The Utility of Surgical Lung Biopsy in Immunocompromised Children

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Objective To determine the utility of lung biopsy in immunocompromised pediatric patients with suspected infectious lung disease and to evaluate the risks and benefits of biopsy in the era of minimally invasive thoracic surgery.
Study design We reviewed charts for 50 immunocompromised patients who underwent surgical lung biopsy between January 2000 and July 2011 at a free-standing, tertiary care, urban children's hospital. The primary outcome variable was "benefit from biopsy," defined as change in therapy based on biopsy results. The secondary outcome variable was survival to discharge. The χ^2 analysis was used for categorical variables and Student *t* test for continuous variables.
Results Biopsy provided a definitive histopathologic or microbiologic diagnosis in 25 patients (50%), the most common diagnosis being fungal infection (22%). Diagnostic and nondiagnostic biopsy results yielded benefit in 25 surviving patients (50%) for whom the biopsy results were used to tailor treatment. Taking more than one biopsy specimen did not improve diagnostic yield. Six patients (12%) had a major morbidity including reinsertion of chest tube after initial chest tube removal (3), prolonged air leak (1), and a new requirement for mechanical ventilation postoperatively (2). Two patients died postoperatively, but the mortalities were not clearly related to surgery. Underlying diagnoses included hematologic malignancy (64%), primary immunodeficiency (12%), organ transplant recipient (12%), and solid malignancy (10%). Twelve patients (24%) had undergone stem cell transplantation.
Conclusion Lung biopsy in immunocompromised pediatric patients alters therapy in 50% of cases, but predictably carries identifiable morbidities. This study is limited by its retrospective nature. *(J Pediatr 2013;162:133-6)*.

Pulmonary infections are a leading cause of therapy-related morbidity and mortality in pediatric oncology patients.[1-3] The management of immunocompromised patients with persistent pulmonary infiltrates is often challenging. Diagnostic procedures should only be performed if results have the potential to change treatment. Bronchoalveolar lavage (BAL), although relatively noninvasive, fails to provide a diagnosis in up to two-thirds of patients.[4,5] Surgical lung biopsy has been recommended as a rapid and accurate method to obtain diagnosis in cases of nondiagnostic BALs or when BAL is deemed unlikely to yield results. Even though open lung biopsy has previously been shown to allow definitive diagnosis in 50%-80% of pediatric patients, complication rates range from 2%-52% depending on patient comorbidities.[4,6]

Over the past 20 years, surgical techniques for lung biopsy have advanced and the spectrum of pulmonary infectious disease in immunocompromised pediatric patients has changed. The incidence of *Pneumocystis carinii* pneumonia, for example—once a common diagnosis at lung biopsy—has decreased dramatically with the introduction of antimicrobial prophylaxis. In addition, video assisted thoracoscopic surgery (VATS) has largely replaced open lung biopsy as a preferred technique. Although VATS biopsy for diffuse interstitial lung disease has been studied, diagnostic VATS lung biopsy in immunocompromised children for infectious concerns has not previously been evaluated for diagnostic yield and outcomes.[7]

We hypothesized that complications from surgical lung biopsy have decreased in the VATS era in comparison with the era of open lung biopsy. Additionally, we hypothesized that the benefit derived from surgical lung biopsy may have diminished due to the decreased incidence of *Pneumocystis carinii* pneumonia.

Methods

We conducted a retrospective chart review of all patients undergoing surgical lung biopsy between January 2000 and July 2011 at a free-standing, tertiary care, urban children's hospital. This was conducted with Institutional Review Board approval (#2011-14468). Patients who underwent a diagnostic lung biopsy for a mass primarily concerning malignancy were excluded (n = 23). Immunocompetent patients who underwent a diagnostic surgical lung biopsy due to concern for infection were also excluded (n = 2). Fifty immunocompromised patients, comprised of children with either primary immunodeficiency syndromes or immunodeficiency due to immunosuppressive treatments, remained and were included in the study.

Patient variables included age, sex, preoperative diagnosis, symptoms, and imaging. Preoperative and postoperative treatments variables included antibiotics,

BAL	Bronchoalveolar lavage
PPP	Post-pull pneumothorax
VATS	Video assisted thoracoscopic surgery

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antiviral agents, antifungals, and steroids. Pathologic and microbiology culture results for lung biopsies were abstracted. Operative factors including approach (VATS vs open), operative time, duration of postoperative thoracostomy tube placement, and postoperative morbidities and mortalities were recorded.

Patients were determined to have benefited from surgical biopsy if (1) there was a change in therapy based on biopsy results; and (2) the patients survived their hospitalization. Patient factors and outcomes of interest were compared using χ^2 test for categorical data and Student t test for continuous data with significance determined by $P < .05$.

Results

We identified 50 immunocompromised patients who underwent a diagnostic lung biopsy in order to identify an infectious agent. Average patient age was 10.1 ± 5.8 years and 20 (40%) were female. The primary underlying diagnoses included hematologic malignancy (n = 32, 64%), primary immunodeficiency (n = 6, 12%), organ transplant recipient (n = 6, 12%), solid malignancy undergoing chemotherapy (n = 5, 10%), and chronic steroid use (n = 1, 2%). Twelve patients were stem cell transplant recipients (24%). Preoperative symptoms prompting radiographic imaging varied greatly, with the most common being fever in 29 (58%), cough in 21 (42%), tachypnea in 5 (10%), and chest pain in 5 (10%). Two patients (4%) were in respiratory failure preoperatively. Seven patients were asymptomatic and presumed to be undergoing routine radiographic screening. Preoperative chest computed tomography revealed nodular infiltrates in 40 patients (80%) and interstitial disease in 10 patients (20%). Prior to surgery, all patients underwent nasopharyngeal swabs for viruses and 9 patients (18%) underwent BAL; none of these examinations was diagnostic.

The decision to proceed with surgical lung biopsy was made on a case-by-case basis. The main indication for biopsy in all patients included in this study was suspicion for an infectious etiology of persistent pulmonary infiltrates with either a nondiagnostic BAL or the clinical judgment that BAL would have a low diagnostic yield. Noninfectious causes for the infiltrates may have been in the differential diagnosis, but the primary suspicion and drive for biopsy was undiagnosed infection. Biopsy sites were chosen by the surgeon and were generally based on the location of prominent imaging findings. A thoracostomy tube was left in place postoperatively in all patients.

Surgical lung biopsy provided a definitive histopathologic or microbiologic diagnosis in 25 patients (50%). Fungal infection was most commonly diagnosed with surgical lung biopsy (n = 11, 22%). Other diagnoses included bacterial pneumonia (n = 4, 8%), posttransplant lymphoproliferative disease (n = 3, 6%), tuberculosis (n = 1, 2%), viral pneumonia (n = 1, 2%), aspiration pneumonia (n = 1, 2%), radiation induced change (n = 1, 2%), graft vs host disease (n = 1, 2%), Hodgkin's relapse (n = 1, 2%), and xanthomatous disease (n = 1, 2%). Lung biopsy was nondiagnostic in 25 patients (50%). We sought to determine predictors for a diagnostic biopsy (Table I). Patients with a diagnostic biopsy were less likely to have a fever ($P = .022$). Taking more than 1 biopsy specimen did not predict a diagnostic biopsy ($P = .74$).

Diagnostic and nondiagnostic biopsy results yielded benefit in 25 surviving patients (50%) for whom the biopsy results were used to tailor treatment (Table II). Treatment changes included change in antimicrobial therapy (n = 19, 38%) and change in immunosuppression (n = 6, 12%). Among 25 patients in whom biopsies did not result in a change in therapy, 23 survived to discharge.

Surgical outcomes are detailed in Table III. The majority of patients underwent a VATS lung biopsy (n = 46, 92%). The choice for an open biopsy in 4 patients was attributable to surgeon preference. Postoperative major morbidity occurred in 6 patients (12%): pneumothorax requiring chest tube reinsertion (n = 3), prolonged air leak requiring 16 chest tube days (n = 1), and postoperative mechanical ventilation (n = 2). Overall, 24 patients (48%) had pneumothoraces after chest tube removal; 21 resolved without intervention. Two patients who were not intubated preoperatively but experienced preoperative respiratory distress were kept

Table I. Predictors of diagnostic lung biopsy in immunocompromised children

	Diagnostic biopsy (n = 25)	Nondiagnostic biopsy (n = 25)	P
Female	8 (32%)	12 (48%)	.39
Age (y; mean ± SD)	10.9 ± 6.1	9.1 ± 5.4	.27
Primary diagnosis			.32
Hematologic cancer	15 (60%)	17 (68%)	
Primary immunodeficiency	2 (8%)	4 (16%)	
Organ transplant recipient	5 (20%)	1 (4%)	
Solid cancer	2 (8%)	3 (12%)	
Chronic steroid use	1 (4%)	0	
Stem cell transplant recipient	8 (32%)	4 (16%)	.32
Preoperative CT findings			
Interstitial infiltrates	3 (12%)	7 (28%)	
Nodular infiltrates	22 (88%)	18 (72%)	.28
Preoperative symptoms			
Fever	10 (40%)	19 (76%)	.02
Cough	10 (40%)	11 (44%)	.77
Tachypnea	5 (20%)	0	.06
Chest pain	3 (12%)	2 (8%)	.64
Fatigue	1 (4%)	1 (4%)	.47
Weight loss	1 (4%)	0	.31
Night sweats	1 (4%)	0	.31
Septic shock	0 (4%)	1 (4%)	.31
Asymptomatic	5 (4%)	2 (8%)	.42
Operative technique			.18
Open	4 (16%)	0	
VATS	21 (84%)	25 (100%)	
Number of biopsies taken			.74
1	18 (72%)	20 (80.0%)	
≥2	7 (28%)	5 (20.0%)	
Preoperative absolute neutrophil count ($10^3/\mu L$; mean ± SD)	3.5 ± 3.7	4.3 ± 4.0	.46
Preoperative treatment			
Antibiotics preoperatively	16 (64%)	15 (60%)	.77
Antifungals preoperatively	14 (56%)	17 (68%)	.56

CT, computed tomography.