Solitary Pulmonary Nodule in the Liver Transplant Candidate: Importance of Diagnosis and Treatment

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Our objectives were to define the incidence and etiology of solitary pulmonary nodules (SPNs) in patients undergoing living donor liver transplantation (LDLT), describe a diagnostic approach to the management of SPNs in LDLT, and define the impact of SPNs on the overall survival of adult LDLT recipients. Nine patients (9/152, 5.9%) were diagnosed with an SPN on the basis of chest radiography findings during the pretransplant survey. All were male. The mean age was 52 years. All the patients had hepatitis B virus–related cirrhosis with hepatocellular carcinoma. All were asymptomatic for the lung lesion. All underwent contrast-enhanced chest computed tomography (CT) to verify the presence and possible etiology of the SPNs. In 3 cases, CT was used to definitely determine that there was no pulmonary nodule; in 2, CT led to a definite diagnosis of pulmonary tuberculosis. In 4, CT led to a definite identification of an SPN but not to an etiological diagnosis. Two patients underwent outright thoracoscopy and biopsy of their SPNs. Biopsy showed cryptococcosis in both patients. One received a therapeutic trial of an antituberculosis treatment, and repeat CT after 1 month showed a regression in the size of the SPN. A diagnosis of tuberculosis was made. One patient had an inconclusive whole body positron emission tomography scan and subsequently underwent thoracoscopy where biopsy showed tuberculosis. A concomitant malignancy, either primary lung cancer or metastasis from the liver tumor, was not identified. All patients were surviving with their original grafts and were lung infection–free. The overall mean posttransplant follow-up was 54 months (range = 33–96 months). Liver Transpl 16:760–766, 2010. © 2010 AASLD.

Received October 29, 2009; accepted February 28, 2010.

Patients undergoing transplantation require a thorough clinical evaluation to exclude overt and occult malignancies that would preclude the planned procedure. This is important because routine immunosuppression use after transplantation may often result in the body’s loss of immunoregulatory functions and thus in a myriad of problems, including oncological and infectious processes. Occult infections may manifest as fulminant, life-threatening sepsis after transplantation.

Indeterminate pulmonary nodules in transplant candidates pose both diagnostic and therapeutic...
challenges for the clinician. Because of its various etiologies, the evaluation of a solitary pulmonary nodule (SPN) is conducted differently from the evaluation of a known carcinoma of the lung or metastasis from liver carcinoma. The clinical importance and course of an SPN in patients undergoing liver transplantation (LT) have been poorly elucidated. Although it is not unusual to encounter LT candidates with lung masses, an approach to the management of this select group of patients has not been provided. We have encountered a few patients with an SPN in the routine course of evaluating our adult LT candidates. Our objectives in this review were to (1) define the incidence and etiology of SPNs in patients undergoing living donor liver transplantation (LDLT), (2) describe a diagnostic approach to the management of SPNs and their treatment in LDLT, and (3) define the impact of SPNs on the overall survival of adult LDLT recipients.

PATIENTS AND METHODS
From June 1994 to December 2006, 152 primary adult LDLT procedures were performed at the Chang Gung Memorial Hospital–Kaohsiung Medical Center (Taiwan). The records of these patients and their follow-up were retrospectively analyzed; they included recipient demographic and clinical data, preoperative imaging, operative outcomes, pathology of the explanted liver, complications, and long-term outcomes. Particular attention was paid to patients whose preoperative diagnostic imaging evaluation showed an SPN.

The demographic data, type of liver disease, donor-recipient characteristics, characterization and etiology of the SPN, complications, outcome of the SPN, and overall recipient transplant outcome were presented with descriptive statistics.

Our protocol for evaluating a live liver donor has been described previously. We emphasized the importance of the donor’s voluntary and altruistic intent before we proceeded with the initial screening, which included the blood type and hepatitis profile. Our protocol for evaluating an adult recipient being considered for transplantation has also been described elsewhere.

Our techniques for donor graft heptectomy and recipient total heptectomy in LDLT have been described in detail previously. The anesthesia management followed the protocol of the Department of Anesthesiology. Red blood cell transfusions were not given to patients with hemoglobin levels > 8.0 g/dL and as long as the intravascular volume was sufficient to maintain normal hemodynamics.

Evaluation of the SPN
An asymptomatic SPN was defined as a circumscribed, single, peripheral lung mass. The criteria for designating a radiographic shadow as an SPN included the following: (1) the shadow was spherical or ovoid, (2) it was ill defined or sharply demarcated, (3) it was surrounded by an air-containing lung, (4) it was less than 3 cm in size, (5) hilar or mediastinal lymphadenopathy was absent, and (6) there was no extrapleural or intrathoracic structure involvement.

A routine upright, posteroanterior (PA) view chest radiograph was mandatory for all patients as previously mentioned. Suspicious lung nodules were verified by contrast-enhanced high-resolution computed tomography (CT) of the chest, and a meticulous evaluation of mediastinal, thoracic, and pleural structures was performed. If chest CT was inconclusive, magnetic resonance imaging (MRI) studies or a positron emission tomography scan was requested to evaluate potential primary lung tumors, infectious or inflammatory processes, and metastases.

Once noninvasive procedures were proven to be inconclusive for the SPN being evaluated, if the lung tumor was accessible, CT-guided needle biopsy, video-assisted thoracoscopic surgery (VATS), or thoracotomy was performed for tissue diagnosis. Bronchoscopy was optional in the diagnostic evaluation of small peripherally located lesions. A decision protocol for the evaluation of SPNs in LT candidates is provided in Fig. 1.

Criteria for the Diagnosis of Pulmonary Tuberculosis (TB)
CT is superior to chest X-rays in evaluating many chest diseases, and many CT features of pulmonary TB have been described. High-resolution chest CT has been found to be superior to standard CT. We used high-resolution chest CT in assessing pulmonary TB in our patients in this series. The criteria for the diagnosis of TB and old TB were based on the criteria presented by Lee and associates using high-resolution CT. A diagnosis of pulmonary TB and active pulmonary TB was made on the basis of the presence of the following on high-resolution CT: micromodules, nodules, tree-in-bud appearance, consolidation, and cavities. The disappearance of the tree-in-bud appearance, the absence of pleural effusion, and the presence of fibrotic changes appear to be indications of the effectiveness of the treatment. Old fibrotic lesions can be differentiated by high-resolution CT.

In addition to the high-resolution CT criteria, the patient must have any of the following clinical data: a history of TB treatment, a history of exposure to TB, a history of previous chest imaging showing an unchanged pulmonary nodule, reactive immunological tests such as pure protein derivative inoculation, or sputum or body fluid positive for TB on polymerase chain reaction assay.

RESULTS
There were 114 male patients and 38 female patients. The disease indications for transplantation included hepatitis B virus with or without hepatocellular carcinoma (HCC; 92), hepatitis C virus infection with or
without HCC (25), primary biliary cirrhosis (12), alcoholic cirrhosis (8), hepatitis B virus and hepatitis C virus with or without HCC (6), Wilson’s disease (4), and other (5).

Nine patients (5.9%) were diagnosed to have an SPN on the basis of chest radiography findings alone during the pretransplant survey. All were male patients. The mean age was 52 years (range = 46-63 years). All were diagnosed with hepatitis B virus–related cirrhosis with HCC. All were asymptomatic for the lung lesion (no chronic cough, no hemoptysis, no dyspnea, and no afternoon fever). Table 1 summarizes the patients’ demographic and clinical profiles.

**Outcomes of SPNs**

All 9 patients underwent contrast-enhanced CT of the chest to verify the presence and possible etiology of the SPNs. In 3 cases, chest CT was used to definitely determine that there was no pulmonary nodule, and in 2 other cases, the chest CT findings led to a definite diagnosis of pulmonary TB. No other ancillary procedures were required in 4 of these 5 patients, and none of them required lung biopsy.

In 2 other cases (patients 5 and 6), chest CT led to a definite identification of an SPN but not to a diagnosis of the etiology. In 2 other cases (patients 7 and 9), an SPN was identified, but whether it was due to TB or a malignancy could not be determined on the basis of the characteristic CT findings. Patients 5 and 6 underwent outright thoracoscopy and excision biopsy of their SPNs, and the biopsy findings showed cryptococcosis in both patients.

Patient 7 underwent repeat chest CT 1 month afterward and showed a regression in the size of the SPN. This particular patient was on the waiting list for more than 1 month. It took approximately 1 month to find a suitable live liver donor for him (23 days). Given a diagnosis of TB versus a malignancy with high-resolution CT, he, while on the waiting list, was placed on a therapeutic trial of an anti-TB regimen. Repeat chest CT 1 month later showed a decrease in the size of the nodule with the presence of fibrotic changes. Following the criteria of Lee and associates, we labeled this pulmonary TB.

Patient 9 underwent whole body positron emission tomography to check for extrahepatic spread of the hepatic malignancy because of slight elevations in the alpha-fetoprotein level and liver tumor number. The positron scan was inconclusive, and the patient subsequently underwent thoracoscopy and excision biopsy. The biopsy findings showed TB. Table 2 summarizes the imaging characteristics, radiological diagnoses, and results of ancillary procedures. A concomitant malignancy, either primary lung cancer or a metastatic tumor from the liver malignancy, was not identified in any patient.

Pulmonary cryptococcosis was treated with fluconazole (3 mg/kg of body weight/day by mouth or 200-400 mg/day by mouth) for 2 weeks before LT, and this was continued for a minimum of 6 months post-transplant. In patient 9, the initial biopsy did not show acid-fast bacilli, and the patient immediately underwent LT 2 days after the lung biopsy. Sputum cultures obtained before the transplant were negative for mycobacteria. An anti-TB treatment was not undertaken before transplantation. However, Ziehl-
Neelsen staining of the lung specimen showed acid-fast–positive bacilli. A mycobacterial culture from the tissue samples was not available before transplantation. The same patient was started on moxifloxacin, isoniazid, ethambutol, and pyrazinamide 1 week after LT and was continued on them for 6 months. Recurrent infection was not seen in any patient up to the latest posttransplant follow-up (a minimum of 33 months).

All 9 patients were surviving with their original grafts. The mean posttransplant follow-up was 54 months (range = 33-96 months).

### DISCUSSION

Indeterminate pulmonary nodules and SPNs in transplant candidates pose diagnostic and therapeutic challenges because of the broad differential diagnoses involved. Transplant candidates require diagnostic clarification of their SPNs, which may represent oncological and/or infectious processes. Particularly in patients whose primary indication for transplantation is HCC, the presence of pulmonary metastasis has to be excluded. In this series, the incidence of SPNs was 5.9%.

Identifying clinical and radiographic factors that are associated with a specific etiology of pulmonary nodules in solid organ transplant patients might be helpful in guiding empiric therapy. Cryptococcosis is the third most common invasive fungal infection in solid organ transplantation. The most common clinical symptom of pulmonary cryptococcosis is coughing. Furthermore, the rate of mortality from Cryptococcus neoformans in patients with cirrhosis, including LT candidates, can be as high as 81%. Because of the high mortality rate associated with pulmonary and disseminated cryptococcosis, a precise diagnosis and early treatment are mandatory.

Transplantation is contraindicated in candidates with active TB, but undetected cases can inadvertently undergo transplantation. Chest radiographs of these patients may show residual fibrotic.
lesions and noncavitated consolidation of the lung. Lung cavitation may also be present in active TB. Although the diagnosis of TB is difficult in transplant candidates, a detailed clinical history, including a family history of TB, should be taken for all candidates suspected of TB, and chest radiographs, purified protein derivative tests, skin hypersensitivity tests, and sputum and urine cultures should be performed. Most candidates are asymptomatic, and half of the patients may show normal chest radiographs.

Disseminated TB is a potential problem in immunocompromised patients, particularly during the early posttransplant period because of the higher doses of immunosuppressants used. However, TB can be cured even in patients with active TB who underwent inadvertent transplantation. Close postoperative follow-up of high-risk patients may enable early identification and effective treatment of the disease.17

Occult malignancy is a problem in SPNs. Resection with CT-guided marking is feasible in lung nodules ≤ 10 mm for histological diagnosis. One problem is that a small number of these pulmonary nodules are malignant. This problem is compounded by the fact that these nodules may form part of an HCC metastasis. Thus, a mandatory thorough investigation of SPNs in transplant candidates must be ensured. In one study using high-resolution CT, pulmonary nodules ≤ 10 mm with ground-glass opacity were considered to have a high possibility of malignancy and to be candidates for lung resection.18

VATS is the recommended diagnostic and therapeutic approach in the management of SPNs due to cryptococcosis14 and small SPNs to rule out malignancy if this is possible, on the day of the planned operation.

Repeat CT of the chest may be of value before outright thoracoscopy in some cases. Repeat chest CT in 2 of the 5 cases in this series with an SPN proved to be of value as the repeat CT scan showed no pulmonary mass. Our average waiting time for elective LDLT is about 1 month as it takes around 1 month for the recipient to find a suitable liver donor and complete the evaluation. We usually wait for 1 month for repeat chest CT if the recipient has been given a nonmalignant diagnosis on the basis of high-resolution CT imaging because around this time the donor has been properly evaluated and the operation may be scheduled. Forty-four percent (44%) of the SPNs were due to TB, 22% were due to cryptococcosis, and 33% showed no pathology. There was no malignancy identified in the SPNs studied. This may be true because most pulmonary metastases present as cannon-ball lesions.

Given an HCC background, if any imaging had provided sufficient evidence that the lesions were malignant, then both patients may have avoided further invasive procedures. This was the primary reason that additional imaging methods were requested before an invasive procedure was undertaken. Patients 5 and 6 were not given any possible etiological diagnosis of TB versus cancer. The problem with infection spread is related to the high mobility of people. The different strains of Mycobacterium tuberculosis not previously found in North America are attributable to migration from Mexico and Asian countries. Similarly, the new virulent strains seen in Western Europe are presumed to have come from Eastern Europe and Central Asia21,22 and in Australia, patients with TB were originally from India, Southeast Asia, and China.23 Knowledge of the epidemiological characteristics of the disease is becoming important. Soon, it may become apparent that it is not unusual to see persons in England or the United States with SPNs sharing the etiology of those of persons coming from Asian countries.

Our series showed that the presence of a properly diagnosed and managed SPN did not influence the overall outcome of the patient after LDLT. Infection was the leading cause of SPNs in this series. Likewise, SPNs also did not influence early and long-term outcomes after LDLT as long as they were adequately treated. If transplantation is urgent, immediate pretransplant treatment and continued treatment after transplantation, as recommended for the individual disease entity, must be considered. Close patient screening after transplantation is mandatory. The susceptibility to TB and encapsulated bacteria is not surprising because of the inhibitory effects of current immunosuppressive therapies on a key host defense: the major histocompatibility complex-restricted, microbial-specific cytotoxic T cell response.24
regulatory cells and cytotoxic T lymphocyte responses are depressed, immunity to multidrug-resistant (MDR) TB strains may become a potential problem. Some MDR TB strains (M and Ra) impair cytotoxic T lymphocyte activity in patients to avoid the killing of macrophages by M-specific cytotoxic T lymphocyte effector cells. Furthermore, experimental T regulatory cell depletion decreases interferon-gamma expression and cytotoxic T lymphocyte activity in TB patients.\textsuperscript{25} If it is unchecked post-transplant, the range of clinical diseases extends to extrapulmonary diseases, particularly in the bones, joints, and gastrointestinal tract.

Because there is a high risk of relapse only with first-line and second-line drugs, a potential solution lies in the use of quinolone (ofloxacin) and new-genera-
tion fluoroquinolones (moxifloxacin) as chemothera-
pic drugs for MDR TB.\textsuperscript{26} Issues exist in the treat-
tment of active TB disease post-transplant because of the interaction between immunosuppressants and the anti-TB regimen and the direct hepatotoxic effects of the anti-TB drugs; this makes decisions about the eti-
ology of hepatic dysfunction post-transplant difficult. In our cases, we have used a combination of bacterio-
static drugs, ethambutol and fluoroquinolone (moxi-
flaxacin), and a standard regimen including pyrazina-
mide and isoniazid for 6 months; this is then reduced to a 2-drug regimen consisting of ethambutol and moxifloxacin for 1 year. We have preferred to use the 4-drug combination as the initial therapy because of anti-TB resistance encountered in our region and the prevalence of drug resistance in isolates from culture-
positive TB patients in Taiwan, which has ranged from 30.5% to 33.0%.\textsuperscript{27,28} The treatment of cryptococcosis is straightforward with fluconazole as recommended by practice guidelines.\textsuperscript{10}

In summary, the presence of an SPN in an LT can-
didate warrants a thorough evaluation and appropri-
tate treatment once its etiology has been ascertained. Infectious diseases are common causes of SPNs. The adequate treatment of these infections can result in a cure even after transplantation. The presence of a nonmalignant SPN does not influence the overall outcome after LDLT.

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