Subcutaneous and Mediastinal Emphysema Complicating Bronchiolitis Obliterans Following Allogeneic Hematopoietic Stem Cell Transplantation

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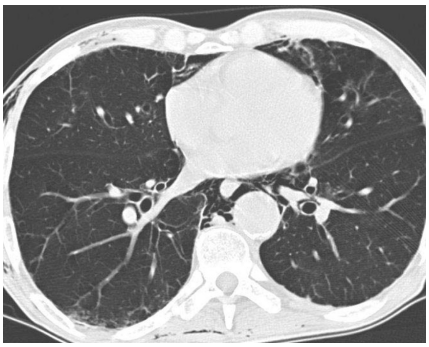
Bronchiolitis obliterans is a serious respiratory obstructive disorder primarily complicating lung transplantation and allogeneic hematopoietic stem cell transplantation. Spontaneous subcutaneous and mediastinal emphysema is an unusual complication of severe bronchiolitis obliterans and rarely is the presenting sign. We describe a patient who developed bronchiolitis obliterans after hematopoietic stem cell transplantation, presenting with severe subcutaneous and mediastinal emphysema.

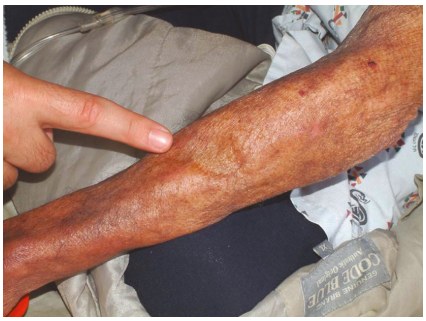
Patient Description

A 64 year old man with an unremarkable medical history except for heavy smoking (100 pack years) underwent bone marrow biopsy because of severe anemia and fever. The bone marrow biopsy showed features of myelodysplastic syndrome with transformation to acute myeloid leukemia. Two months later the patient underwent allogeneic HSCT from his HLA-matched sister. The conditioning for the transplantation consisted of an ablative dose of busulphan and fludarabine. Post-transplant graft-versus-host disease prophylaxis with methotrexate and cyclosporine was administered. Starting several months after the transplant, the patient began to suffer from a skin rash that was attributed to chronic GVHD. Twenty months after the transplant, the patient was admitted to the internal medicine ward with progressive dyspnea and a non-productive cough.

Physical examination revealed a tachypneic patient with reduced air entry to both lung bases. Lung function tests showed a severe obstructive disorder with forced expiratory volume in the first second 45% of predicted. Similar tests conducted 2 weeks previously showed only a mild obstructive disorder. A thoracic computed tomography scan showed mediastinal emphysema with small infiltrates in the right upper lobe. The patient was treated with antibiotics, inhalation of bronchodilators and an increased dose of prednisone. Two weeks later, the patient was admitted again with worsening dyspnea and signs of subcutaneous emphysema, including a wide area of crepitus over the anterior thorax and neck and an altered voice. A thoracic CT scan performed at that time showed a large amount of air in the patient's soft tissue, worsening of the mediastinal emphysema, and areas of reduced vascular markings [Figure A]. A diagnosis of broncheolitis obliterans was made based on the combination of clinical findings, pulmonary function tests and radiographic findings. The patient began treatment with cyclosporine and an increased dose of prednisone. Treatment with azithromycin as a possible therapeutic option was started shortly thereafter. Despite treatment, the patient's situation continued to deteriorate. The subcutaneous emphysema worsened, causing marked swelling of the patient's face, back and limbs [Figure B]; additionally, at this time the crepitus could be felt extending all the way from his ears to his legs. Eventually, the patient developed septic shock and died approximately 2 months later.



[A] Chest CT scan showing air in the mediastinum and soft tissue, bronchiectasis and reduced peripheral vascular markings. All these findings are important signs in bronchiolitis obliterans.



[B] Marked swelling of the patient's arm, secondary to subcutaneous emphysema, demonstrated by pitting left after mild pressure by the physician.

Comment

Broncheolitis obliterans is an obstructive respiratory disorder occurring mainly after lung transplantation and allogeneic HSCT, but also after infections, irritant inhalation or treatment with certain drugs. It is not a rare complication, affecting over 50% of patients surviving more than 3 months

HSCT = hematopoietic stem cell transplantation
GVHD = graft-versus-host disease

after lung transplantation and up to 40% of patients after HSCT [1]. In the setting of HSCT, broncheolitis obliterans usually develops about 1 year after transplantation, though times vary from a few months to several years. The most important risk factor for the development of this disease in HSCT recipients is acute or chronic GVHD. Other risk factors include treatment with certain drugs, mainly busulfan and methotrexate [2]. The patient described here had all of the above-mentioned risk factors.

While the exact pathogenic mechanism of broncheolitis obliterans is unknown, its association with HSCT suggests an alloimmune mechanism. It is postulated that a defective mucosal regeneration reaction, possibly caused by inflammatory profibrotic cytokines, is responsible. Under the effect of these cytokines, the epithelium reacts to injury, even by non-specific causes, with a fibro-obliterative response instead of the usual regenerative one [1,3]. Histologically, broncheolitis obliterans is an organizing inflammatory response centered on the respiratory and terminal bronchioles, causing obliteration of their lumen. The gold standard for diagnosis of this disorder is open lung biopsy, but this procedure is rarely performed for this purpose. Transbronchial biopsy has low sensitivity because of the patchy distribution of the lesions. An alternative route to diagnosis is based on a combination of pulmonary function tests with clinical and radiographic findings. Clinically, broncheolitis obliterans initially manifests as progressive dyspnea and non-productive cough. Radiographically, high resolution CT scan shows a constellation of findings, primarily central bronchial dilatation, peripheral bronchial narrowing and diminution of peripheral vascular markings. Lung function tests show a decrease in expiratory flow. Broncheolitis obliterans has a grave prognosis, with patients usually dying of superimposed infections. Reported survival rates are 10% five years after the diagnosis and the disease is known to sometimes take a more aggressive course, with patients surviving only a few months, as in our patient. Traditionally, treatment of broncheolitis obliterans consisted of augmented immunosuppression and the use of different immunomodulatory drugs, with prednisone being the mainstay of treatment. These treatments have usually had very limited success in halting the progression of the disease and were unable to reverse its effects. In patients able to withstand the procedure, lung transplantation is an important option [1]. Lately, several new treatments have been proposed, the most important being treatment with azithromycin. It has shown an ability to dramatically reverse the air flow obstruction in patients with established broncheolitis obliterans [4]. Pulmonary function tests can be performed as a screening tool in patients following HSCT to seek signs of obstructive pulmonary disease before symptomatic broncheolitis obliterans develops. This would allow early treatment with azithromycin. However, the yield of such a screening test is not yet established.

Subcutaneous and mediastinal emphysema is a rare complication of broncheolitis obliterans. It is usually caused by penetrating chest trauma, soft tissue infection by fermenting bacteria, or an increased pressure gradient between the alveoli and surrounding parenchyma. In the case of broncheolitis obliterans, an increased pressure gradient is caused by the airway obstruction. This pressure causes alveoli to rupture and release air into the surrounding soft tissues. The clinical course of subcutaneous and mediastinal emphysema is usually benign, and spontaneous resolution is the rule [5]. However, in the case of broncheolitis obliterans, management of subcutaneous and mediastinal emphysema is especially challenging due to the irreversible nature of the airway obstruction. As seen in our patient, when the underlying problem cannot be addressed, the emphysema can sometimes become a serious problem by itself, causing respiratory compromise and significant discomfort.

In conclusion, broncheolitis obliterans is a serious, often fatal, manifestation of chronic GVHD after allogeneic HSCT. Mediastinal and subcutaneous emphysema is an unusual complication of the disease, but is sometimes the presenting sign. After the diagnosis is made, usually by high resolution CT and pulmonary function tests, prompt treatment should be initiated in an effort to preserve lung function.

References

1. Boehler A, Kesten S, Weder W, Speich B. Bronchiolitis obliterans after lung transplantation: a review. *Chest* 1998;114: 1411–26.
2. Dudek AZ, Mahaseth H. Hematopoietic stem cell transplant-related airflow obstruction. *Curr Opin Oncol* 2006;19:115–19.
3. Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. *Am J Respir Crit Care Med* 2002;166:440–4.
4. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2005; 172:772–5.
5. Maunder R, Pierson D, Hudson L. Subcutaneous and mediastinal emphysema. Pathophysiology, diagnosis, and management. *Arch Intern Med* 1984;144: 1447–53.

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It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.

Sir Arthur Conan Doyle (1859-1930), Scottish physican and writer, most noted for his stories about the detective Sherlock Holmes, considered a major innovation in the field of crime fiction. He was a prolific writer whose other works include science fiction, historical novels, plays and romances, poetry, and non-fiction.