported that his home medication regimen included 20 mg of prednisone, which was increased to 1 mg/kg. Broad-spectrum antibiotics were administered to provide prophylactic infection protection. He was discharged from the hospital a few days later, against medical advice, for follow-up in the outpatient clinic.

During the next two years, Mr. G had numerous hospitalizations for fever, shortness of breath, and cough. Each time, he was treated with antibiotics and steroids and then would return to baseline functioning. His quality of life was diminished with each admission as his baseline functioning declined.

On his last admission for fever and cough, Mr. G was in severe respiratory distress and received emergency intubation. He was started on high-dose steroids and antibiotics. Unfortunately, his condition worsened despite therapy. He had multisystem organ failure, and life support was withdrawn.

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**References**


Rapid Recap

**Bronchiolitis Obliterans Organizing Pneumonia: A Late Complication of Stem Cell Transplantation**

- Bronchiolitis obliterans organizing pneumonia (BOOP) is an inflammatory lung disease characterized by the formation of granulation tissue plugs in the alveoli.
- Causes of BOOP include idiopathic (most common), stem cell transplantation (second most common), infection, and medications.
- BOOP occurs in about 10%-20% of long-term survivors of allogeneic stem cell transplantation.
- Common presenting symptoms are vague complaints (e.g., fever, cough, dyspnea, wheezing, fatigue).
- Definitive confirmation of BOOP requires surgical or transbronchial lung biopsy.
- Prednisone (1 mg/kg per day for one to three months) is used commonly to treat BOOP.

For more information on this topic, visit the following Web sites.

University of Pittsburgh Medical Center: Bronchiolitis Obliterans
www.path.upmc.edu/divisions/pulmpath/bron02.htm

Bronchiolar Airway Disorders and Bronchiolitis Obliterans
www.epler.com/boop1.html

eMedicine: Bronchiolitis Obliterans Organizing Pneumonia
www.emedicine.com/radio/topic117.htm

Links can be found at www.ons.org.