In the immunocompromised patient, the pulmonary nodule remains a diagnostic and therapeutic challenge. We studied the incidence, cause, diagnosis, and therapy of pulmonary nodules after lung transplantation (LTxs). Eight out of 64 patients (12.5%) developed pulmonary nodules after a median follow-up of 5.8 months (range, 1 to 10 months). The median age was 30.5 years (range, 21 to 62 years). Solitary pulmonary nodules (n=2) disappeared spontaneously within 3 weeks and were suspected to be of infectious origin. The cause of multiple nodules (n=6) was posttransplant lymphoproliferative disorder (PTLD [n=3]), aspergillosis (n=2), and abscesses caused by Pseudomonas aeruginosa and Staphylococcus aureus (n=1). After an initial chest radiograph, CT with fine-needle biopsy was the most valuable diagnostic tool. In six patients, nodules resolved within 10 weeks (median, 8 weeks). Two patients, however, died of sepsis (P. aeruginosa and S. aureus and Aspergillus, respectively). The differential diagnosis of pulmonary nodules after LTx primarily comprises PTLD and infection (bacterial or fungal). To improve the outcome, early, aggressive treatment is mandatory; therefore, serial CT scans are strongly recommended to be part of the diagnostic armamentarium in LTx recipients.

(Chest 1995; 107:1317-22)

ATG=antithymocyte globulin; BAL=bronchoalveolar lavage; CMV=cytomegalovirus; LTx=lung transplantation; PTLD=posttransplant lymphoproliferative disorder

Key words: computed tomography; fine-needle biopsy; lung transplantation; pulmonary nodule

Immunosuppression

Induction immunosuppression consisted of methylprednisolone and rabbit antithymocyte globulin (ATG-Fresenius, Homburg, Germany) as described previously. Maintenance immunosuppression was a triple drug regimen including prednisolone (0.5 mg/kg/d), azathioprine (Imurek, Wellcome; London, England) with the leukocyte count adjusted to 4.0-6.0x10^9/L, and cyclosporin A (Sandimmun, Sandoz; Basel, Switzerland) to achieve a high-performance liquid chromatography whole blood level of about 200 to 300 ng/mL (Bio-Rad, Hercules, Calif). Rejection episodes were treated by pulse methylprednisolone courses (1 g/d for 3 days), repeated rejection episodes were treated with a murine monoclonal CD3-antibody (Orthoclone OKT3, Ortho Pharmaceuticals; Raritan, NJ) or equine ATG (ATG-Sero, Sero-Mérieux; Lyon, France) was administered. Every patient received peroral trimethoprim, 150 mg, and sulfamethoxazole, 800 mg, twice daily for 4 days per week to prevent Pneumocystis carinii infection.

Follow-up

Routine follow-up included a chest radiograph, lung function testing, routine blood samples, screening for viral infections (cytomegalovirus [CMV], Ebstein-Barr virus, herpes simplex) in blood, sputum, and urine twice a week during the second and third postoperative weeks, then weekly up to the seventh postoperative week and later on at 3-month intervals. Fiberoptic bronchoscopy with transbronchial biopsies and bronchoalveolar lavage (BAL) as well as CT scans were routinely performed at 3 to 6 month intervals and whenever the clinical situation required.

All CT scans were obtained during suspended full inspiration with the patient in the supine position, with and without intravenous administration of contrast medium. The CT scanning...
Table 1—Demographics of Lung Transplant Recipients Developing Pulmonary Nodules (n=8)

<table>
<thead>
<tr>
<th>Patient Age, yr</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>LTx*</th>
<th>Immunosuppression Therapy</th>
<th>Localisation/Lobe</th>
<th>Onset After Transplantation, mos</th>
<th>Diameter, mm</th>
<th>Diagnostic Procedures</th>
<th>Cause</th>
<th>Therapy ‡</th>
<th>Outcome, Status After Transplantation, (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 33 M Bronchiectasis</td>
<td>D 3P</td>
<td>Right upper</td>
<td>8</td>
<td>9.5</td>
<td>X, CT</td>
<td>Unknown</td>
<td>No</td>
<td></td>
<td></td>
<td>Resolved (2)</td>
<td>Alive (26.8)</td>
</tr>
<tr>
<td>2 28 F Fibrosis</td>
<td>S 6P, 10K3</td>
<td>Left upper</td>
<td>9</td>
<td>7</td>
<td>X, CT</td>
<td>Unknown</td>
<td>No</td>
<td></td>
<td></td>
<td>Resolved (3)</td>
<td>Alive (25.8)</td>
</tr>
<tr>
<td>Multiple nodules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 62 M Fibrosis</td>
<td>S 1P</td>
<td>Left</td>
<td>15-10</td>
<td>10</td>
<td>X, CT</td>
<td>pPTLD</td>
<td>Immunosuppressive reduced</td>
<td></td>
<td></td>
<td>Resolved (10)</td>
<td>Alive (40.3)</td>
</tr>
<tr>
<td>4 25 M Secondary pulmonary hypertension Bronchiectasis</td>
<td>D 2P, 20K3</td>
<td>Left</td>
<td>45-10</td>
<td>4.5</td>
<td>X, CT</td>
<td>pPTLD</td>
<td>Immunosuppressive reduced</td>
<td></td>
<td></td>
<td>Resolved (8)</td>
<td>Alive (17)</td>
</tr>
<tr>
<td>5 21 F Fibrosis</td>
<td>D 3P, 1ATG</td>
<td>Bilateral</td>
<td>8-45</td>
<td>3</td>
<td>X, CT, M</td>
<td>mPTLD</td>
<td>Combination</td>
<td></td>
<td></td>
<td>Resolved (8)</td>
<td>Alive (28.8)</td>
</tr>
<tr>
<td>6 51 M Fibrosis</td>
<td>D 4P, 10K3</td>
<td>Bilateral</td>
<td>10</td>
<td>7</td>
<td>X, CT</td>
<td>Aspergillus</td>
<td></td>
<td></td>
<td>Not resolved</td>
<td>Died of sepsis (8)</td>
<td></td>
</tr>
<tr>
<td>7 26 M Cystic fibrosis</td>
<td>D 2P</td>
<td>Bilateral</td>
<td>10-20</td>
<td>1.2</td>
<td>X, CT</td>
<td>Aspergillus</td>
<td></td>
<td></td>
<td>Resected (7)</td>
<td>Died of sepsis (6.3)</td>
<td></td>
</tr>
<tr>
<td>8 56 M Emphysema</td>
<td>D 3P</td>
<td>Right middle</td>
<td>30</td>
<td>1</td>
<td>X, CT</td>
<td>Aspergillus</td>
<td></td>
<td></td>
<td></td>
<td>Resected (8)</td>
<td>Alive (7.3)</td>
</tr>
</tbody>
</table>

*LTx: D=double, S=single.

1Immunosuppression before diagnosis of nodules: 2P=2 courses of pulse methylprednisolone; 20K3=2 courses of OKT3; 1ATG=1 course of ATG;

2Diagnostic procedures: X=chest x-ray; CT+P=computed tomography with CT-guided fine-needle biopsy; M=mediastinoscopy; A=autopsy.

3Cause: p=polyclonal; m=monoclonal.

4AB=antibiotics.

Consisted of sequential acquisition of 10-mm sections at 10-mm intervals from the lung apex to the diaphragm (1-s scan time, 137 kilovolt (kV), 145 mA), with immediate reconstruction of mediastinal images by means of a standard algorithm and retrospective reconstruction of lung images by means of high-spatial frequency algorithm. All images were viewed at lung (width, 1,600 Hounsfield Units [HU]); center, -600 HU) and mediastinal (width, 350 HU; center, 50 HU) window settings (SR7000 Philips; Eindhoven, the Netherlands). In the two last patients, spiral CT with 8-mm-thick sections was used (Somatom Plus-S, Siemens; Erlangen, Germany).

The CT-guided-fine-needle biopsies were performed as described elsewhere. From each nodule, about five specimens were taken by using the 18- to 22-gauge (Autovac, Angiomed; Karlsruhe, Germany) or a needle system (Surecut TSK; Tokyo, Japan). Biopsy specimens were fixed in 7.5% buffered formaldehyde solution (Formalin), embedded in paraffin, and sectioned serially at 4 μm. Sections were stained with hematoxylin and eosin, Giemsa stain, periodic acid-Schiff (PAS), elastin van Gieson's stain, Grimori's or Grocott-Gomori methenamine-silver stain, Gram's stain, and acid-fast stains. In situ hybridization was performed by using biotinylated DNA probes to CMV, herpes simplex virus, and adenovirus (Enzo Diagnostics; Farmingdale, NY). Epstein-Barr virus infection was detected immunohistochemically with a monoclonal antibody to Epstein-Barr-encoded latent membrane protein (DAKO; Glostrup, Denmark), CMV pneumonitis by characteristic cellular inclusions and hybridization, and Aspergillus species by typical branching hyphae. Posttransplant lymphoproliferative disorders (PTLDs) were assessed using histopathologic criteria, by immunostaining with a panel of antibodies to leukocyte differentiation antigens, and by immunohistochemical examination of cytoplasmic immunoglobulins (CLA, CD3, C3, C19, L26 [Dakopatts, Copenhagen, Denmark]; Leu7 [Beeton Dickinson, San José, Calif]; IgG, IgM, and IgA [Behring; Marburg, Germany]). Western blot analysis was used to diagnose clonality of PTLDs by detection of immunoglobulin gene rearrangement. Bacterial and fungal cultures also were obtained.

Results

Patients

Eight patients of 64 (12.5%) developed nodules in the transplanted lung at a median follow-up period of 5.8 months (range, 1 to 10 months) after LTx. There were 5 men and 3 women with a median age of 50.5 years (range, 21 to 62 years [Table 1, chronological order]). Two had a single, and 6 had a double-lung allograft. Indications for LTx were fibrosis (n=5), bronchiectasis (n=2), emphysema (n=1), cystic fibrosis (n=1), and secondary pulmonary hypertension (n=1). Solitary nodules were found in two and multiple nodules in 6 patients. All patients had received at least one pulse of methylprednisolone (up to 6 courses; median, 3); 1 patient received additional ATG; 3 patients had OKT3 (1 to 2 courses) before the diagnosis of pulmonary nodules.

Clinical and Radiologic Findings

Six patients out of 8 (75%) were symptom-free, and the nodules were incidentally detected on routine chest x-ray film. Only 2 patients (cases 6 and 7) presented with symptoms such as dyspnea and hemoptysis, which prompted further investigation.

In 7 cases out of 8 (88%), the nodules were first seen on the chest x-ray film; in one case the x-ray film disclosed no abnormalities, and diagnosis was made only by CT scan. Posterior-anterior projection was diagnostic in 6 cases; in 1 patient (case 4), nodules were only recognized on the lateral view. All nodules appeared on normal background. Diameter ranged...
from 8 to 9 mm in the solitary and from 8 to 45 mm in the multiple cases. In all patients, additional CT scans were performed. A CT-guided, fine-needle biopsy was carried out in 5 cases (4 positive, patients 3, 4, 7, and 8; 1 inconclusive, patient 2). Mediastinoscopy with biopsy led to the diagnosis in a patient with hilar and paratracheal masses preceding the onset of pulmonary nodules (patient 5). One patient with a solitary nodule did not undergo invasive investigation (patient 1), and in 1 case with multiple nodules, diagnosis was only obtained at autopsy (patient 6). Bronchoscopy with BAL and transbronchial biopsy was performed in all patients. (Only patient 6 did not undergo transbronchial biopsy because of her bad clinical condition.)

Etiology

Solitary nodules remained of unknown origin (n=2): In patient 1, biopsy was not performed because of the small size and the benign course, and in patient 2, biopsy was not conclusive. It was not repeated because the nodule decreased within a short time. Infection is discussed to be the most likely cause of the nodules (bacterial, fungal, or viral) as BAL showed colonization by *Pseudomonas aeruginosa* in patient 1 and recurrent bronchitis and bronchiolitis caused by *Staphylococcus aureus* (as well as intermittent colonization with Aspergillus) in patient 2. Both patients had histories of recurrent CMV infections too. Histologic diagnosis was obtained in all cases with multiple nodules (n=6). The underlying pathologic findings were PTLD in 3 (2 polyclonal, 1 monoclonal), *Aspergillosis* species in 2 patients, and abscesses caused by *P aeruginosa* and *S aureus* in 1 patient.

Response and Mortality

Nodules resolved in 6 patients after a median interval of 8 weeks (range, 2 to 10 weeks). These patients are alive 7 to 40 months (median, 26 months)
after LTx. Two patients subsequently died of generalized sepsis 8 and 6.3 months after LTX, respectively, as indicated in the case reports of patients 6 and 7.

Case Reports and Therapy

The patients with the solitary nodules (patients 1 and 2) did not receive any specific therapy, and the nodules resolved within 2 to 3 weeks. Both patients had empirical therapy with ayclovir, and patient 2 received additional antibiotic treatment for recurrent bronchitis (S aureus).

Patients 3 and 4

These patients had polyclonal PTLD (Fig 1,2) that responded to a reduction of immunosuppressive therapy, and nodules disappeared within 8 to 10 weeks.

Patient 5

This patient presented with hilar and paratracheal masses 6 weeks after double LTx; mediastinoscopy with biopsy demonstrated a monoclonal PTLD. Reduction of immunosuppression and irradiation failed; besides, multiple big nodules appeared 3 months after LTx, progressing rapidly. With chemotherapy and monoclonal CD24-antibodies (murine anti-B-cell IgG1), the nodules resolved within 2 months. A solitary residual node in the left upper lobe was resected by thoracotomy; the diagnosis was scar tissue.

Patient 6

A cachectic 51-year-old woman developed increasing dyspnea 7 months after double LTx. At admission, the chest x-ray film was negative and PaO₂ value was 40 mm Hg with the patient breathing room air. Empirical pulse prednisolone therapy failed, and her condition deteriorated within hours. A CT scan revealed multiple bilateral nodules which had not been detected on an x-ray film before. Four days after admission, the patient died of respiratory failure. Autopsy revealed Aspergillosis with multiple abscesses in both lungs and in the myocardium.

Patient 7

This patient (Fig 3) had double LTx for cystic fibrosis. Six weeks after the operation, he had hemoptysis; a chest x-ray film showed two nodules in the right upper lobe. A CT-guided, fine-needle biopsy showed necrotic tissue. In the BAL fluid, P aeruginosa and S aureus organisms were found. Because 7 weeks of antibiotic therapy failed, the two nodules were surgically excised to exclude suspected PTLD. Histologic findings and cultures confirmed the diagnosis of abscesses caused by P aeruginosa and S aureus. Four months after onset, the patient died of generalized sepsis.

Patient 8

This patient presented with a 8-mm diameter nodule in the right middle lobe 4 weeks after double LTx. When it increased to 2 cm within 2 weeks, a CT-guided, fine-needle biopsy was performed. Histologic analysis and culture revealed an aspergillosa. CT scan showed additional tiny nodules in the left lower lobe. The main nodule in the middle lobe showed progression up to 3 cm but resolved by colloidal amphotericin B treatment (Amphocil, Liposome Technology; Menlo Park, Calif) within 8 weeks.

Discussion

Pulmonary infiltrates are common findings in lung transplant recipients; their main cause is infection or rejection. According to Lillington, a nodule is a spherical or oval intrapulmonary opacity on the x-ray film that is well enough circumscribed to permit
measurement of the various diameters; its size is often limited up to 6 cm or less in diameter.7

The cause of nodules in the nonimmunocompromised host is well known. The most common underlying pathologic characteristics for solitary nodules are bronchial carcinoma and metastases; multiple nodules frequently are caused by metastases or multicentric alveolar cell carcinoma.1 In the immunocompromised host, however, nodules are most commonly caused by bacterial or fungal infections or PTLD.2,6-8,11 Due to the large surface open to environmental influences and other factors such as depressed cough reflex, altered airway clearance, and airway ischemia, the transplanted lungs are more susceptible to develop infiltrates than other organs. With increasing numbers of transplantations and broader experience in treating AIDS patients, more causes will become known. Thus, pulmonary nodular opacities shown on x-ray film may be caused by focal hematomas after transbronchial biopsy in LTx.12 Cytomegalovirus pneumonia also has been described as an unusual cause of a nodule in a patient with AIDS13; even bronchiolitis obliterans organizing pneumonia may present as a solitary nodule.14 A large series of pulmonary nodules and masses in cardiac transplant recipients showed an incidence of 9.7% (25 patients); 75% of the nodules were caused by infectious pathogens; Aspergillus and Nocardia organisms were the most frequent ones.15

We present 3.5 years of experience in LTx and a follow-up study of patients whom we screened for the development of pulmonary nodules and who survived longer than 2 weeks postoperatively. About 13% (8 of 64) developed nodules in the allograft at a median follow-up period of 5.8 months (range, 1 to 10 months). Infections predominated PTLD (63 vs 37%). Most patients, ie, 75% (6 of 8), had no signs or symptoms; the nodules incidentally were diagnosed by being evidenced on chest x-ray film. In the 2 patients presenting with symptoms such as dyspnea and hemoptysis, a chest x-ray film disclosed abnormalities in one patient, but it was false-negative in the other one. In the latter, multiple nodules were only recognized by the CT scan and turned out to be aspergillomas. Thus, chest x-ray film remains the most valuable tool in the early diagnosis of pulmonary nodules, especially in patients who are symptom-free. The case involving the nondisclosing x-ray film but positive CT scan induced us to use a CT scan generously as a routine in the follow-up at 3- to 6-month intervals and additionally if there is any unclear clinical or roentgenologic finding. More recently, we also have used spiral CT, which is reported to be superior to conventional CT in the detection of pulmonary nodules.16

In a series of four heart transplant recipients, Mc- Calmont et al11 showed the usefulness of CT-guided, fine-needle biopsies of aspergillomas and claimed its wider use for the evaluation of pulmonary nodules. Its sensitivity is reported to be 81% and is increased to 95% with repeat biopsies in a series of 54 patients with a history of malignant lymphoma.4 In our experience, needle biopsy proved its value in cases with multiple nodules or nodules with a diameter of 1 cm or more. In these cases, the underlying disease is often a more “malignant” one, such as PTLD or abscesses (bacterial or fungal), where a prompt histologic or cultural diagnosis enables immediate therapy and may thus improve the survival rates of LTx recipients. Although fungal disease constitutes a minority of infection-related morbidity, it carries a high risk of mortality.11,17 No effort should be spared to promptly obtain a histologic diagnosis of fungal involvement because in most cases bronchoscopies with BAL and serologic determinations fail.2,18 Because mortality in monoclonal PTLD is as high as 70%,19 an aggressive diagnostic approach is required.

Solitary well-defined nodules up to 1 cm in diameter without any growing potential, however, seem to have a better prognosis. In our two patients, fine-needle biopsy failed in one; the other one had no invasive procedure. In both patients, the nodules disappeared within 3 weeks without any specific treatment. The cause remains unclear, although we consider infection (bacterial, fungal, or viral) to be the most probable cause. Herman20 reported on two lung transplant recipients with similar findings in whom no cause for the nodules was ever established; he also assumed that the nodules might have been related to self-limited infections. We recommend that the size of these solitary nodules be carefully monitored by CT scan and that the immunosuppressive regimen be reduced. If there is any increase in size or number, fine-needle biopsy—even repeatedly—is mandatory. If it fails, open-lung biopsy should not be delayed. Depending on the location, it may be performed via a thoracotomy or by video-assisted thoracoscopic surgery. Before histologic diagnosis is available, empirical treatment with antibiotics and antifungal and antiviral agents is warranted but needs to be individualized.5

Prevention of disease in LTx often cannot be achieved because of the complexity and diversity of pathologic conditions. Thus, the difficult tightrope walk between infection and rejection has to be continued. It is hard to judge if prevention of nodules would have been possible in some cases by keeping immunosuppression at a lower level. In retrospective analysis, we are convinced that the fatal outcome in patient 6 was accelerated by overimmunosuppression (pulse methylprednisolone courses and OKT3 therapy because of histologically verified obliterator
bronchiolitis). From the lessons we have learned, we strongly suggest, for the long-term follow-up, that a histologic diagnosis of rejection be achieved before treatment and that the empirical high-dose prednisolone courses be minimized whenever possible.

In summary, pulmonary nodules are not an unusual finding after lung transplantation, mostly being incidentally detected on chest radiographs. The CT scans should be routinely performed at 3- to 6-month intervals to go beyond the diagnostic capacity of chest radiographs. Rapid diagnosis by fine-needle biopsy is necessary. If there is an inconclusive finding, open-lung biopsy should not be delayed in cases of bigger or multiple nodules or nodules that are both bigger and multiple which are suspected of being affected by PTLD or infection. Although smaller solitary nodules (less than 1 cm in diameter) might resolve spontaneously in some cases, close monitoring, ie, weekly CT scanning, is mandatory. Reduction of the immunotherapy in conjunction with acyclovir is the treatment of polyclonal PTLD, whereas in monoclonal PTLD an aggressive multimodality approach is necessary. Aspergillus organisms should be consistently treated with colloidal or liposomal amphotericin B, the less nephrotoxic forms of this drug.

In the management of pulmonary nodules in lung transplant recipients, a high index of suspicion and the consideration of "unusual" causes are essential to improve the outcome.

ACKNOWLEDGMENTS: We thank Thomas Inhauser, MD, and Anton Stift, MD, for cooperation in patient management.

REFERENCES
4 Wittich GR, Nowels KW, Korn RL, et al. Coaxial transthoracic fine-needle biopsy in patients with a history of malignant lym-
phoma. Radiology 1992; 183:175-78