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Open-lung biopsy in patients with undiagnosed lung lesions referred at a tertiary cancer center is safe and reveals noncancerous, noninfectious entities as the most common diagnoses

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Abstract

We evaluated the diagnostic yield of open-lung biopsies (OLBs) in a large tertiary cancer center to determine the role of infectious diseases as causes of undiagnosed pulmonary lesions. All consecutive adult patients with either single or multiple pulmonary nodules or masses who underwent a diagnostic OLB over a period of 10 years (1998–2007) were retrospectively identified. Their risk factors for malignancy and clinical and radiological characteristics were reviewed, and their postoperative complications were assessed. We evaluated 155 patients with a median age of 57 years (range, 19–83 years). We identified infectious etiologies in 29 patients (19 %). The most common diagnosis in this group was histoplasmosis (12 [41 %]), followed by nontuberculous mycobacterial infection (7 [24 %]) and aspergillosis (4 [14 %]). The majority of

the 126 remaining patients had nonmalignant diagnoses, the most prevalent being nonspecific granuloma (26 %), whereas only 17 % had malignant diagnoses. We observed no significant differences among the patients with infectious, malignant, or both noninfectious and nonmalignant final diagnoses regarding their demographic, laboratory, and clinical characteristics. Six percent of the patients had at least one post-OLB complication, and the post-OLB mortality rate was 1 %. OLB is a safe diagnostic procedure which frequently identifies a wide variety of infectious and inflammatory diseases.

Introduction

Lung lesions, especially nodules and masses, are diagnostic dilemmas because of the diversity of their diagnoses and considerable differences in management and outcome [1]. Invasive procedures are required to establish a definitive diagnosis in the majority of cases. Percutaneous fine-needle aspiration (FNA) biopsy is usually recommended for peripheral lesions, whereas bronchoscopy with bronchoalveolar lavage (BAL) with or without transbronchial biopsy is usually performed for endobronchial or central lesions [1]. However, these procedures often fail to lead to a definitive diagnosis [2, 3]. Consequently, open-lung biopsy (OLB) is frequently used to establish the diagnosis for lung lesions [4–10].

Therefore, the aims of this study were to evaluate the diagnostic yield of OLBs in a large tertiary cancer center and determine the role of infectious diseases as causes of undiagnosed pulmonary lesions in a contemporary cohort of unselected patients with a high risk of malignancy according to their clinical and radiographic characteristics.

Patients and methods

All adult patients with either single or multiple pulmonary nodules or masses who underwent diagnostic OLBs at The University of Texas MD Anderson Cancer Center from January 1, 1998, to December 31, 2007, were retrospectively reviewed. Cases in which OLB was performed for therapeutic purposes for previously diagnosed lung lesions were excluded. Patients' electronic records were reviewed for demographic characteristics, history of malignant or autoimmune diseases in the 5-year period prior to OLB, presence of respiratory symptoms, radiological characteristics of the pulmonary lesions, postoperative complications, and mortality rate at 12 weeks after OLB. Final diagnosis of their lung lesions was based on histological evaluation and/or lung tissue culture.

A solitary pulmonary nodule was defined as a single, spherical, well-circumscribed radiographic opacity measuring less than 3 cm in diameter and completely surrounded by aerated lung without associated atelectasis, hilar enlargement, or pleural effusions [11, 12]. A lung mass was defined as a focal lesion that was more than 3 cm in diameter [11, 12]. Significant tobacco use was defined as a smoking history of more than 20 pack-years. Neutropenia and monocytopenia were defined as a neutrophil count less than $500/\text{mm}^3$ and monocyte count less than $100/\text{mm}^3$, respectively, during the 6 months prior to surgical resection. High-dose treatment with corticosteroids was defined as the administration of at least 600 mg of a prednisone equivalent in the 3 months prior to surgical resection. The study protocol was approved by the MD Anderson Institutional Review Board.

In our statistical analysis, categorical variables were compared using the chi-square test, and continuous variables were compared using the Student *t*-test. All comparisons were unpaired, and tests for significance were two-tailed. *P*-values less than 0.05 were considered to be indicative of statistical significance.

Results

We identified 195 patients who underwent OLB during the study period. We excluded 40 patients because they underwent OLB and resection for therapeutic purposes. In the remaining 155 patients who underwent diagnostic OLB, 80 were male (52 %) and the mean age $\pm$ standard deviation was 57 ± 13 years (range, 19–83 years). Ninety-nine (64 %) of them were Texas residents. Eighty-four (54 %) and 6 (4 %) patients had a prior history of malignant or autoimmune diseases, respectively, whereas only 47 patients (30 %) reported prior respiratory symptoms, such as cough, dyspnea, and wheezing. Eight-six patients (55 %) reported significant tobacco use. Ninety-four patients (61 %) had solitary lung lesions, and 79 patients (51 %) previously underwent nondiagnostic BAL or FNA. Moreover, 26 patients (17 %) underwent fluorodeoxyglucose (FDG)-positron emission tomography (PET), and 69 % of them had hypermetabolic activity. Only 11 patients (7 %) were evaluated by an infectious diseases consultant prior to OLB.

Infectious etiology was recognized in 29 patients (19 %) (Table 1). The most common diagnosis was histoplasmosis (12 patients [41 %]), followed by nontuberculous mycobacterial infection (7 patients [24 %]) and aspergillosis (4 patients [14 %]) (Table 2). Of note, in 20 patients (69 %) with infectious etiologies, physicians established the diagnosis using histological evaluation, in four patients (14 %) using positive tissue culture of OLB material, and in five patients (17 %) with both diagnostic methods.

The remaining 126 patients (81 %) had noninfectious etiologies. Specifically, we identified malignancies in 27 patients (17 %). Of these, 16 patients (59 %) had primary lung cancers (14 nonsmall-cell and 2 small-cell lung cancers), 6 patients (22 %) had metastatic solid tumors, 4 patients (15 %) had hematological malignancies, and 1 patient (4 %) had malignant disease of unknown origin. Nevertheless, the majority (99 [64 %]) of our patient population with noninfectious etiologies had nonmalignant diagnoses, the most prevalent being nonspecific granuloma (41 [26 %]) (30 patients had necrotizing granuloma, including 5 patients with caseating necrosis), fibrosis (25 [16 %]), and hamartomas (14 [9 %]) (Table 1).

More patients with a final diagnosis of malignant disease underwent FDG-PET ($p = 0.001$) and nondiagnostic FNA ($p = 0.010$) prior to OLB than patients with infectious and noninfectious, nonmalignant disease. Nine patients (6 %) had post-OLB complications; two of them died within 60 days after OLB, although only one death (1 %) was attributed to the OLB procedure. We observed no significant differences in demographic, laboratory, or clinical characteristics between patients with infectious and noninfectious diagnoses (Table 1). Nevertheless, patients who had final diagnoses of malignancies were more frequently tobacco users ($p = 0.031$). Of note, 14 of 16 patients (88 %) with primary lung cancer were tobacco users. In addition, masses were more common in patients with underlying infections and malignancies than in patients with noninfectious, nonmalignant diagnoses ($p = 0.000$).

Discussion

OLB is a valuable diagnostic tool that provides accurate diagnosis of lung lesions of uncertain etiology, especially in patients with a high risk of underlying malignancy [13]. The probability of a lung lesion, particularly a solitary pulmonary nodule, being malignant increases with the patient's age, history of past or current smoking, history of previously diagnosed malignancy, and several radiographic characteristics of the lesion, such as size and border spiculation [14]. Interestingly, our patient population had multiple risk factors for malignancy and no overt manifestations of infection. This may explain the low rate of infectious disease consultations prior to OLB (7 %), as 69 % of the patients were more than

50 years old, 68 % had lung lesion diameters greater than 1 cm, 54 % had a prior history of malignant disease, and 55 % reported significant tobacco use. Notably, because MD Anderson is a tertiary care cancer center, patients are frequently referred there to rule out the presence of neoplastic disease. Nevertheless, in the present study, we found that the majority (83 %) of our patient population had benign underlying disease. Of these, 19 % had treatable infectious etiologies. Of note, the differences in the reported numbers of underlying diseases and prevalences of infections (1–68 %) and malignant diseases (20–93 %) in patients submitted to OLB [4–10] in several institutions are considerable, which probably reflects referral biases for patients seeking care in these centers. The other factors that may account for these differences are dissimilarity in the size or and/or numbers of pulmonary opacities in each study, the experience of the physicians performing the biopsy procedures, and the initial interventional diagnostic procedure used (OLB versus video-assisted thoracoscopic surgery or FNA).

In agreement with the results of previous studies, we found that occult fungal infections (72 %), particularly endemic fungal infections (52 %; especially histoplasmosis), were the most common causes of infectious lung lesions, followed by mycobacterial infections (28 %; tuberculous and nontuberculous) [5, 7–9]. Geographically restricted endemic mycoses can be imitators of lung cancer [15]. Also, the epidemiologic data suggest that nontuberculous mycobacterial lung infections are occurring with increasing frequency in the United States and, likely, other parts of the world [16]. Likewise, nontuberculous mycobacterial infections can present as solitary or multiple lung nodules and be misdiagnosed radiographically as lung cancer or tuberculomas [17]. Not surprisingly, none of the patients in our study was identified as having conventional bacterial infections, which corroborates the existing reported evidence that routine antibiotic treatment rarely results in the improvement of pulmonary nodules [18]. Of note, researchers have occasionally identified a variety of other infectious causes of solitary and multiple pulmonary nodules in immunocompetent and immunocompromised hosts after OLB, such as *Dirofilaria immitis* [7, 19, 20], *Pneumocystis jirovecii* [21], Varicella zoster virus [22], *Cytomegalovirus* [23], *Nocardia asteroides* [23], *Echinococcus granulosus* [23], *Bartonella henselae* [24], *Paragonimus westermani* [25], and *Achromobacter xylosoxidans* [26].

The contribution of infections to final diagnoses in our series was probably underestimated, as the majority of the patients (41 [26 %]) had a histopathological diagnosis of granulomatous inflammation. The majority of cases of granulomatous lung diseases worldwide are caused by either sarcoidosis or infections resulting from low burdens of fastidious organisms, such as fungi and mycobacteria [27].

Undoubtedly, the principal goal during the evaluation of patients with pulmonary nodules or masses was to diagnose their etiologies using the safest, least invasive, least costly tests [28]. Not surprisingly, our patients who had final diagnoses of malignant diseases more often had a history of tobacco use ($p = 0.031$), which is the primary risk factor for lung cancer [29], than the patients with infectious and noninfectious, nonmalignant diseases. In addition, patients with final diagnoses of malignant diseases more often underwent FDG-PET ($p = 0.001$) and nondiagnostic FNA ($p = 0.010$) prior to OLB, which reflects both clinicians' increased suspicion of cancer in these cases and diagnostic difficulty. However, in accordance with the results obtained by previous investigators [4], we observed no other significant differences between patients with and without final diagnoses of infections regarding their demographic, laboratory, and clinical characteristics that could have guided clinicians in their diagnostic evaluations of lung lesion etiology before OLB. Although computed tomography-guided percutaneous biopsy can establish accurate diagnoses of malignancies in a large majority of patients, it is less sensitive for diagnosing infections and inflammatory conditions [2]. Therefore, in cases in which pulmonary lesion etiology cannot

be diagnosed otherwise, thoracotomy remains the most accurate and a relatively safe diagnostic procedure [5, 6].

Undoubtedly, our study had several limitations, as we retrospectively collected the data, and the cases spanned a decade. Moreover, the study population might not be representative of the average patient with undiagnosed lung lesions, as MD Anderson is a tertiary care cancer center and patients with pulmonary lesions referred to our center were most likely at high risk for malignancy, although the assessment of smoking history was rather difficult in this retrospective study. In addition, our results regarding infectious diseases reflect the local epidemiology and cannot be generalized. For example, parts of Texas are areas of high endemicity for geographically restricted dimorphic mycoses [30]. Another limitation was the selection bias regarding the evaluation of post-OLB complications, as high-risk patients are not usually submitted to OLBs. Finally, the abundance of non-specific granulomas found in our retrospective study makes the underdiagnosis of low-burden atypical infections likely [31]. Specifically, we did not collect information about prior anti-infective regimens nor the adequacy of microbiological methods for the cultivation of fastidious organisms. Furthermore, histopathologic specimens were not subjected to molecular diagnostic methods [e.g., polymerase chain reaction (PCR) or in situ hybridization]. Nevertheless, our data verify that OLB is an accurate and safe diagnostic procedure that should be implemented even for patients with indeterminate pulmonary lesions at high risk for malignancy, as it frequently identifies a wide variety of infectious and inflammatory diseases.

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Table 1

Patients' demographic, clinical, and radiological characteristics according to lung lesion etiology

Characteristic	Infectious (<i>n</i> = 29)	Malignant (<i>n</i> = 27)	Other ^a (<i>n</i> = 99)	<i>p</i> -value
Sex				0.099
Male	11 (38)	18 (67)	51 (51)	
Race				0.434
White	26 (90)	23 (85)	79 (80)	
Mean age (standard deviation), years	54 (11)	60 (14)	57 (13)	0.079
Tobacco use	10 (34)	18 (67)	58 (59)	0.031
Respiratory symptoms ^{b,c}	9 (31)	7 (26)	32 (32)	0.816
History of cancer ^d	14 (48)	16 (59)	54 (54)	0.707
Solid tumor	11 (38)	12 (44)	43 (43)	
Hematological cancer	3 (10)	4 (15)	11 (11)	
History of autoimmune disease ^{d,e}	0	1 (4)	4 (4)	0.550
Neutropenia (<500/mm ³) ^c	3 (10)	3 (11)	3 (3)	0.144
Monocytopenia (<100/mm ³) ^c	2 (7)	3 (11)	5 (5)	0.521
Prior corticosteroid use (>600 mg) ^{f,g}	1 (3)	2 (7)	3 (3)	0.574
Prior nondiagnostic FNA ^f	5 (17)	14 (52)	46 (46)	0.010
Prior nondiagnostic BAL ^f	4 (14)	6 (22)	23 (23)	0.546
Number of lesions ^h				
Single lesion	17 (59)	13 (48)	64 (65)	0.289
Multiple lesions	12 (41)	14 (52)	35 (35)	
Diameter of lesions ^h				0.000
<1 cm	4 (14)	9 (33)	36 (36)	
1–3 cm	16 (55)	8 (30)	56 (57)	
>3 cm	9 (31)	10 (37)	7 (7)	
Lesion edge spiculation	4 (14)	4 (15)	10 (10)	0.732
Prior FDG-PET	4 (14)	11 (41)	11 (11)	0.001
Increased FDG uptake	3 (75)	9 (82)	6 (55)	0.369
Postoperative complications ⁱ	1 (3)	3 (11)	5 (5)	0.409
Infectious diseases consult ^f	2 (7)	3 (11)	6 (6)	0.663
Death within 3 months after OLB	1 (3)	2 (7)	4 (4)	0.722

^aNoninfectious and nonmalignant^bCough, dyspnea, and wheezing^cIn the 6 months prior to OLB^dIn the 5 years prior to OLB^eRheumatoid arthritis (*n* = 3), sarcoidosis (*n* = 1), and systemic erythematous lupus (*n* = 1)^fIn the 3 months prior to OLB

^gPrednisone equivalent

^hSpecified by computed tomography

ⁱProlonged pleural air leak ($n = 3$), empyema ($n = 2$), hematoma ($n = 2$), cardiac arrest on day 7 after OLB ($n = 1$), failure to wean off ventilation and death on day 45 after OLB ($n = 1$)

Table 2

Isolated pathogens in the 29 patients with infectious pulmonary lesions

Pathogen	n (%)
<i>Histoplasma capsulatum</i>	12 (41)
Nontuberculous <i>Mycobacterium</i> species ^a	7 (24)
<i>Aspergillus</i> species	4 (14)
<i>Coccidioides</i> species	3 (10)
<i>Cryptococcus</i> species	2 (7)
<i>Mycobacterium tuberculosis</i>	1 (3)

^a *Mycobacterium avium* (n = 4), *Mycobacterium gordonae* (n = 1), and unspecified acid-fast stain-positive bacilli (n = 2).