Diagnostic Approaches to Pulmonary Complications of Marrow Transplantation

Marrow transplantation, once undertaken only after failure of all other forms of therapy, is currently an accepted approach to treatment of malignant diseases such as acute and chronic leukemias, lymphomas and selected solid tumors, as well as non-malignant conditions, such as aplastic anemia, thalassemia and immunodeficiency syndromes. The success of marrow transplantation is, in part, limited by complications of the cyto-reductive conditioning regimens, the immunologic sequelae of engraftment of allogeneic lymphoid cells, and infections during immunosuppression. Frequently, these complications are manifested by pulmonary involvement. As transplant units are developed at centers throughout the world, increasing numbers of physicians are involved in the care of these patients and inevitably confront difficult decisions in the diagnostic approach to pulmonary complications in marrow recipients.

Experience with acute pulmonary complications in a wide spectrum of immunocompromised patients has resulted in diagnostic principles that can clearly be applied in the setting of marrow transplantation. However, there are special considerations in marrow recipients which distinguish these patients from other immunocompromised hosts and help focus attention on the most likely diagnoses in individual patients. The purpose of this commentary is to discuss these considerations in developing a differential diagnosis and diagnostic approach to acute lung diseases in marrow recipients.

First, while the spectrum of acute pulmonary complications following marrow transplantation is not unique, the relative frequency of specific lung diseases in marrow transplant recipients differs from that encountered in other immunocompromised hosts. Cytomegalovirus (CMV) pneumonia and idiopathic pneumonia account for the vast majority of diffuse nonbacterial pneumonias in marrow recipients. The prominence of serious viral infections may be in part due to the essentially total ablation of virus-specific immunity by the intense pre-transplant conditioning. Although *Pneumocystis carinii* pneumonia is a major concern in other immunocompromised patients, especially those with the acquired immune deficiency syndrome (AIDS), the prophylactic administration of trimethoprim-sulfamethoxazole prior to marrow transplant and following engraftment has virtually eliminated the disease in marrow recipients. These antibiotics may also have reduced the incidence of Gram-negative and pneumococcal pneumonia. Similarly, the prompt use of broad spectrum antibiotics in febrile patients during the period of neutropenia has greatly reduced the incidence of bacterial pneumonia. Bronchopneumonia is found in less than 2 percent of open lung biopsies at the Fred Hutchinson Cancer Research Center.

Secondly, some commonly encountered extrapulmonary post-transplant complications are associated with characteristic pulmonary disorders that can be presumptively diagnosed and treated. For example, aspiration is a frequent cause of basal infiltrates in the setting of severe oral mucositis and narcotic analgesia following marrow transplantation. Similarly, pleural effusion is frequently associated with hepatic veno-occlusive disease. In such instances, invasive diagnostic procedures to search for other causes may not be indicated.

Finally, major pulmonary complications associated with marrow transplantation occur in relatively well-defined time periods after the onset of profound immunosuppression associated with the conditioning regimen. For example, pulmonary edema (both cardiogenic and non-cardiogenic) is frequently encountered in the first few weeks after marrow transplantation. CMV is uncommon during this interval, but it is the main cause of pneumonia in the subsequent weeks. The risk for specific infections can be further related to a sequence of post-transplant events including neutropenia, marrow engraftment, post-transplantation immunosuppression therapy and graft-versus-host disease.

These considerations are often helpful in arriving at a differential diagnosis and in planning diagnostic strategy. In deciding upon a diagnostic approach, it is also important to distinguish between focal and diffuse lung involvement. Regardless of the interval since transplantation, focal lung infiltrates have a higher likelihood of yielding a specific (usually infectious) diagnosis than do diffuse infiltrates and usually warrant empiric antibiotic therapy or a definitive diagnostic procedure. When bacterial bronchopneumonia is not a major clinical consideration, we advocate prompt pursuit of a definitive diagnosis. We have successfully used percutaneous fine needle aspiration to recover Aspergillus in six of eight patients with focal lung infection. Several factors may have contributed to this success rate without complications. All of the patients had peripheral lesions and platelet counts above 30,000/cu mm. They were not in respiratory distress and were able to cooperate with the procedure, and the aspiration was carried out by an experienced radiologist using fluoroscopic guidance. Open lung
biopsy may be indicated if this approach is not diagnostic since bronchoscopy is of limited use in evaluating peripheral lesions, and cutting needle biopsy is associated with an unacceptably high complication rate.

Diffuse pulmonary infiltrates represent a more complex problem with regard to the differential diagnosis and diagnostic approach. The radiographic presentation is nonspecific with few exceptions. "Interstitial pneumonia" has been used to describe the entire spectrum of disease presenting with a diffuse radiographic pattern, although cardiogenic pulmonary edema is implicitly excluded. CMV pneumonia is the main infectious disease in this setting and accounts for 60 percent of non-bacterial pneumonias occurring in the first 100 days after transplantation at this center. Occasionally, bacterial or fungal pneumonia presents as a diffuse process. "Idiopathic pneumonia" refers to a heterogeneous subgroup of noninfectious interstitial disorders that include pulmonary edema without parenchymal inflammation, diffuse alveolar damage with hyaline membrane formation (the clinical entity of adult respiratory distress syndrome), and interstitial pneumonia characterized by inflammation and fibrosis. These non-infectious disorders account for almost all of the remaining 40 percent of diffuse infiltration in the first 100 days after marrow transplantation. However, their relative prevalence varies during this time interval.

During the first few weeks after transplantation, diffuse lung infiltrates are frequently encountered in the setting of extracellular volume excess, sepsis syndrome, acute graft-versus-host disease, and hepatic veno-occlusive disease. Although the precise nature of diffuse lung disease under these circumstances may be uncertain, the frequent occurrence of pulmonary edema syndromes and the relative rarity of viral pneumonia in this early period have led us to direct our efforts toward evaluating and improving fluid management, often guided by right heart catheterization for hemodynamic monitoring, prior to or in lieu of other diagnostic modalities.

After the first three to four weeks, the high incidence of CMV pneumonia as well as non-infectious ("idiopathic") pneumonia must be considered in the diagnostic approach to diffuse parenchymal disease in marrow transplant recipients. Potential treatment with steroids, investigational antiviral agents, or other specific antimicrobial agents may hinge on making a specific diagnosis. Bronchoalveolar lavage (BAL) has been advocated as a safe and effective diagnostic procedure in immunocompromised patients, especially patients with AIDS. However, the overall yield from the procedure is greatly influenced by selection of the patients and the spectrum of disease encountered in the patients. For example, BAL has been useful in defining Pneumocystis carinii and mycobacterial infection in patients with AIDS, but these infections are infrequent after marrow transplantation. Conversely, the experience with viral pneumonia is limited because it is an uncommon diagnosis in reported studies of BAL, accounting for only 13 percent of diffuse pneumonias in one large series. In a previous study from this center, CMV was detected by cytology or fluorescent-antibody staining of BAL samples in four of six patients with CMV diagnosed at open lung biopsy. New techniques for rapid viral culture and identification with CMV-specific monoclonal antibodies have enhanced the sensitivity of BAL for rapid detection of CMV infection, but the specificity of these measures in the diagnosis of CMV pneumonia is presently uncertain. As expected, we have not found BAL useful in diagnosing non-infectious pneumonia, and we have encountered false negatives in the presence of fungal infection. We find percutaneous needle aspiration and transbronchial biopsy to have little diagnostic use in diffuse parenchymal lung disease due to the low yield and high risk in thrombocytopenic patients.

Open lung biopsy is still the mainstay for diagnosis of diffuse pulmonary infiltrates after marrow transplantation, and we recommend this course when a specific diagnosis is expected to alter management. The development of effective antiviral drugs will increase the need for rapid and accurate diagnosis of diffuse pulmonary infections in the immunocompromised patient. Bronchoalveolar lavage holds promise as the diagnostic tool to replace lung biopsy if rapid viral culture and identification techniques are shown to provide accurate diagnostic information.

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REFERENCES

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Introduction to the New Department, Exercise and the Heart

Recent advances have clarified three of the applications of exercise testing: exercise testing in patients after myocardial infarction, screening, and for predicting disease severity. In regard to post-MI exercise testing, there are numerous clinical reasons for performing the test. However, its prognostic value is not as straightforward as once thought. Algorithms have been published based on various exercise test responses, particularly ST depression, recommending that patients with such responses have coronary angiography and be considered for interventions. The recent American College of Cardiology position paper on exercise testing clearly states that ST-segment depression is the most important predictor postinfarction. However, a careful review of the 24 available follow-up studies using a new technique called metaanalysis demonstrates that only an abnormal blood pressure response and a decreased exercise capacity occurred more frequently than by chance as significant risk predictors in these studies. This means that the other responses clearly do not identify an increased risk group and algorithms based on the results of selected studies should be strongly reconsidered.

A factor not considered in these studies, however, is the severity of the response (that is, the amount of ST depression). Also, it appears that exercise test responses mean different things in subsets of postmyocardial infarction patients. Exercise studies using thallium scintigraphy have demonstrated that in patients with large anterior infarcts, ST-segment shifts can be quite marked, but not at all related to ischemia. However, ST-segment depression clearly seems to be related to ischemia in patients with initial inferior wall infarcts and in non Q-wave infarcts. ST-segment elevation over diagnostic Q-waves appears to identify a group with more severe ventricular dysfunction, but does not necessarily mean ischemia.

SCREENING

Recent studies markedly change the understanding of the application of exercise testing as a screening tool. These studies include four follow-up studies using hard endpoints, and one study from the CASS population. The CASS study was based on 195 individuals with abnormal exercise test results by ST-segment criteria, and normal coronary angiograms who were followed for seven years. In this latter study, no increased incidence of cardiac events was found. The concerns raised by the findings of Ericksson et al that such individuals were still at increased risk even with normal angiograms was not substantiated. The other new follow-up studies (MRFIT, Seattle Heart Watch, Indiana State Police, Lipid Research Clinic) had quite different results from prior studies, because hard cardiac endpoints rather than angina were required criteria. Most of the prior studies included angina as an endpoint in the incidence of coronary heart disease. This led to a bias for individuals with abnormal test results who subsequently report chest pain to be diagnosed as having angina. When only hard endpoints (death or MI) were used, the results are very discouraging. ST-segment depression could identify only one third of the patients who later developed hard events, and 95 percent of abnormal responders were false positive; that is, they did not die or have a myocardial infarction. This contrasts with a 60 percent sensitivity and 25 percent predictive value shown in the earlier studies.

PROGNOSTICATION

Lee, Cook and Goldman have developed a strategy to identify patients with left main coronary artery disease (LMCAD). It is a simple model that predicts the probability of LMCD from a combination of clinical and exercise test variables and can be applied using a pocket calculator or graphs published in their paper. The model was derived from multivariate analysis of already published data obtained clinically without exercise testing and then from exercise test variables. They found that the model using only three variables (age, angina, amount of ST depression) provided reasonably accurate estimates of the prevalence of left main coronary artery disease in subsets of patients.

The key question in trying to identify high-risk coronary artery disease is: can those who are recog-