Pulmonary Alveolar Proteinosis
Lung Transplant or Bone Marrow Transplant?

To the Editor:

We read with interest the report by Parker and Novotny (May 1997) regarding the recurrence of pulmonary alveolar proteinosis (PAP) after double lung transplantation. Although the authors acknowledge that the disorder in this case might result from diminished alveolar macrophage function and hypothesize that this might be caused by a primary defect in circulating monocytes, they state that the fundamental cellular alteration has yet to be determined. The molecular defect in a murine model of PAP has been established. It supports the authors’ hypothesis and has a direct bearing on the treatment and outcome of this case.

Mice bearing a homozygous targeted disruption of the granulocyte-macrophage colony-stimulating factor (GM-CSF) gene develop PAP at approximately 1 year of age. An identical phenotype has been observed in mice with a targeted disruption of the common beta chain of the GM-CSF receptor (GMR c). More recently, defective expression of the GMR c gene has been shown in several human patients with PAP, perhaps as a result of germline mutation of the GMR c gene. These data suggest that a subgroup of individuals with idiopathic PAP (perhaps including the patient reported by Parker and Novotny) have a deficiency of GM-CSF or its receptor. Bone marrow transplantation can reverse the lung disease in GMR c/— mice, thus indicating that this form of PAP is clearly a disorder of bone marrow-derived monocytes. Therefore, it is not surprising that PAP might recur after lung transplantation in these cases. This case illustrates the need to consider a congenital defect in GM-CSF signaling as a cause of PAP before lung transplantation.

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To the Editor:

I appreciated Dr. Egermayer’s interest in our case report. I think we are in agreement that an abnormal ventilation-perfusion scan is nonspecific and may not always be due to venous thromboembolic disease. This was the purpose of publishing the report.

I disagree with his comments concerning the incidence of “high probability” scintigrams in the presence of tumor microembolism. Sostman and colleagues1 report on two patients with histories of breast cancer who were ultimately found to have diffuse tumor emboli. The lung scintigram in each case was described as having “multiple subsegmental perfusion defects which delineated the major fissure, the basilar segments, and the lingula”—the so-called “contour” pattern. Green and colleagues2 describe four patients with tumor emboli, all of whom had multiple irregular peripheral defects on their perfusion scans. Four other authors3-6 with a total of 14 patients describe similar perfusion defects. More importantly, although 2 of the 14 scintigrams were labeled “high probability,” none of them revealed a unilateral near absence of flow, as in our case. In Seminars in Nuclear Medicine, Sutter and Stadnik7 reviewed unilateral absence or near absence of pulmonary perfusion on lung scanning. Though they list over 55 diagnostic possibilities in 39 major categories, ranging from common to uncommon to rare causes, they do not even mention tumor microemboli.

As Dr. Egermayer correctly states, tumor macroembolization and microembolization of the pulmonary arteries are more common than originally thought. In the setting of a known prior malignancy, most practitioners today would probably include lymphangitic spread and tumor emboli in their differential diagnosis of dyspnea or unexplained right heart failure. However, the tumor embolization can be the presenting syndrome in a minority of the patients. It is therefore important to keep this in mind in any patient being evaluated for possible thromboembolic disease, regardless of previous history. Martino and colleagues8 suggest criteria which might lead one to search for nontromboembolic causes of a high probability perfusion lung scan. First, the persistence of symptoms despite adequate anticoagulation is not usual in pulmonary embolism. Second, a perfusion defect maintained over a prolonged period of time without evidence of adverse clinical outcome suggests an anatomic abnormality, rather than embolic origin. Finally, massive, one-sided perfusion defects warrant the consideration of nonembolic origin. It remains to be seen whether D-dimer testing will be another useful screen for abnormalities of nontromboembolic origin.

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Mice bearing a homozygous targeted disruption of the granulocyte-macrophage colony-stimulating factor (GM-CSF) gene develop PAP at approximately 1 year of age. An identical phenotype has been observed in mice with a targeted disruption of the common beta chain of the GM-CSF receptor (GMR c). More recently, defective expression of the GMR c gene has been shown in several human patients with PAP, perhaps as a result of germline mutation of the GMR c gene. These data suggest that a subgroup of individuals with idiopathic PAP (perhaps including the patient reported by Parker and Novotny) have a deficiency of GM-CSF or its receptor. Bone marrow transplantation can reverse the lung disease in GMR c/— mice, thus indicating that this form of PAP is clearly a disorder of bone marrow-derived monocytes. Therefore, it is not surprising that PAP might recur after lung transplantation in these cases. This case illustrates the need to consider a congenital defect in GM-CSF signaling as a cause of PAP before lung transplantation,