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Diagnosis of Small Lung Biopsy

An Integrated Approach

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To my wife, Lamia, and our two lovely sons, Yousef and Karim, who provided love and care that were the inspiration for this endeavor, for them I am eternally indebted.

Preface

No doubt, there are several excellent pulmonary pathology textbooks with comprehensive and encyclopedic coverage of the topic in the market. However, we sensed a void when it comes to more pressing issue; when it comes to small biopsies, what the general pathologist deal with in their daily practice is more nuanced and different from what we can appreciate on a large resection specimen. In the current era, when we as pathologists are asked to do more with less, it becomes imperative that we adjust our perspective and sharpen our tools.

Most cases of lung lesions are biopsied with tiny biopsies from fine needle aspiration, needle cores, transbronchial biopsy, and more recently cryobiopsies. In all these instances, the tissue is scant and the artifacts abound. Yet the information expected to be gleaned from such biopsy is remarkable considering the size and the hindrances. There is a void in the library for a book to provide a concise and synoptic approach to the interpretation of this type of biopsies. This book is an attempt to provide this type of approach. It is to be as beside the microscope quick reference for the general pathologist and pathologist in training to get a quick understanding of basic pulmonary pathology.

The authors are attempting to provide practical tips and tried methods for the interpretation of these biopsies based on interaction with radiologists and pulmonologists, medical oncologists, and other multidisciplinary team members over the years. The reduction in the amount of tissue has to be compensated for by the provision of more clinical and imaging information to complete the picture. It is a difficult task in the busy shuffle of daily practice to expect such information on regular basis. However, current billing practice is requiring this information to be included on the requisition form. The introduction and promotion of Electronic Health Records (HER) is providing an easy access to such information to the average pathologist even in small community setting and have take to advantage of that.

Lung biopsies are expensive and difficult to obtain and every effort should be made to maximize the benefit and information gained from them. This includes talking to the physician taking care of the patient and discussing the history and clinical suspicion.

The integrated approach is nothing new and every book tries to cover the clinical and radiologic findings in the discussion of a given disease in the lung.

In this book, we try to reiterate and emphasize the importance of those findings in the proper interpretation of those small biopsies. Descriptive diagnoses can be useless and even downright harmful when they are rendered in isolation and without an understanding of the clinical context.

We hope this book can serve its intended purpose and be a modest contribution to the enrichment of pulmonary pathology practice.

Louisville, KY, USA Mostafa M. Fraig, M.D.

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Rafael L. Perez

Introduction

Nonsurgical approaches to sample focal or diffuse, solid, or infiltrative pathology of the lung offer the advantages of lower risk, comfort, and cost compared to surgical biopsy techniques. However, sample size obtained by nonsurgical techniques can challenge pathological assessment. Sampling error and artifacts of manipulation, in addition to small size, are problematic. These problems may be overcome to some extent by providing multiple intact samples that are well directed by various imaging techniques. Ultimately, a collaborative approach between the clinician, pathologist, and radiologist will optimize diagnosis.

This chapter will focus on the nonsurgical techniques used to obtain small samples of pulmonary tissue characterized by location of the pathological tissue in the airways and lung parenchyma. How the pathological diagnosis informs the clinician's assessment and approach to the case in question will demonstrate the importance of an accurate diagnosis. Most small tissue samples obtained by nonsurgical approaches are in the sub-centimeter size range, but can reach 1 cm depending on the technique used. Therefore, we define small lung biopsy samples as tissue obtained by nonsurgical techniques that are 1 cm or less in the longest axis.

Small lung biopsy samples are obtained by various techniques. Flexible fiberoptic bronchoscopy (FOB) with endobronchial and transbronchial biopsy with forceps is a standard procedure performed by all pulmonologists, while endobronchial biopsy via rigid scope, cryobiopsy, and navigational bronchoscopy biopsy require additional training and experience. Transthoracic core biopsy is a radiological procedure. All of these procedures have in common that they can be performed outside the operating room.

Small Sample Lung Biopsy Techniques by Fiberoptic Bronchoscopy

In 1966, Dr. Shigeto Ikeda introduced the technique of flexible fiberoptics to access and visually inspect the lungs [1]. The advantages of flexible FOB as a nonsurgical procedure quickly brought it into widespread use. It could be performed in much less complicated settings than the operating room, and moderate sedation with topical anesthesia could be used in most cases. Elective FOB is a routine outpatient procedure where various applications to sample bronchial and parenchymal tissues in stable non-acute individuals can be obtained. FOB is easily transportable to the operating room and to the acute care setting where it

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has an important diagnostic and therapeutic role in the intensive care units.

The bronchoscope has been refined over time for a variety of applications [2–4]. Bronchoscopes have working channels of 1.4–2.8 mm in diameter, the larger ones to allow the use of an array of interventional instruments. Preparation and performance for FOB regardless of the type of procedure requires the same key considerations. Foremost is patient safety. Many who come to bronchoscopy already have underlying lung disease that affects ventilation and oxygenation. Benzodiazepines and opioids generally used for sedation and comfort may degrade both critically. A clinical professional, usually a trained nurse, monitors ventilation, oximetry, blood pressure, and other vital signs continuously during the procedure. Reversal agents are on hand, and the equipment and drugs are within reach to administer cardiopulmonary resuscitation, if necessary. A current history and physical is required before the procedure with emphasis on allergies, concomitant medications, and coagulation status. The history and physical speaks not only to patient safety but also to the reason why the individual is having the procedure and the anticipated samples to be obtained. It is imperative that the appropriate media and fixatives are available and ready to receive the samples.

Most diagnostic tissue sampling is done with the standard instrument that typically returns tissue samples measuring only a few millimeters. Therefore, a high degree of specificity is paramount to obtain an accurate diagnosis. The operating characteristics of the FOB also vary depending on the location of the abnormal tissue to be sampled. The diagnostic accuracy of a directly visualized endobronchial lesion is better than a lesion located in the lung parenchyma. Parenchymal lesions may be sampled under fluoroscopic guidance, but the more distal and smaller the lesion, the greater the chance of sampling error. The accuracy of obtaining a diagnostic sample from deep in the lung parenchyma has increased greatly in the past few years using navigational bronchoscopy as described in a subsequent section.

Endobronchial Diseases Diagnosed by Small Sample Lung Biopsies

Sampling of the airways affords the lowest risk to benefit ratio involved in FOB. The abnormalities are usually visible, so the diagnostic accuracy is good. Complications, mostly bleeding, can be directly controlled with topical vasoconstrictors or tamponade. Forceps sometimes accompanied by bronchial brushings and washings are used to take multiple biopsy samples of the lesion. There are no specific guidelines for the number of endobronchial biopsies that needs to be taken to maximize diagnostic yield. Four to five samples are common, but the aware bronchoscopist may obtain greater numbers since the samples are small, and sufficient tissue for special stains or biomarkers may be required. Table 1.1 lists the spectrum of diseases diagnosed by sampling of the airways.

Endobronchial Tumors

Endobronchial biopsies in adult patients are mostly done for the diagnosis of bronchogenic malignancies. Patients with bronchogenic malignancies come to biopsy with symptoms that are generally not specific, overlap with other airway diseases, and involve other organ systems as the disease progresses [5]. Wheezing, cough, and dyspnea are the most common symptoms in tumors of the airways and are shared with diseases that cause

Table 1.1 Endobronchial diseases diagnosed by small sample lung biopsies

Endobronchial tumors
• Malignant
• Carcinoid tumors
• Hamartomas
Infectious and other endobronchial diseases
• Mycoplasma and viral
• Endobronchial tuberculosis
• Allergic bronchopulmonary aspergillosis
• Bronchocentric granulomatosis
• Sarcoidosis

airflow obstruction, most notably chronic obstructive pulmonary disease and asthma. The classic paraneoplastic symptoms associated with some bronchogenic cancers that lend some diagnostic specificity are not common. Hypertrophic osteoarthropathy, a periosteal inflammatory condition of the long bones, and hypercalcemia can be found in squamous cell cancer of the lung. The Lambert–Eaton myasthenic syndrome with weakness and visual disturbance is seen in small cell lung cancer. Bronchorrhea is occasionally associated with adenocarcinoma in situ. Hemoptysis is occasionally the presenting symptom for bronchogenic cancer and portends more extensive involvement of the airway and poorer outcome [6]. Pneumonia, especially if it is recurrent in the same location, may indicate an obstructing lesion of the airway. Bronchoscopy may be a challenge in such cases because of the inflammation with swelling and purulence that make it difficult to biopsy the lesion. The clinician may elect to postpone the procedure until the pneumonia is treated and well into resolution.

Like their malignant counterparts, benign endobronchial tumors present with similar symptoms of airway obstruction with wheezing, cough, dyspnea, and sometimes with hemoptysis or post-obstructive pneumonia. Carcinoid tumors are derived from neuroendocrine tissues of the gastrointestinal (GI) and respiratory tracts. They are predominantly found in the GI tract, but up to 20 % occur in the airways [7, 8]. Compared to tumors in the GI tract, pulmonary carcinoids are less likely to produce the carcinoid syndromes of flushing, diarrhea, and heart failure. They can be found from the most proximal to the most distal conducting airways where neuroendocrine rests are found. On bronchoscopy, they have a very smooth, shiny, and sometimes very vascular surface in contrast to malignant tumors that have irregular lobulated borders with varying degrees of necrosis.

Hamartomas are the most common benign lung tumors, but only 10 % of those occur in the bronchi [9]. They usually come to attention in patients who present with post-obstructive symptoms or by chance in an abnormal chest film. On bronchoscopic inspection, they have no distinguishing features that separate them from malignant lesions. The histological diagnosis leads to a second therapeutic bronchoscopy with the removal of the tumor that is curative in most cases.

Infectious and Other Endobronchial Abnormalities

Diseases of the airways extend well beyond the malignant and benign tissue transformations described above. These diseases include infectious and noninfectious disorders that present with a broad constellation of symptoms that may extend beyond the respiratory system. The history and presentation of the individual is more complex with questions about immune status and lung function abnormalities at the forefront. Fever and metabolic abnormalities also become more prominent. The path to bronchoscopy usually takes longer and only after clinical, laboratory, and radiological evaluation has not yielded an answer.

Fever and weight loss will put infection at the top of the disease differential, so tissue sampling for both histological examination and culture and staining is prepared. On inspection, infections of the airways can take any form such as single or multiple nodules, ulcerated epithelium, discolored patches, or even only mild erythema and edema. Bronchial washings and brushings typically accompany tissue biopsies in these cases. Multiple samples for culture are taken first to avoid any possibility of contamination of the bronchoscope channel or forceps with fixative. While a positive culture of a non-commensal or opportunistic organism is sufficient to initiate specific therapy, demonstration of tissue invasion may be necessary in some circumstances.

Diffuse infections of the airways can cause them to become hyperresponsive and produce symptoms that are indistinguishable from asthma. Though asthma is very prevalent worldwide, individual cases sometimes present out of context with respect to risk factors, a history of atopy, exacerbating exposures, or response to therapy. The clinician may therefore elect to perform inspection and biopsy of the airways. *Mycoplasma pneumoniae* has been associated with and even

implicated as the cause of asthma in some case series, the latter conclusion on the basis that the asthma was controlled after treating the infection [10]. Rhinovirus, respiratory syncytial virus, and influenza viruses have a strong relationship with asthma exacerbations and may be relevant in chronic uncontrolled asthma that may lead one to obtain bronchial tissues for examination [11]. The key point on reviewing bronchial biopsies of subjects with reactive airways is that, in addition to the anticipated inflammatory changes, awareness and detection of concurrent infection will aid the clinician with treatment.

Endobronchial tuberculosis is an uncommon manifestation of infection with *Mycobacterium tuberculosis* (MTB) [12, 13]. Cough, wheezing, fever, and dyspnea are nonspecific symptoms, and it is not usually detectable on plain chest radiography. Moreover, sputum cultures for MTB may be negative. On bronchoscopy, the lesions have no distinguishing features that would make the operator suspect MTB. The lesions may appear as endobronchial masses or ulcerations. They may obstruct airways or cause tracheal or bronchial stenosis. Expedient identification and medical treatment of endobronchial MTB are therefore essential to prevent fixed stenosis and need for surgical reconstruction.

Allergic bronchopulmonary aspergillosis (ABPA) and bronchocentric granulomatosis (BCG) are entities that overlap with asthma in their clinical presentation [14, 15]. ABPA is mostly associated with *Aspergillus fumigatus*, but other fungi less commonly produce a similar syndrome. In addition to the symptoms and examination findings of asthma, the presence of mucus plugging or infiltrates may lead to bronchoscopic examination and biopsy of the involved airways. The hallmark demonstration of fungal hyphae in bronchial tissue, along with supportive findings of elevated IgE and cutaneous reactivity or precipitins to *A. fumigatus*, significantly impacts therapy. In ABPA, systemic steroids are required in addition to bronchodilator therapy. In recalcitrant cases, treatment with antifungals may be necessary.

BCG was first described in 1972 by Liebow as a focal bronchial and bronchiolar destructive granulomatous lesion [16, 17]. About one third of individuals with BCG have asthma, and three fourths of them will have *A. fumigatus* hyphae detected in their bronchial biopsies. Of the two thirds who do not have asthma, hyphae are present in only about one third. Radiographically, BCG may appear as a lung mass that will prompt the bronchoscopic examination. Steroid treatment is very effective, but the disease may recur so individuals must be monitored regularly.

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology with a variety of clinical presentations depending on the organ involved [18]. Respiratory symptoms are nonspecific and include chest tightness, cough, and dyspnea on exertion. A high proportion of patients with pulmonary sarcoidosis will have some evidence of airflow obstruction suggesting endobronchial involvement with this disease [19]. On bronchoscopy, the bronchial mucosa may appear normal to erythematous with "cobblestoning" that indicates a heavy granuloma burden in the airways. The yield of random biopsies of the bronchial mucosa depends on the degree of involvement and in practice is a supplement to transbronchial biopsies and transbronchial needle aspiration of enlarged hilar, paratracheal, or other mediastinal nodes.

Parenchymal Diseases Diagnosed by Small Sample Lung Biopsies

New technologies have extended the reach and accuracy of small sample biopsies of solid and infiltrative diseases in the lung parenchyma. Table 1.2 lists parenchymal diseases categorized by radiological appearance. This categorization is useful for differential diagnosis and the selection of the biopsy technique and approach to diagnosis. Unlike endobronchial diseases, imaging using fluoroscopy and ultrasound assists in the localization and biopsy of lesions in the lung parenchyma. New tools for performing navigational bronchoscopy, linear and radial endobronchial ultrasonography, and cryobiopsy have extended the reach and accuracy of bronchoscopic biopsy of even the deepest pulmonary abnormalities.

Table 1.2 Parenchymal diseases diagnosed by small sample lung biopsies

Focal solid parenchymal lesions
• Lung masses
• Metastatic disease
• Solitary pulmonary nodules
Focal and diffuse infiltrative diseases
• Granulomatous diseases
– Sarcoidosis
– Hypersensitivity pneumonitis
• Non-granulomatous diseases
– Idiopathic pulmonary fibrosis
– Nonspecific interstitial pneumonitis
– Smoking-related interstitial lung diseases
– Organizing pneumonia

Focal Solid Parenchymal Lesions

Standard flexible fiberoptic biopsy guided by fluoroscopy is the mainstay procedure for locating and sampling solid parenchymal lesions. Fluoroscopy is also used for safety purposes mainly to mitigate and assess for pneumothorax. Lung masses that are larger and centrally located are usually approached in this way. Lesions that are smaller and located peripherally are more accurately biopsied using navigational or ultrasound-guided bronchoscopy as described below [20, 21].

Lung masses by definition are discrete lesions greater than 3 cm in diameter by radiography [22]. A single mass in an adult is considered to be malignant until proven otherwise. Age, smoking history, and presence of chronic obstructive pulmonary disease all increase the pretest probability of primary lung cancer [23]. Therefore, it is imperative that the bronchoscopic sample demonstrates malignancy to avoid a more invasive biopsy approach. Radio- or chemotherapy is very rarely undertaken without a true-positive histological evidence of malignancy. The bronchoscopist maximizes diagnostic yield using fluoroscopy to locate the mass and take multiple transbronchial biopsies using a forceps "punched" into the lung parenchyma. Angling the tip of the bronchoscope slightly with each pass is done to sample different regions of the mass. Finally, ample tissue must be recovered for possible biomarker probing that may influence therapy.

Nonmalignant lung masses can sometimes be seen in chronic inflammatory and granulomatous diseases produced by infection, as pulmonary involvement in autoimmune diseases, or through environmental exposures. Though mostly presenting as lung nodules, fungal infections may sometimes present radiographically as lung masses [24]. Histoplasmosis or blastomycosis may present as a mass-like consolidations in immunocompetent patients, while cryptococcosis is found mainly in immunosuppressed individuals. Similar to malignant masses, the diagnostic approach is by transbronchial biopsy supplemented by bronchial washings with saline for culture.

Mass-like lung densities may also be seen in autoimmune diseases like sarcoidosis, rheumatoid arthritis, and granulomatosis with polyangiitis. When lung masses are detected in the context of an autoimmune disease, the individual is often on immunosuppressive therapy. Opportunistic infection must be considered, and appropriate preparation to receive samples for *Pneumocystis jirovecii*, other fungi, and acid-fast organisms should be done. Often, bronchoalveolar lavage (BAL) supplements biopsy by accessing deep respiratory surfaces not obtained by simple washings. BAL involves wedging the bronchoscope into a fourth- to sixth-generation bronchus to produce a tight seal. Then, sterile saline is instilled in 30–50 mL. Aliquots are recovered by gentle suction. An acceptable BAL sample will demonstrate a "foamy" meniscus in the suction receptacle indicating recovery of pulmonary surfactant from alveolar surfaces and return few to no ciliated epithelial cells indicating little contamination from the conducting airways.

Occupational exposures to silica, coal dust, beryllium, and kaolin will produce one or more discrete lesions that must be differentiated from malignancy. The occupational history must be provided to the reviewing pathologist to prepare the appropriate microscopic assessment for the presence of particulates. Beryllium is indistinguishable from sarcoidosis histologically, but the lack of certain extrapulmonary manifestations found in

sarcoidosis and the exposure history will increase the confidence that the noncaseating granulomas are the result of beryllium exposure [25].

Metastatic malignancies to the lungs may present as solitary or multiple lesions of varying size. Colorectal cancers occasionally present as solitary nodules. Identifying these lesions as originating from these organs is key since resection may improve survival [26]. In the setting of known cancer, patients with solitary metastases may go directly to surgery after risk assessment. However, if diagnosis is elected, then navigational bronchoscopy, described in more detail below, can accurately sample even peripheral metastases 1 cm in diameter or more.

Lymphangitic metastases are typically addressed with standard transbronchial biopsy with fluoroscopic guidance. Five to six passes in one selected lung lobe are done and yield an almost 70 % chance of diagnosis [27]. Although the risk of pneumothorax is low, the bronchoscopist never performs transbronchial biopsy in both lungs in the same procedure.

The approach to the diagnosis of solitary or multiple pulmonary nodules begins with a thorough interview of the patient emphasizing respiratory exposures and risk assessment. Then, the decision to observe over time, perform biopsy, or go directly to resection can be made. The advent of low-dose computerized tomography (LDCT) and comfort of practitioners to order this test have produced an upsurge of studies demonstrating pulmonary nodules. Indeed, in the National Lung Screening Trial in the United States in which over 53,000 individuals at risk for lung cancer underwent LDCT, a reduction in lung cancer mortality and discovery of earlier stage disease were demonstrated [28]. Still, the vast majority of nodules assessed were benign through observation over time or by diagnostic sampling or by resection. Biopsy and resection incur both cost and risks including mortality. The challenge is the decision to wait and watch biopsy or resect.

Solitary pulmonary nodules are by definition single nodular lesions of 3-cm diameter or less surrounded by normal lung tissue [22]. Location and size, along with risk factors for malignant potential, determine to a large degree how the nodule is to be approached. Sub-centimeter nodules may be observed by serial radiology and applying various algorithms based on risk, smoking history, and lung function [29]. Nodules that are one or more centimeters in diameter may be resected or sampled for diagnosis. Risk factors for malignancy, surgical risks, and patient desires determine the approach.

The advent of electromagnetic guidance has improved the diagnostic reach and accuracy of bronchoscopy in the assessment of pulmonary nodules by a technique called navigational bronchoscopy. Navigational bronchoscopy is a complicated procedure that matches the location of a subject's lesion on computerized tomography to the anatomy of the subject who is enveloped in a magnetic field during the procedure [30]. A process called "registration" matches the image and magnetic field. Then, a probe with an extended working channel is inserted through the bronchoscope and guided to the lesion through a virtual image on screen. Once the lesion is located, the extended channel is locked in place. A biopsy forceps is inserted to sample the lesion under fluoroscopic guidance. The diagnostic yield of navigational bronchoscopy alone is about 60 %, and when combined with radial endobronchial ultrasound to confirm location, the yield approaches 90 % [31].

Focal and Diffuse Infiltrative Diseases

Infiltrative diseases of the lung prove challenging when diagnosis is attempted using small sample biopsy techniques. Routine transbronchial lung biopsy may be attempted in settings where there is clear expertise by both the clinical and pathological personnel involved in making the diagnosis. In general, granulomatous lung diseases like sarcoidosis and hypersensitivity pneumonitis are more likely to be diagnosed by transbronchial lung biopsy [32] than the non-granulomatous idiopathic interstitial pneumonias (IIPs) including idiopathic pulmonary fibrosis [33, 34]. Surgical lung biopsy is recommended for the latter despite the attendant risks of anesthesia and operation

in patients who may already have significant pulmonary impairment.

Sarcoidosis is a granulomatous multisystemic disease with unknown etiology [18]. The most commonly involved organ is the lung, and it is thought that the causative agent or agents gain access via the respiratory route. The respiratory symptoms are nonspecific ranging from generalized chest discomfort, or tightness, to cough and wheezing. In many cases, the disease is suspected on the basis of accompanying symptoms such as dry mouth and eyes (Sjogren's syndrome), pain in the large joints, or even unexplained weight loss. Acute disease may present with painful iritis or uveitis and occasionally erythema nodosum of the lower extremities. The classic noncaseating granulomas are not found in the joints or nodosum lesions, but in the more chronic keloid-like lesions that can be found on any region of the body. The diagnosis can be reliably made by skin biopsy alone in the context of the presenting illness and exclusion of mycobacterial or fungal infection or lymphatic malignancies.

As noted in a previous section, pulmonary sarcoidosis often involves the airways and can be sampled by endobronchial biopsy. Parenchymal disease usually presents with several components that include mediastinal and hilar adenopathy with or without pulmonary infiltrates. Occasionally, sarcoidosis may present with multiple pulmonary nodules or as a lung mass. Finally, pulmonary impairment may be present with no radiological evidence of disease in the lungs. In all of these presentations, standard transbronchial lung biopsy has a very good diagnostic yield of up to 90 % when 4–5 transbronchial biopsies are performed [32]. In cases where there is obvious adenopathy abutting the airways, endobronchial ultrasound-guided fine-needle aspiration is becoming the preferred way to make the diagnosis because of its high yield and better safety profile compared to transbronchial lung biopsy [35, 36].

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a granulomatous lung disease caused by a host of environmental antigens [37, 38]. The acute form presents with fever, cough, dyspnea, malaise, and diffuse pulmonary infiltrates in the sensitized individual. The symptoms resolve when the antigen is removed and recur on exposure to the antigen. The predominant immune response in acute disease is the Arthus, or type III hypersensitivity response, involving immune complexes. The more subtle subacute presentation with cough, dyspnea, and fatigue displays centrilobular infiltrates by computerized tomography. Subacute HP represents a transition to cell-mediated immunity generating the granulomatous response that characterizes this disease. Continued exposure to the antigen may result in chronic HP of which the hallmark is the development of pulmonary fibrosis. The removal of the individual from the exposure is paramount to prevent disease progression. Therapy with corticosteroids is effective, but should not supplant avoidance of the causative antigen.

Like sarcoidosis, the granulomatous phase of HP is readily obtainable by transbronchial biopsy. The site of biopsy is guided by radiological appearance. The disease tends to be concentrated in the upper lobes, and this is where multiple passes with the biopsy forceps are taken. Although adenopathy is not a prominent feature of HP, this disease may need to be differentiated from sarcoidosis in some cases. In this situation, some clinicians elect to perform BAL with cell differential and flow cytometry to assess the ratio of CD4 to CD8 lymphocytes. Both diseases present with a lymphocytic alveolitis, but sarcoidosis has an elevated CD4/CD8, usually greater than 3, while HP presents with an inverted ratio of less than 1.

While standard bronchoscopy with transbronchial biopsy is sufficient to diagnose diffuse granulomatous diseases, the diagnostic accuracy drops significantly in diffuse non-granulomatous lung diseases [33, 34]. A new bronchoscopic biopsy technique born out of endobronchial cryotherapy may enhance the diagnostic accuracy of the transbronchial approach to diagnosis in diffuse lung diseases. Cryobiopsy uses a super cold probe to obtain parenchymal lung tissue of up to 1 cm in diameter [39]. The probe is inserted through the bronchoscope into the region of interest. The tip is cooled to −89 °C by rapidly expanding nitrous oxide gas. Within seconds, the probe and

bronchoscope are removed as a unit to recover the tissue for fixation. Bleeding does not appear to be increased by cryobiopsy compared to standard forceps biopsy, but the risk of pneumothorax may be increased by this technique. Nevertheless, the advantage of cryobiopsy is that it recovers tissue that has three times the sectional area of transbronchial biopsies and avoids the crush artifact commonly seen in the latter procedure. This technique will likely find application in the focal and diffuse parenchymal lung diseases described below.

The IIPs, autoimmune-related interstitial lung diseases, and the more recently recognized group of smoking-related interstitial lung diseases [40] require ample tissue to make a confident diagnosis. Sufficient tissue is usually obtained by surgical lung biopsy, typically by video-assisted thoracoscopy, or VATS. Aside from the complexity and risks of general anesthesia and surgery, selection of biopsy sites by VATS or open lung biopsy is critical. The tissue is preferably sampled in transitional areas of varying degrees of disease activity to enhance pathological description and diagnostic accuracy. Surgical experience and collaboration between the surgeon, clinician, and radiologist are needed to acquire optimal tissue for sectioning.

Idiopathic pulmonary fibrosis, or IPF, is the most common of the IIPs [41]. It has a highly variable disease progression with random exacerbations and is uniformly fatal. Dyspnea on exertion, with profound exercise hypoxemia, and sometimes violent cough paroxysms are the progressive symptoms. There is no approved drug therapy in the United States as of this writing. The disease at one time required the pathological finding of usual interstitial pneumonitis (UIP) on lung biopsy, but the findings of lower lobe predominant peripheral reticular infiltrates, traction bronchiectasis, honeycombing, and lack of "ground-glass opacification" on high-resolution computed tomography (HRCT) are now accepted for the diagnosis of IPF [42]. Lung biopsy is not required when other causes of diffuse lung disease are excluded and these key findings are displayed on HRCT. A recent update to the classification of IPF defines HRCT findings in IPF as UIP, possible UIP, and inconsistent UIP. Lung biopsy is recommended in the latter two designations, surgical risks permitting [42].

Nonspecific interstitial pneumonia, or NSIP, presents with similar clinical symptoms and time course as IPF but differs greatly in its pathogenesis and response to therapy [43]. There is much overlap on HRCT findings between NSIP and IPF, but NSIP tends to spare the subpleural parenchyma, and honeycombing is uncommon [44]. Ground-glass opacification is more common in NSIP, but just over one half of the cases may not have this feature. NSIP is found in a wide variety of diseases that result from alterations of the immune response such as the connective tissue diseases, infections including HIV, and drug reactions. However, the UIP pattern can be found in these diseases as well, most often in rheumatoid arthritis-associated interstitial lung disease. A proportion of individuals have the idiopathic form of NSIP that occurs when no causative etiology can be discerned after a thorough search. In effect, there are no current clinical or radiological findings that can confidently separate IPF/UIP from NSIP. Differentiating NSIP from IPF is critical because NSIP has a variable, but significant, response to immunomodulating therapies [43]. Lung biopsy is necessary for patients who present with the idiopathic form of NSIP and may be considered when patients who have a known underlying cause do not respond to therapy. In these cases, the underlying histopathology may have prominent areas of UIP intermingled with the NSIP. Surgical lung biopsy is the accepted method to obtain sufficient tissue for examination. The role of transbronchial cryobiopsy is yet to be determined.

The relationship between smoking and certain diffuse lung diseases has been recognized over the past 50 years. Virtually, all smokers develop respiratory bronchiolitis (RB) that can be detected histologically [45, 46]. In general, RB is not symptomatic, and lung function measures are normal. A minority of individuals will progress with dyspnea and cough as they develop the diffuse interstitial phase termed RB-ILD. Pulmonary function testing will demonstrate a

mixed restrictive and obstructive pattern with decreased total lung capacity and relative increase in residual volume indicating air trapping. Radiologically, a patchy ground-glass appearance may be noted. Desquamative interstitial pneumonitis (DIP), more accurately an influx of macrophages filling alveolar spaces, presents as a uniformly restrictive impairment and diffuse confluent ground-glass opacification on CT scanning. The bronchiolocentric localization of inflammatory cells of RB-ILD and alveolar filling presentation of DIP can be found together suggesting that they represent a spectrum of smoking-related inflammatory reaction extending from respiratory bronchioles to the alveolar spaces. Treatment of the smoking-related ILD mandates tobacco cessation sometimes combined with corticosteroids. The distribution of disease is such that surgical lung biopsy is required to appreciate the extent and pattern of DIP and RB-ILD.

Organizing pneumonia filling the alveolar spaces and respiratory bronchioles has a variable focal distribution that typically involves both lungs. The primary form termed cryptogenic organizing pneumonia, or COP, is found most commonly in the sixth decade of life [47]. Unlike most of the other IIPs, it has a very favorable response to corticosteroid therapy. Secondary organizing pneumonia can be found as a reparative reaction to many forms of lung injury including infection, autoimmune diseases, and malignancies [48]. Perhaps because of the underlying diseases, the outcome and survival seem to be worse than in primary COP [49]. The presenting symptoms in primary and secondary organizing pneumonia are not specific with cough and dyspnea on exertion being most common. Fever is variable and there are no distinguishing laboratory findings. The radiological presentation is protean ranging from dense areas of parenchymal consolidation, patchy bronchocentric infiltrates, to discrete centrilobular densities [50]. Accurate diagnosis is currently made mostly by surgical lung biopsy, but this approach may be supplanted as experience grows with transbronchial cryobiopsy.

Conclusion

The development of pulmonary diagnostic procedures founded on FOB has allowed access to virtually every region of the airways and lung parenchyma avoiding the complexity, risks, and costs of surgery. These procedures are transportable to settings outside the operating room into specialized outpatient medical procedure units and inpatient acute care wards including intensive care units. The main drawback to these non-surgical approaches is the limitation on the size of the biopsy samples that are typically in the sub-centimeter size range. Selection of sampling technique, selection of the biopsy site, and procurement of multiple samples overcome this disadvantage to some extent. Most importantly, the multidisciplinary collaboration between the pathologist, radiologist, and clinician will yield the highest diagnostic "wisdom."

References

1. Ikeda S, Yanai N, Ishikawa S. Flexible bronchofiberscope. Keio J Med. 1968;17(1):1–16. PubMed PMID: 5674435. Epub 1968/03/01. eng.
2. Bolliger CT, Mathur PN, Beamis JF, Becker HD, Cavaliere S, Colt H, et al. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. Eur Respir J. 2002;19(2):356–73. PubMed PMID: 11866017. Epub 2002/02/28. eng.
3. Rath GS, Schaff JT, Snider GL. Flexible fiberoptic bronchoscopy. Techniques and review of 100 bronchoscopies. Chest. 1973;63(5):689–93. PubMed PMID: 4703621. Epub 1973/05/01. eng.
4. Zavala DC. Diagnostic fiberoptic bronchoscopy: techniques and results of biopsy in 600 patients. Chest. 1975;68(1):12–9. PubMed PMID: 168036. Epub 1975/07/01. eng.
5. Cooley ME. Symptoms in adults with lung cancer: a systematic research review. J Pain Symptom Manage. 2000;19(2):137–53.
6. Hirshberg B, Biran I, Glazer M, Kramer MR. Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital. Chest. 1997;112(2):440–4.
7. Oberg K, Castellano D. Current knowledge on diagnosis and staging of neuroendocrine tumors. Cancer Metastasis Rev. 2011;30 Suppl 1:3–7. PubMed PMID: 21311954. Epub 2011/02/12. eng.