Hypersensitivity Pneumonitis

Just Think of It!

Ambient air contains variable amounts of respirable foreign substances. Some of these substances are capable of inciting immune responses in the host inhaling them. Hypersensitivity pneumonitis (HP) represents one possible response of the lung to the inhalation of these antigenic substances. Subjects who are exposed to respirable antigens occasionally react to this by a complex immune response, involving both T-lymphocyte and B-lymphocyte activation in the lower respiratory tract. Disease resulting from antigen exposure is uncommon, even among subjects with similar exposures to the relevant antigens. This variability in disease expression following exposure suggests that the genetic background of affected individuals or other factors such as concomitant viral infection may be responsible for disease expression.

Although the exact pathogenesis of HP is not known, patients with the disease have several characteristic features that allow a firm diagnosis in most cases. These features include a history of exposure to respirable antigens, the relief from symptoms with antigen avoidance, and a recrudescence of symptoms with re-exposure. The symptom complex can be quite variable and includes severe presentations that are similar to that of ARDS, subacute presentations with malaise, cough, and weight loss, and the development of chronic fibrosis. These variable forms of presentation pose a considerable challenge to the clinician. The clinician must first consider the possibility that HP may be causing the disease. Then the physician must question the patient about exposure to relevant antigens. Unfortunately, the spectrum of potential antigens is quite broad, and these antigens may be concealed in the environment. However, in most cases the amount of antigen in the inhaled air is quite large. Thus, affected patients usually have an idea that they are being exposed to something. They may notice that the air that they breathe is dusty or has an objectionable odor. In some cases, the patient’s occupation is a powerful clue to a potential exposure.

Once the possibility of exposure has been determined, support of the diagnosis may be provided by a CT scan of the chest and by lung function tests. HP is associated with the combination of ground glass changes and small nodular lesions that are visible on the CT scan. Pulmonary physiology usually shows a mixture of restrictive and obstructive changes. Neither a CT scan nor a lung function test provides a diagnosis, but both provide soft support. Subsequently, the clinician may proceed by attempting to identify immune responses against the probable antigens. The easiest test to perform is the search for precipitating antibodies. The antigens responsible for common forms of HP such as farmer’s lung and pigeon-breeder’s disease are well-characterized and can be tested by commercial laboratories. In other cases, antibodies may be difficult to detect, and previously unknown antigens cannot be assessed by standard antibody methods in commercial laboratories. If antibodies cannot be detected, the patient
may be exposed to the potential antigen in a controlled environment. This type of exposure can cause significant physiologic reactions including fever and lung function changes. Fortunately, these reactions are usually well-tolerated. The physiologic response to challenge may be quite helpful in arriving at a firm diagnosis.

The intrapulmonary reactions associated with HP are quite predictable. Deceased subjects have a significant increase in the number of lymphocytes in the lower respiratory tract. The percentage of lymphocytes is increased threefold to fivefold, and the total number of cells recovered by BAL is increased twofold to threefold compared to control subjects who have a similar smoking status. The composition of lymphocytes in the respiratory tract also is altered. The normal respiratory tract has a lymphocyte composition similar to that of circulating cells. Specifically, the ratios of helper to suppressor cells are consistent with those ratios in the blood. Patients with HP have a significant increase in the number of suppressor/cytotoxic cells recovered. This results in a significant reduction in the helper/suppressor cell ratio. These lavage findings are seen in few other diseases and provide significant support for the diagnosis.

If the diagnosis is still in doubt, an open or thoracoscopic lung biopsy can assist by demonstrating changes that are compatible with the diagnosis. Importantly, other diseases may be excluded by their absence in biopsy material.

Once a diagnosis has been made, the treatment of choice is antigen avoidance. This can be achieved by several fairly simple steps. A high-efficiency filter mask can protect the wearer from the great bulk of antigens in inspired air. This may be adequate for many workplace or hobby exposures. Living places can be protected by high-efficiency particle filters for the ambient air. In some cases, a good house cleaning has been reported to yield benefits. Corticosteroid therapy can significantly reduce acute symptoms. However, there is some concern that steroid-treated patients are more likely to relapse than those who are untreated. Thus, steroids should be reserved for patients with severe symptoms or for those who fail to respond to antigen avoidance.

In this issue of CHEST, the article by Tsushima et al (see page 1085) is not the first description of HP resulting from the inhalation of fungal spores in mushroom workers. However, it is a nice description of and methodology for the diagnosis of HP. These investigators have used techniques that would be available to the average clinician. These techniques (ie, CT scan, lung function testing, BAL, and biopsy) should be available in most hospitals. The only study not readily available as a clinical test was the lymphocyte transformation assay. In this case, the assay was necessary for a clear determination that the fungal material had induced immune response in the exposed workers because antibody levels could not be measured. This type of assay might well be necessary in a workplace incident in which compensation to the affected employees was being considered. However, I believe that most clinicians would accept the evidence of HP in the absence of this type of test. The positive exposure test provides similar information and would have convinced me of the causal nature of the mushroom exposure.

In summary, the greatest challenge in these cases is for the clinician to consider that HP is among the possible diagnoses. Once this is considered, a panel of tests can be performed. These tests, without biopsy in most cases, will be adequate. Biopsy should be considered for patients whose presentation is puzzling or for those who fail to respond appropriately to antigen avoidance.

William Merrill, MD, FCCP
New Orleans, LA

Dr. Merrill is Director, Medicine Service Line, New Orleans Veterans Affairs Medical Center, and Professor of Medicine, Tulane University School of Medicine. Correspondence to: William Merrill, MD, FCCP, Chief-Medical Service III, 1601 Perdido, New Orleans, LA 70112-1207; e-mail: william.merrill@med.va.gov

References
A Simple Method to Assess Postoperative Risk

Major surgery under general anesthesia poses a significant stress to the cardiopulmonary system. Previous investigators have shown that postoperative morbidity and mortality are higher in those patients with limited cardiopulmonary reserves. Patients with pulmonary disease have a higher incidence of postoperative complications, and the frequency of complications increases in proportion to the severity of the pulmonary impairment. Similarly, the presence of increasing numbers of cardiac risk factors increases the risk of postoperative complications in patients with cardiac disease.

While cardiac performance and respiratory function each can be evaluated individually, exercise testing offers the advantage of examining both systems in a single study. Formal exercise testing with analysis of gas exchange and measurement of maximal oxygen uptake (VO₂max) can provide information regarding the extent and cause of a patient’s limitation, whether it be cardiac or pulmonary in origin. However, this form of exercise testing requires specialized equipment, is expensive, is time-consuming, and is not readily available at all hospitals. In this issue of *CHEST*, the study by Girish and colleagues (see page 1147) takes us back to a simpler era before this sophisticated exercise equipment was available and reminds us of several important points.

Stair climbing is the traditional and time-honored form of exercise testing that was incorporated into the preoperative evaluation of many surgeons long before the ability to measure VO₂ became available in clinical practice. Its tradition is so ingrained in surgical lore that it is unclear who was the first physician to actually observe a patient climbing stairs. Nonetheless, in a retrospective review of patients undergoing pneumonectomy at the University of Minnesota from 1947 to 1965, Van Nostrand and colleagues noted an unacceptably high 50% mortality rate in those patients who were unable to climb two flights of stairs, whereas the mortality rate was only 10% in patients who were able to complete this test. Thus, patients were considered to be suitable candidates for pneumonectomy if they could climb two or more flights of stairs. Subsequent investigators have confirmed that stair climbing can be a valuable adjunct to the preoperative assessment. Holden et al studied 16 patients at high risk for thoracotomy because they had an FEV₁ < 1.6 L. Four of 5 patients who were unable to climb > 44 steps (equivalent to two flights of stairs in most hospitals), but only 1 of 11 patients who exceeded 44 steps died in the postoperative period.

Stair climbing is a simple form of exercise that imposes a progressive burden on the cardiopulmonary system. In healthy individuals, VO₂max measured during stair climbing is comparable to that measured during treadmill exercise. Since the presence of either cardiac or pulmonary disease can limit exercise capacity, it is not surprising that patients with underlying cardiopulmonary disorders have difficulty climbing stairs. The degree of limitation is roughly proportional to the severity of the impairment in cardiac or pulmonary function.

Previous studies have shown that VO₂max measured in the exercise laboratory is a good indicator of postoperative risk in patients undergoing thoracic procedures. A VO₂max > 20 mL/kg/min is associated with a low risk of postoperative complications, whereas a VO₂max < 10 mL/kg/min or 1 L/min is associated with markedly increased morbidity and mortality. The risk of complications is intermediate in patients with a VO₂max between these values. In patients with chronic airflow obstruction, climbing two flights of stairs corresponds to a VO₂max of about 12 mL/kg/min, whereas the VO₂max exceeds 20 mL/kg/min in those patients who are able to climb five flights of stairs.

The study by Girish et al extends these observations in several ways. They studied a large group of diverse patients prior to elective thoracotomy or upper abdominal surgery and found a significant inverse relationship between the number of flights of stairs climbed and postoperative morbidity. Only 1 of 20 patients who successfully climbed five flights of stairs had a postoperative complication, thus confirming previous studies that have shown an excellent correlation between cardiopulmonary fitness and postoperative outcome. In contrast, 10 of 15 patients who were unable to climb more than two flights of stairs experienced postoperative complications.

Second, Girish et al found that the inability to climb stairs, irrespective of the reason, was associated with a poor outcome. Eight of nine patients who refused or were unable to climb a single flight of stairs had postoperative complications, including one death. Previous investigators have shown that an