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Biopsy Examination

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Invasive procedures have been developed for the diagnosis of neoplastic and nonneoplastic thoracic disease by pathologic means.[1–10] They range in complexity from open lung biopsy and mediastinoscopy, which are surgical procedures that require general anesthesia and entail some morbidity, to flexible bronchoscopy with transbronchial biopsy and cytology, which use only topical anesthesia, to transthoracic biopsy and fine needle aspiration (FNA), which can be performed in outpatient facilities.[11–30] Tissue and cytologic samples can be obtained with these procedures (Display 4-1).

CLINICAL HISTORY AND CHEST IMAGING STUDIES

Biopsy procedures are indicated for patients with nodules, interstitial infiltrates, lung infections, and other conditions.[31–40] It is important to correlate the pathologic findings with the clinical history and the results of imaging studies. This information should be made available to the pathologist at the time the biopsy specimen is received or earlier for the best handling of the specimen. For example, if the patient has a pulmonary nodule and the transbronchial biopsy is negative, it may be necessary to prepare deeper sections of the biopsy specimen to detect a possible lesion at a different level. If the biopsy specimen is from an immunosuppressed patient, it is imperative to apply special stains for microorganisms, even in the absence of significant inflammation in the tissue slides.

FIBEROPTIC BRONCHOSCOPY

Fiberoptic bronchoscopy (FOB) is one of the most frequently used invasive diagnostic procedures for patients with pulmonary nodules and infiltrates, and it can be performed under topical anesthesia, with minimal discomfort.[1–3,41–54] It allows the pulmonologist to view the central airways up to the sixth generation of bronchi and to obtain cytologic samples by brushing, washing, or lavaging the bronchi with saline or obtaining transbronchial FNA. Tissue samples by bronchial and transbronchial biopsy can be obtained under direct visual control or under fluoroscopic guidance.[54] The morbidity of the procedure is low, with complications such as significant hemoptysis, pain, and pneumothorax occurring in fewer than 5% of patients. The mortality related to the procedure is low, although a few patients died of massive hemoptysis, particularly in instances of severe pulmonary hypertension and fibrosis.[41–54] FOB is indicated primarily for patients with pulmonary nodules, infection, and long-standing pulmonary infiltrates.[7,22,25,27,53]

The diagnostic accuracy of FOB varies with the underlying clinical condition and the type of sample obtained, with diagnostic yields from approximately 40% to more than 95% of patients.[41–54] The yield is increased by obtaining multiple tissue and cytologic samples. In a recent study by Popp and associates, the diagnostic sensitivity for lung tumors was 84.9% for biopsy imprints, 80.6% for brush biopsy specimens, and 62.9% for tissue samples.[53] The diagnostic sensitivity was as high as 97.3% with 100% specificity when cytologic and biopsy methods were combined.

The yield of flexible bronchoscopy with combined bronchoalveolar lavage and transbronchial biopsies is as high as 90% in patients with acquired immunodeficiency syndrome (AIDS) and slightly lower in those with other infections.[9,33,41] The yield of transbronchial biopsy is considerably lower for chronic restrictive lung diseases and long-standing interstitial infiltrates.

PERCUTANEOUS TRANSTHORACIC NEEDLE BIOPSY

Percutaneous transthoracic needle biopsy (PTNB) of lung, hilar, and mediastinal lesions with transthoracic FNA or Tru-cut tissue biopsy has become more widely used in the past decade.[4,5,29,55–58] The procedure is performed under fluoroscopic or computed tomography guidance using needles ranging from Tru-cut needles

DISPLAY 4-1. BIOPSY MODALITIES IN PULMONARY DISEASE

Fiberoptic bronchoscopy
- Transbronchial biopsy
- Bronchial brush cytology
- Bronchial wash cytology
- Bronchoalveolar lavage
- Transbronchial fine needle aspiration

Transthoracic or percutaneous biopsy of lesions
- Fine needle aspiration
- Tru-cut biopsy

Mediastinoscopy

Rigid bronchoscopy

Open lung biopsy
- Limited thoracotomy
- Thoracoscopic lung biopsy

Pleural biopsy
- Transthoracic or percutaneous biopsy
- Thoracoscopic pleural biopsy

that allow the biopsy of 2 to 3 mm of tissue to 22-gauge fine needles for the aspiration of cytologic samples.

Transthoracic biopsies are indicated for patients with pulmonary nodules, multiple intrapulmonary lesions, lobar consolidation, diffuse pulmonary infiltrates, mediastinal lymphadenopathy, tumors, and cysts.[4,29,34,57,59] PTNB can be performed without anesthesia and is accompanied by significant morbidity, with as many as 10% of patients developing pneumothorax. In about 1% of patients, the pneumothorax requires the placement of a chest tube.[4] PTNB with FNA transthoracic biopsy can be as sensitive as flexible bronchoscopy for 75% to 95% of patients with peripheral pulmonary tumors.[4] The sensitivity for patients with benign conditions is 12% to 57%.[4,59]

MEDIASTINOSCOPY

Mediastinoscopy was introduced in 1954 by Harken and associates to determine the resectability of lung cancer.[38] It is now also used for the diagnosis of mediastinal lesions, including lymphadenopathies, cysts, and thymic lesions.[60–63] The procedure is performed under general or local anesthesia and allows exploration of the peritracheal portions of the superior and middle regions of the mediastinum.[61]

Techniques are available for extended mediastinoscopies that include the anterior mediastinum.[35,61] The patient is placed in a supine position, and the mediastinoscope tube is inserted through a transverse neck incision into the suprasternal notch area. Biopsies are taken under direct visualization. Mediastinoscopy is usually a safe procedure, but complications include hemorrhage and perforation of the trachea, main stem bronchi, or esophagus. Air embolism and mediastinitis can occur in 1% to 3% of patients.[60–63] Biopsy samples of mediastinal lymph nodes or focal lesions are usually submitted for frozen section or cytologic examination and should be fixed in appropriate solutions according to the most likely diagnosis (Fig. 4-1).

RIGID BRONCHOSCOPY

Rigid bronchoscopy is performed under general anesthesia and requires hospitalization.[64] A rigid metal tube approximately 10 to 15 mm in diameter is inserted into the larynx, and the trachea, carina, and main bronchi can be viewed and biopsied. The technique is particularly useful in patients with bronchial obstruction or vascular lesions; for extraction of mucus plugs, blood clots, aspirated materials, and broncholiths; and for the resection of endobronchial tumors.

OPEN LUNG BIOPSY

Several surgical procedures can be performed to obtain relatively large samples of lung tissue, including limited thoracotomy and thoracoscopic biopsy.[15,36,65–74] These procedures are performed under general anesthesia and require hospitalization. Limited thoracotomy implies a partial disruption of the chest cage with placement of a chest tube in most instances; it is associated with significant postoperative pain but low mortality rates. Newer techniques of thoracoscopic biopsy are associated with lower morbidity because the ribs are not disrupted.

Open lung biopsy is reserved for seriously ill patients with lesions that cannot be diagnosed by the less invasive diagnostic procedures previously described. It is also performed in patients with severe interstitial lung disease, pulmonary hypertension, and immunosuppression with progressive pulmonary infiltrates.[70–74] Open lung biopsy with intraoperative frozen section is also frequently performed in patients with pulmonary nodules not previously diagnosed. It is a relatively complex invasive diagnostic procedure that requires good communication between the thoracic surgeon and the pathologist to ensure that the tissues are handled optimally.

It is important to send small fragments of lung tissue, rather than swabs, for bacterial, mycobacterial, fungal, and viral cultures; to snap-freeze tissues for immunopathologic studies; and to fix tissues in solutions other than formalin, such as B-5 fixative in suspected pulmonary lymphomas or other lymphoproliferative procedures and glutaraldehyde for electron microscopy.

The role of open lung biopsy in patients with acute pulmonary infiltrates or chronic interstitial lung disease has been the subject of controversy.[65–74] It is difficult to develop standard indications, and the procedure should probably be considered on an individual basis and only if the biopsy is likely to render information of therapeutic or prognostic value. This dilemma may be minimized soon with the development of biopsy techniques through thoracoscopy that require shorter hospitalizations and are associated with lower morbidity than traditional open lung biopsies obtained through limited thoracotomy.

Open lung biopsies offer considerable advantages over transbronchial biopsies, such as information about the distribution of the disease, and allow better sampling of changes, such as granulomas (Fig. 4-2), vasculitis, obliterative bronchiolitis (Fig. 4-3), and focal stellate scars. Exceptionally, the diagnosis of bronchiolitis obliterans can be made in a transbronchial biopsy specimen (Figs. 4-4 and 4-5). In patients with severe acute infiltrates, open lung biopsies are indicated if less invasive techniques such as bronchoalveolar lavage and transbronchial biopsies have failed.

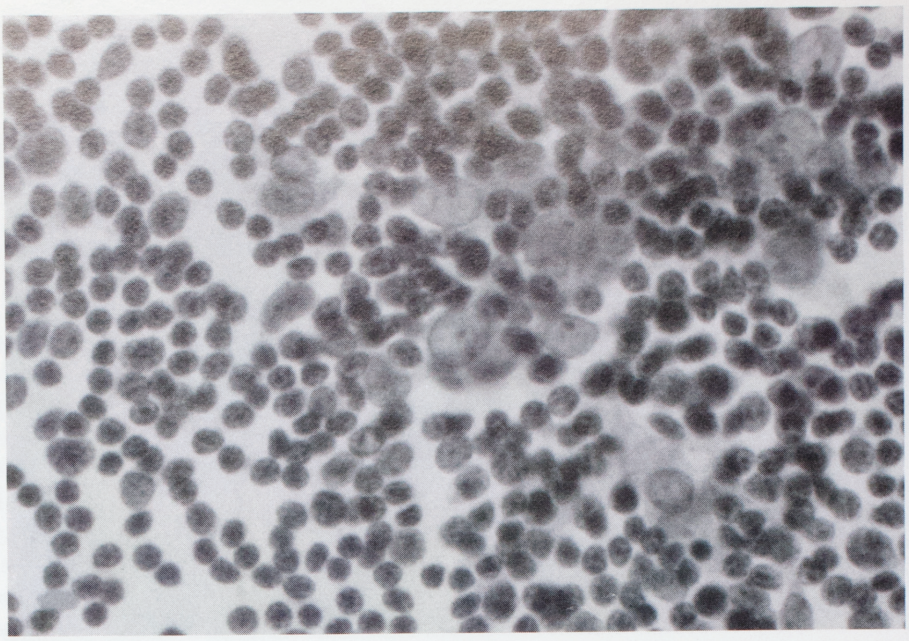

FIGURE 4-1. Biopsy of an anterior mediastinal mass is performed by transthoracic fine-needle aspiration. The aspirate shows lymphoid and epithelial cells characteristic of thymoma. (Toluidine blue stain; intermediate magnification.)

Open lung biopsy frequently renders additional information for patients with AIDS, lymphoma, or other immunosuppressive conditions. For example, in a study of 61 patients by Walker and associates, the procedure yielded a specific diagnosis for 36% of the biopsies (*e.g.*, infections, bronchoalveolar carcinoma, lymphoma, vasculitis, lymphomatoid granulomatosis) and provided therapeutically relevant information for 54% of the patients.[12]

For patients with chronic interstitial lung disease, open lung biopsy enables diagnoses such as eosinophilic granuloma, bronchiolitis obliterans organizing pneumonia, vasculitis, and pneumoconiosis.[64–74] Because approximately 50% of patients with chronic interstitial pulmonary problems have an idiopathic syndrome, usual interstitial pneumonia, the results can be disappointing from a therapeutic standpoint.

PLEURAL BIOPSIES

Tru-cut needle biopsies of pleural tissues or thorascopically directed pleural biopsies are frequently performed in patients with pleural effusions or mass lesions.[75–77] Specific findings may include granulomas in pleural tuberculosis, metastatic carcinoma, primary pleural tumors (*e.g.*, malignant mesothelioma, benign fibrous tumor, sarcomas), malignant lymphomas, and less frequent findings, such as amyloidosis in pleural blood vessels.[75,76]

The procedure is usually performed under local or no anesthesia and is associated with low morbidity. Complications include pain and pneumothorax. Needle biopsy of the pleura yields a diagnosis in 50% to 70% of patients with tuberculosis or malignant effusions.[75–77] A few patients may develop dissemination of

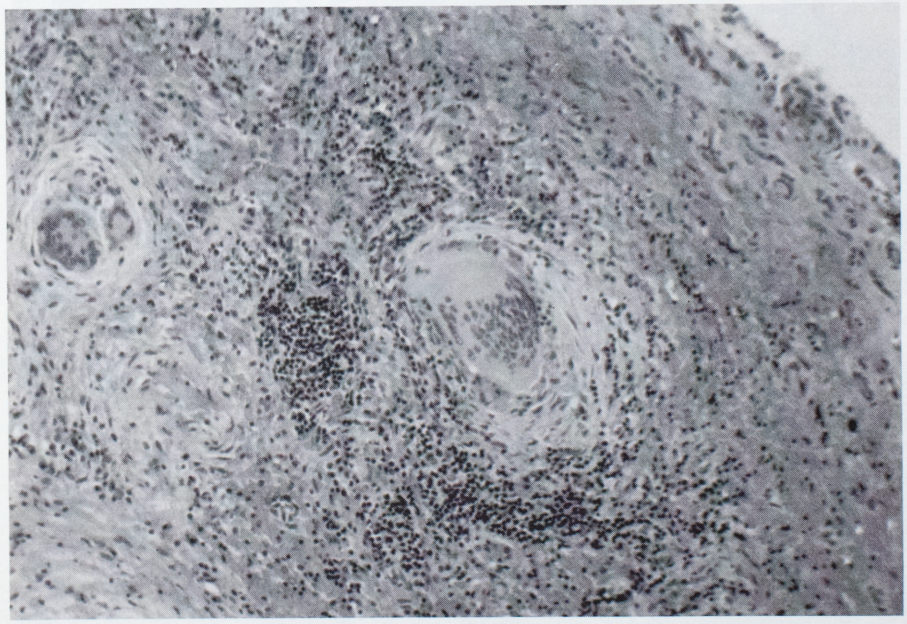

FIGURE 4-2. Open lung biopsy demonstrates granulomas in a patient with tuberculous pleuritis. Acid-fast bacilli were demonstrated in the granulomas. (H & E stain; low magnification.)

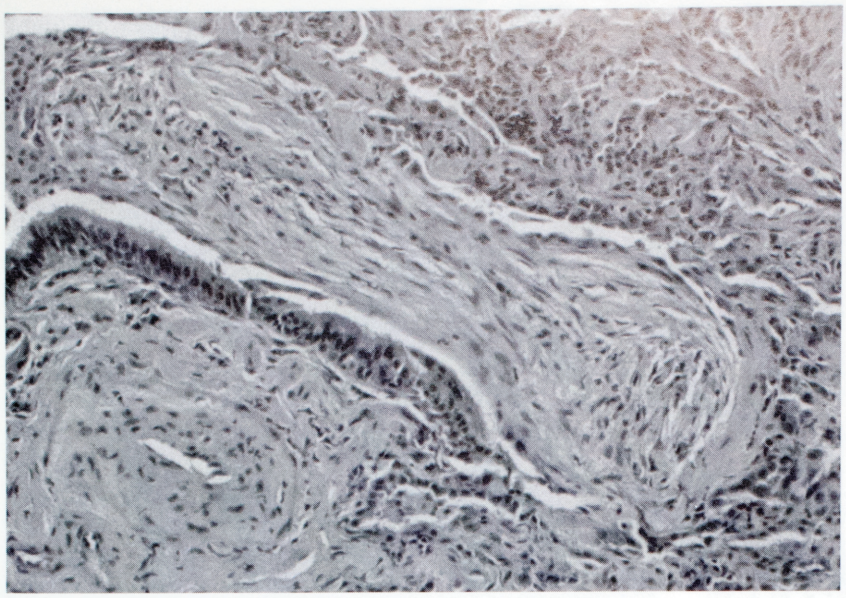

FIGURE 4-3. Open lung biopsy is best to diagnose interstitial lung disease with lesions such as bronchiolitis obliterans organizing pneumonia. (H & E stain; low magnification.)

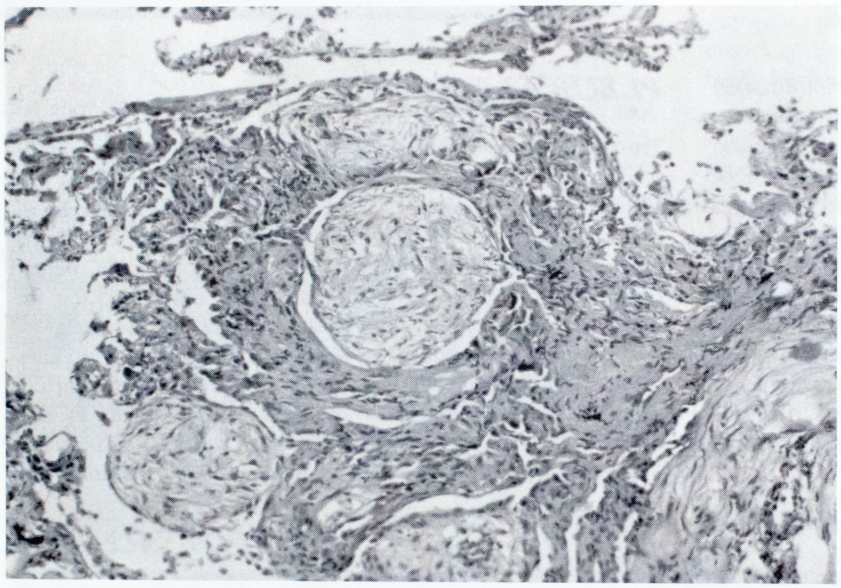

FIGURE 4-4. An unusual instance of bronchiolitis obliterans organizing pneumonia was diagnosed by transbronchial biopsy. The characteristic polyps of myxoid tissue (*i.e.*, Masson bodies) are surrounded by atelectatic and inflamed lung tissue. (H & E stain; low magnification; contributed by the editor.)

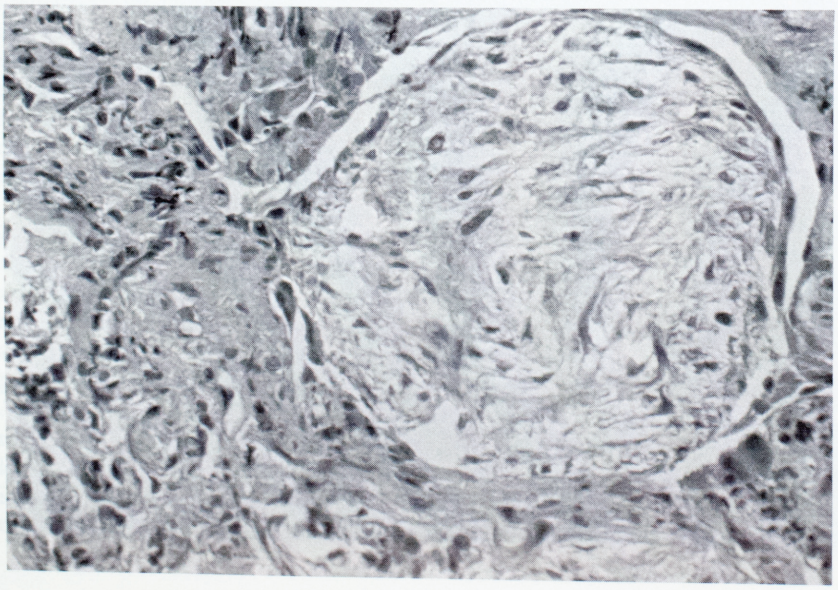

FIGURE 4-5. Higher magnification of same patient shown in Figure 4-4 shows an intrabronchiolar myxoid polyp or Masson body, characteristic of bronchiolitis obliterans organizing pneumonia. (H & E stain; intermediate magnification; contributed by the editor.)

tumor cells in the needle tract, a complication that is rare after transthoracic FNA.

TECHNICAL ASPECTS OF PROCESSING BIOPSY SAMPLES

Fixation and Initial Handling of Biopsied Tissues

Small biopsy tissues should be handled carefully to avoid unnecessary squeezing leading to tissue artifacts (Display 4-2.) Fixation with buffered formaldehyde is adequate for the diagnosis of most pulmonary diseases, although some pathologists prefer Bouin or Zenker solutions because they produce less tissue shrinkage and better nuclear detail. The clinical impression should influence the choice of fixatives other than formalin. For example, for a patient with suspected viral infection, the tissues can be submitted for culture or fixed in glutaraldehyde for ultrastructural studies to detect viral particles (Fig. 4-6). In patients with suspected collagen-vascular disease or malignant lymphoma, fresh samples of tissue should be snap frozen and retained for possible immunopathologic studies with immunofluorescence, immunoperoxidase, or DNA analysis.

Tissues obtained by open lung biopsy can be inflated with formalin to improve histologic details and facilitate morphologic interpretation. This is accomplished by introducing a needle into a bronchus, if available, or by injecting the tissues directly with a syringe and fine needle.[78]

Serial Sections and Special Stains

It is important to examine serial sections of small bronchoscopic biopsies to maximize the detection of focal findings such as granulomas, viral inclusions, and tumor cells. For detecting microorganisms, special stains such as Ziehl-Neelsen, Gomori methenamine silver, periodic acid-Schiff (PAS), Gram, and Giemsa must be used

DISPLAY 4-2. METHODS FOR THE STUDY OF LUNG BIOPSY SPECIMENS

Microbiologic Studies

Smears for special stains

Tissue fragments for cultures

Fixation

Formaldehyde: most instances

Bouin or Zenker solutions: study of pulmonary edema, better nuclear detail

B-5 or Zenker solution: lymphoproliferative disorders

Glutaraldehyde: electron microscopy of suspected small cell carcinoma or unusual tumors; study of viral infections; eosinophilic granuloma; amyloidosis

Frozen Tissue

Collagen-vascular disease

Interstitial lung disease

Lymphoproliferative disorders

Molecular biology techniques

Special Stains

Acid-fast bacillus, Gomori methenamine silver, Giemsa, Brown and Brenn: bacteria and fungi

Trichrome: interstitial fibrosis

Elastic: vasculitis, pulmonary hypertension

Congo red, crystal violet: amyloidosis

Immunofluorescent Studies

Goodpasture syndrome

Collagen-vascular disease

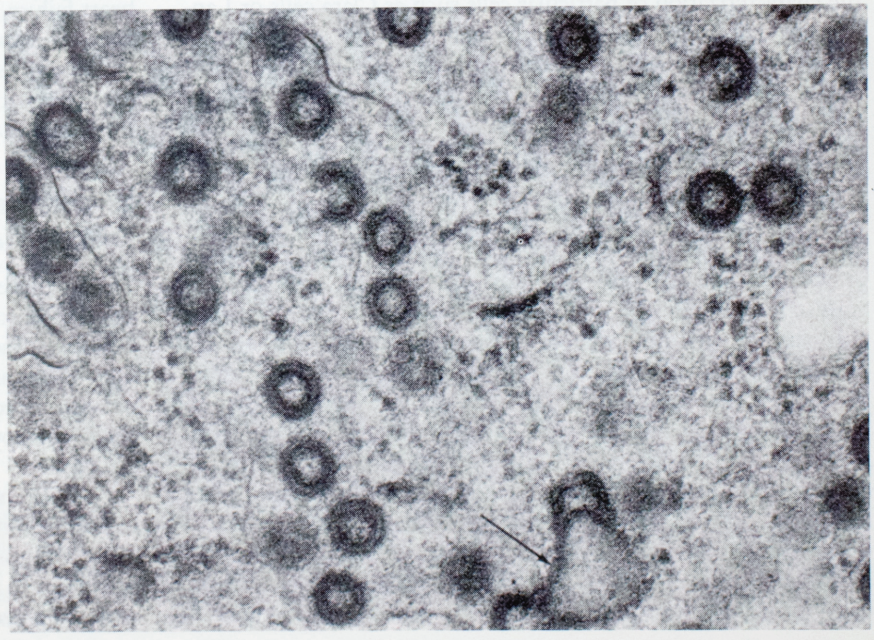

FIGURE 4-6. Micrograph of an open lung biopsy specimen fixed in glutaraldehyde shows virions of Epstein-Barr virus. (Original magnification × 100,000.)

in patients with suspected infections. Additional stains can be useful in selected situations, such as Congo Red or crystal violet stains for patients with presumed amyloidosis, trichrome stains to assess the degree of fibrosis, elastic stains for patients with pulmonary hypertension and suspected vasculitis, and mucicarmine and diastase-PAS stains to differentiate adenocarcinomas from other non-small cell carcinomas.

Polarization Microscopy

A simple method for examining lung biopsies is polarized light for the detection of birefringent inorganic particles such as silica, silicates, and talc.[79] This method can highlight areas of fibrosis with collagen deposition.

Immunopathologic Techniques

Immunopathologic methods employing indirect fluorescence are used on lung biopsies. Staining of frozen sections of lung tissue with antibodies to immunoglobulins, complement, fibrin, and albumin are helpful in assessing Goodpasture syndrome, vasculitis, and systemic lupus erythematosus.[80] Because immunoglobulin deposition has been demonstrated in lung biopsies from patients with usual interstitial pneumonia, drug reactions, diffuse alveolar damage, and other conditions, the use of immunofluorescence techniques is limited by the nonspecific findings.[80] Immunopathologic methods with the peroxidase-antiperoxidase or the avidin-biotin conjugate can aid in the diagnosis of infections such as cytomegalovirus, herpesvirus, and *Pneumocystis carinii*; the identification of Langerhans histiocytes; and for the characterization of lymphoid and neoplastic cells.[32,33]

Ultrastructural Techniques

Electron microscopy can be helpful in the study of selected pulmonary diseases. It is most widely used for the characterization of pulmonary neoplasms, especially small cell carcinomas and spindle cell tumors.[81] It can be used in selected instances for the detection of viral inclusions (see Fig. 4-6) and other microorganisms or for the characterization of particular cells such as Clara cells or Langerhans cells.[80] Transmission electron microscopy is essential for the study of patients with suspected disorders of the cilia apparatus of the airway epithelium.[82]

Analytic Methods for Identifying Inorganic Materials

Several bulk analytic and microanalytic techniques have been described for the identification and quantitation of inorganic materials in lung biopsies.[79] These methods can be applied to fresh or formalin-fixed tissues. Some methods can be applied to tissues embedded in paraffin. Bulk analytic methods include x-ray diffraction for the detection of quartz polymorphs and silicates and x-ray fluorescence and atomic absorption spectroscopy for the detection of fly ash and beryllium.[79] In these methods, the tissues are destroyed by digestion and ashing, and the inorganic residues are studied. Microanalytic techniques allow the study of tissue sections with electron microscopy and energy-dispersive x-ray spectroscopy for the detection of silica and asbestos fibers, electron diffraction analysis for particle identification, and other methods.[79]

BIOPSY INTERPRETATION

Pitfalls

The morphologic findings cannot be adequately interpreted without correlation with the clinical history and roentgenographic findings, particularly for interstitial lung diseases. In many patients, areas of peribronchial fibrosis on small biopsies are frequently interpreted as severe although there may be no or only minimal radiologic infiltrates and relatively good pulmonary function tests. Likewise, the diagnosis of usual interstitial pneumonia is frequently rendered on the basis of little biopsy information, without regard for the extent of the radiologic findings or clinical information on the evolution of the disease. Focal vascular changes of pulmonary hypertension or airway obstruction in patients with obliterative bronchiolitis can be easily overlooked in the absence of an adequate clinical history.

It is important to consider the location and distribution of morphologic findings. Are they around airways, vascular spaces, lymphatic routes, alveoli, interstitium, or the pleura? Although these features are more easily interpreted in open lung biopsy specimens, they can sometimes be appreciated in smaller transbronchial biopsy specimens. For example, the presence in a transbronchial biopsy specimen of focal intraalveolar early fibrous tissue with involvement of a respiratory bronchiole supports, in the appropriate clinicoradiologic context, the diagnosis of bronchiolitis obliterans organizing pneumonia. Lymphoid infiltrates in a perivascular location in a lung allograft recipient are diagnostic of acute cellular rejection in the absence of infection; identical features in other patients may represent a viral pneumonia, or a nonspecific finding.

Transbronchial Biopsies for Acute Pulmonary Infiltrates

Patients with acute pulmonary infiltrates frequently undergo flexible FOB with bronchoalveolar lavage or other cytologic sampling and bronchial and transbronchial biopsies.[52,53] In these patients, the most frequent differential diagnoses include infections, left heart failure, drug reactions, and less frequently, neoplasms. It is important to gather information before attempting to interpret these samples, in particular to know whether the patient is immunosuppressed (Fig. 4-7) or on any particular medication (*e.g.*, chemotherapeutic agents) or has received radiotherapy.[41–54]

Transbronchial Biopsies for Chronic Interstitial Infiltrates

These biopsies often exhibit various degrees of interstitial or intraalveolar fibrosis, chronic inflammation, and thickening of the walls of pulmonary vessels. The clinical, radiologic, and pathologic correlations are important because similar radiologic findings may be seen in collagen-vascular diseases, previous radiotherapy or chemotherapy, viral infections, pneumoconiosis, or idiopathic disorders.

Peribronchial fibrous tissue is a normal finding, but squeezing of the biopsy specimen (*i.e.*, atelectasis) can lead to the diagnosis of fibrosis. In assessing atelectatic samples of lung tissue, it is important to pay attention to the cells in the apparently thickened septa to prevent the overdiagnosis of severe fibrosis. Atelectatic

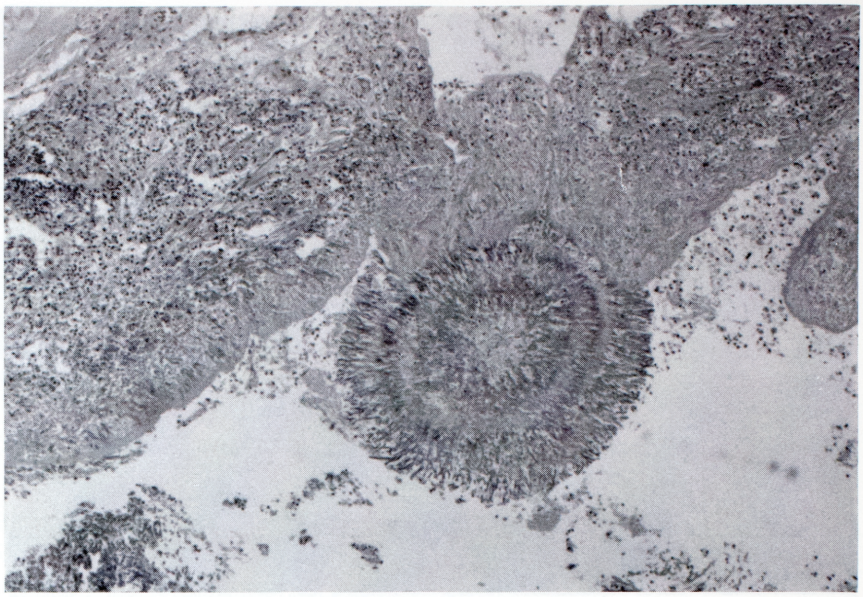

FIGURE 4-7. Transbronchial biopsy is a sensitive procedure for the diagnosis of infection in immunocompromised patients. This specimen reveals invasive aspergillosis in a cancer patient. (H & E stain; low magnification.)

alveoli are lined by flat pneumocytes, there are no inflammatory cells or pneumocyte hyperplasia, and the alveolar capillaries contain erythrocytes. Special stains such as Masson trichrome are useful to confirm fibrosis.

Biopsies of Pulmonary Nodules

Patients often undergo flexible FOB or transthoracic FNA biopsies. The latter procedure has a higher diagnostic yield in patients with peripheral nodules, and bronchoscopy allows examination of the airways and the location of more proximal lesions.[2,4,53] The value of these procedures for patient management is a topic of controversy; some pulmonologists prefer to establish a preoperative diagnosis in all patients, but others argue that a thoracotomy with frozen section is preferred because the patient will undergo surgery. Biopsies can be helpful for diagnosing conditions that preclude surgery, such as small cell carcinoma of the lung, granulomas, and hamartomas. Although a diagnosis of Wegener granulomatosis of the lung requires open lung biopsy, in rare instances, the diagnosis can be made by transbronchial biopsy (Figs. 4-8 through 4-10).

Biopsies for Airway Diseases

Bronchial and transbronchial biopsies can be useful for diagnosing acute bronchitis, bronchiolitis, and tumors of the airways.[41–54] They are of more limited value for assessing patients with chronic bronchitis, asthma, and obliterative forms of bronchiolitis. The finding of chronic inflammation in the bronchial wall cannot be interpreted as chronic bronchitis because patients with asthma also exhibit this finding.[47,48] The diagnosis of bronchiectasis is difficult to establish by transbronchial or open lung biopsy without a proper clinical history. The bronchial wall shows severe chronic inflammation, fibrosis, and focal areas of squamous metaplasia.

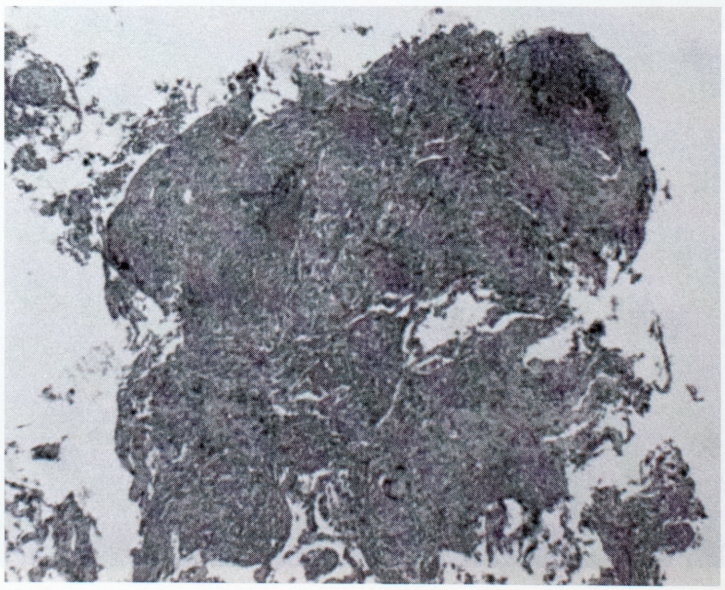

FIGURE 4-8. An unusual example of Wegener granulomatosis diagnosed by transbronchial biopsy. The darker geographic area of necrosis produced by disintegrating neutrophils suggests this disease, particularly if associated with nodular lesions in the chest x-ray film. (H & E stain; low magnification; contributed by the editor.)

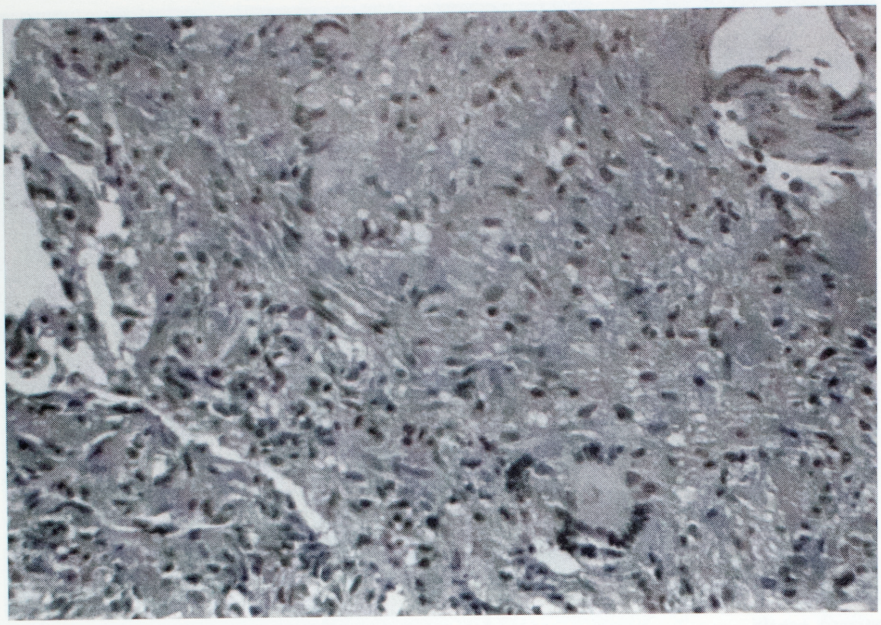

FIGURE 4-9. In the same patient as in Figure 4-8, another feature of Wegener granulomatosis is present: a diffuse granulomatosis inflammation, including giant cells. (H & E stain; intermediate magnification, contributed by the editor.)

The diagnosis of diseases of the ciliary apparatus should be considered for patients with chronic bronchitis or bronchiectasis.[82]

The diagnosis of obliterative bronchiolitis can be difficult on transbronchial biopsy because of sampling limitations. Trichrome and elastic stains help to highlight the diagnostic areas. Open lung biopsy should be considered for patients after inhalation of smoke, NO_2, or ammonia and for patients with collagen-vascular disease.

Biopsies for Granulomatous Conditions

Granulomas with necrosis should prompt the investigation of acid-fast organisms and fungi with appropriate stains. In cases with negative results, cultures of the biopsy specimen and the results of skin tests are indispensable. The diagnosis of sarcoidosis is frequently possible with transbronchial biopsy (Figs. 4-11 and 4-12). A detailed description of granulomatous conditions and their diagnoses is presented in Chapter 66.

Biopsies for Pulmonary Hypertension, Vasculitis, and Other Vascular Conditions

Open lung biopsies are better suited for the diagnosis of diseases of the pulmonary vasculature than transbronchial biopsies, which are of limited value because of size and sampling limitations. Transbronchial biopsies must be performed with caution because of the potential of severe hemorrhage at the time of the procedure or thereafter. The samples should be studied with multiple serial sections and the tissue sections stained with elastic stains to highlight blood vessels.[80]

Open lung biopsies are performed for patients with severe pulmonary hypertension to establish the grade of the disease and

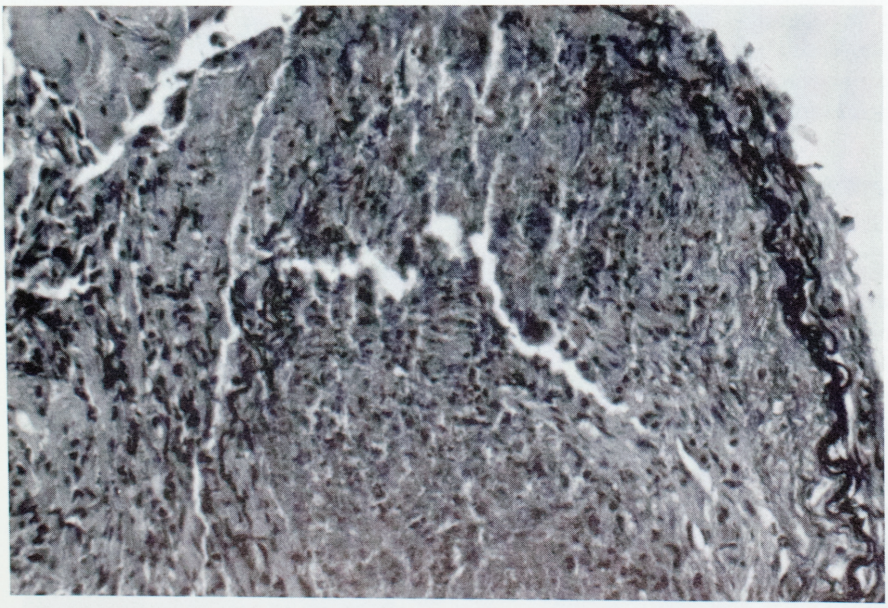

FIGURE 4-10. In the same patient as in Figures 4-8 and 4-9, the presence of highly necrotizing vasculitis with suppurativelike features confirms the diagnosis. (Elastic stain; intermediate magnification; contributed by the editor.)

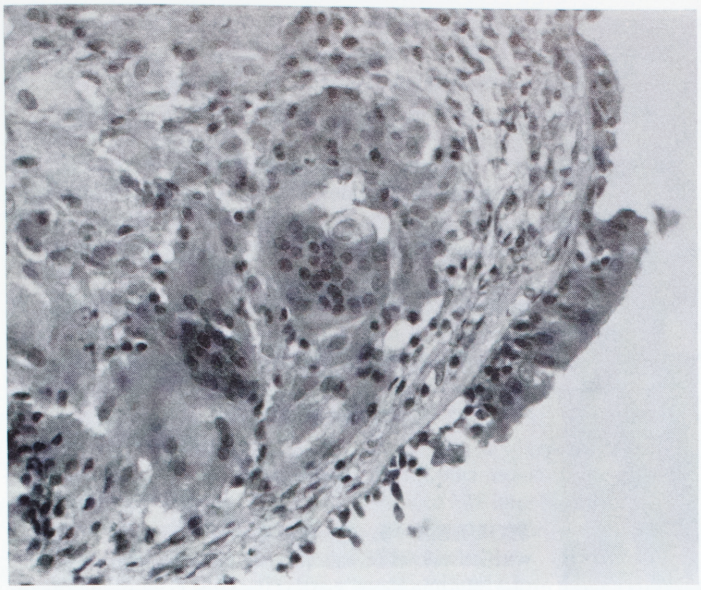

FIGURE 4-11. Transbronchial biopsy is performed in a patient with sarcoidosis. Discrete, submucosal granulomas are characteristic of this disease, particularly if associated with no necrosis of the overlying mucosa. Necrosis suggests an infectious granulomatosis process, such as tuberculosis. (H & E stain; intermediate magnification; contributed by the editor.)

potential reversibility of the vascular changes, particularly for children who are candidates for heart surgery and patients being considered for pulmonary transplantation.[83] The procedure can help to establish the diagnosis of vasculitis and related conditions and venoocclusive disease, because pulmonary veins are seldom properly sampled in transbronchial biopsies.[84]

Immunopathologic studies are indicated for patients with vasculitis to detect immune complexes in the pulmonary vasculature.[85] Electron microscopy has a limited role; intracellular tubuloreticular inclusions may be seen in patients with systemic lupus erythematosus.[86]

Biopsies for Pneumoconiosis

Transbronchial and open lung biopsies from patients suspected of having pneumoconiosis should be interpreted in light of the history of environmental exposure. Specific findings in the routine histologic sections include asbestos bodies (Fig. 4-13), birefringent particles under polarization microscopy (*e.g.*, talc, silica, silicates), fibrotic nodules with laminated collagen bands, and birefringent particles in patients with diseases such as silicosis.[79] Formalin-fixed tissues from these patients can be studied with electron diffraction analysis, fiber counts and other specialized techniques usually available only in selected laboratories.[79]

Diagnosis of Tumor Cell Type by Transbronchial Biopsy or Transthoracic Fine Needle Aspiration

Transbronchial biopsy and transthoracic FNA are sensitive and specific for the diagnosis of most lung malignancies, but they may not be useful for the diagnosis of cell type in non-small cell lung tumors, because these tumors are frequently heterogeneous and perceived in a somewhat subjective manner by different pathologists.[87,88] Several studies report specificities for these procedures of 80% to 90%, but others analyzing poorly differentiated lung neoplasms indicate reproducible results in the 50% range.[89]

It is my practice to label poorly differentiated pulmonary neoplasms as non-small cell carcinomas on small biopsies or FNA and reserve the diagnoses of specific carcinomas for lesions with obvious morphologic features, usually in samples from open lung biopsies.

The bronchioloalveolar variant of adenocarcinoma is difficult to diagnose in small transbronchial specimens or FNA because bronchial adenocarcinomas frequently grow in a bronchioloalveolarlike pattern at their peripheries. I do not render the diagnosis of bronchioloalveolar carcinoma on the basis of small biopsies and prefer to designate the lesions as adenocarcinomas and mention that the tumor exhibits a bronchioloalveolarlike growth

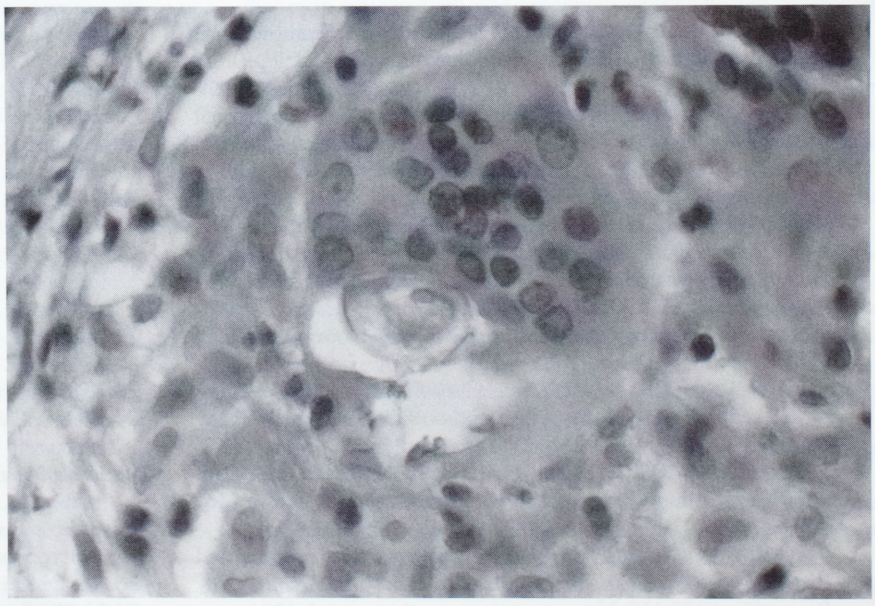

FIGURE 4-12. In the same patient as in Figure 4-11, detail of the sarcoid granuloma, including the presence of a Schaumann body. (H & E stain; high magnification; contributed by the editor.)

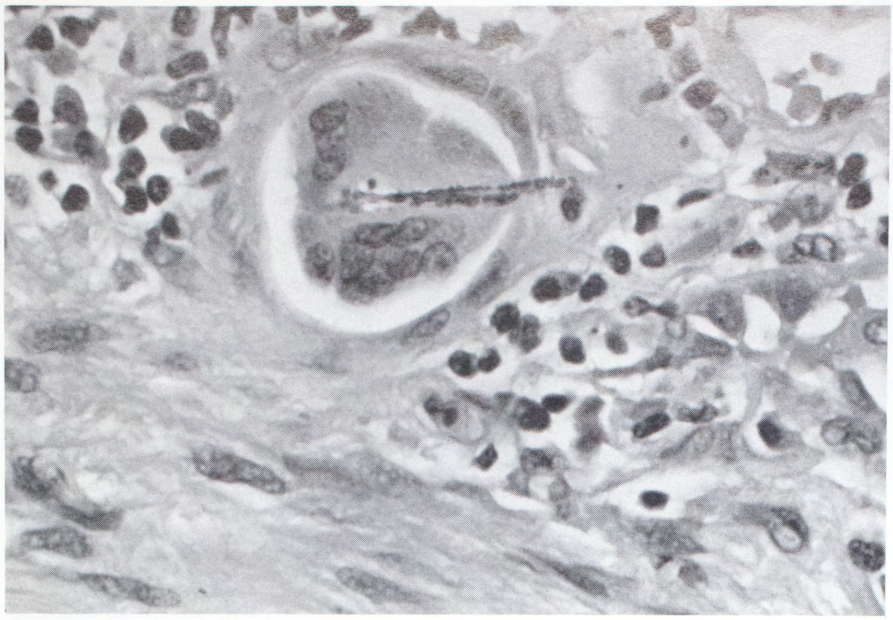

FIGURE 4-13. Transbronchial biopsy of patient with asbestosis reveals a ferruginous body in the center of a multinucleated giant cell. (H & E stain; intermediate magnification.)

pattern, without ruling out the possibility of a bronchogenic adenocarcinoma.

The difference between small cell carcinoma and non-small cell carcinoma of the lung can be established in most cytologic and biopsy materials.[90] However, there is no consensus about what constitutes the standard for the diagnosis of small cell carcinoma. In general, the diagnosis is based on cell size and nuclear features. These findings can be difficult to interpret in borderline situations, such as the intermediate cell variant of small cell carcinoma and certain types of non-small cell undifferentiated carcinomas. Differentiating small cell carcinoma from atypical carcinoid tumors can also be difficult. Small cell carcinomas may be mixed with squamous cell carcinoma, adenocarcinoma, or large cell carcinoma.[90] Immunocytochemical stains and electron microscopy can help in this situation.

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