Chapter 15

THE PROBLEMS WITH CONSTRICTIVE BRONCHIOLITIS: HISTOPATHOLOGICAL AND RADIOLOGICAL PERSPECTIVES

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INTRODUCTION

Much of the focus of pulmonary health issues following deployment of US service members to Iraq and Afghanistan has centered on the diagnosis of constrictive bronchiolitis (CB). This is largely because of the article published in 2011 by King et al[1] that reported that 38 of 49 soldiers who underwent lung biopsy had "changes that were diagnostic of constrictive bronchiolitis." Of those 38 soldiers, 28 (74%) reported a history of exposure to sulfur fires in 2003, for which CB could be an expected sequela. However, in 10 of 38 soldiers (26%), the exposure leading to the development of CB was less clear, although dust storms, burn pits, exposure to human waste, and combat smoke were reported exposures for between 33 of 38 (87%) and 17 of 38 (45%). Twenty-five of the 38 soldiers (66%) were reported to have been lifetime nonsmokers.[1] This chapter provides background information concerning CB, highlighting some of the problems associated with this histopathological diagnosis. The information is presented to place the histopathological diagnosis of CB in context so that it may be neither overemphasized nor underemphasized as an entity associated with the clinical picture of postdeployment respiratory illnesses among US military service members.

HISTOPATHOLOGICAL CLASSIFICATION OF NONNEOPLASTIC LUNG DISEASE

Nonneoplastic lung diseases are generally classified histopathologically by light microscopic observations made from formalin-fixed, paraffin-embedded, routinely stained 3- to 5-μm-thick lung tissue sections mounted on glass slides. Each slide from an open lung biopsy may contain as much as a 2 × 3 cm (essentially two-dimensional) sample that provides a limited, but high (microscopic)-resolution picture of the lung, compared with the virtual three-dimensional images of the entire thorax provided by radiological imaging. Histopathological diagnosis is optimized by correlation with clinical and laboratory data and radiological imaging studies, such as high-resolution computed tomography (HRCT).

Additional tests that can be performed on lung biopsy specimens include histochemical special stains, for example, for the detection of infectious microorganisms; immunohistochemical tests, primarily for immunophenotyping of tumors and viral infections; molecular studies; and, in certain circumstances, chemical analytical studies, such as infrared microspectroscopy and scanning electron microscopy with energy dispersive X-ray analysis. Transmission electron microscopy routinely uses different fixation than formalin, but also has diagnostic utility in rare situations (eg, evaluation of ciliary dyskinesia). Light microscopic evaluation includes addressing the following questions:

- Is the specimen adequate?
- What part(s) of the lung is (are) involved?
- What type of process is present?
- Can the duration of the process be determined?
- How is the process distributed anatomically and chronologically?
- Can additional tests performed on the tissue specimen confirm the cause of the process?

Is the Specimen Adequate?

Clinicians wish to establish a diagnosis quickly and with minimal risk of harm to the patient. Therefore, they strive to perform the least invasive procedure and obtain the smallest amount of tissue that will allow them to attain their diagnostic goals. Unfortunately, the least invasive procedures, primarily transbronchial and percutaneous needle biopsies, rarely obtain a sufficient amount of tissue for the evaluation of nonneoplastic lung diseases, such as CB. In the case of CB, this outcome is primarily because of the patchy distribution of the histopathological lesions within the lungs.[2,3] Therefore, more invasive techniques, such as open lung biopsy or video-assisted thoracoscopic surgery biopsy, are usually required.

What Part(s) of the Lung Is (Are) Involved?

The key task for the pathologist is to determine distribution of disease, which, in nonneoplastic lung disease, frequently requires correlation of chest imaging studies with histopathology. Upper versus lower lobe and central versus peripheral zone distribution of disease in the lung are readily assessed with chest CT (computed tomography). Chest CT is also valuable for determining distribution of abnormalities in the secondary lobule of the lung for correlation with histology. Identifying, histologically, whether a process is distributed specifically to anatomical sites within the secondary lobule (eg, the bronchioles) is critical to understanding the route of injury. The anatomical sites, or compartments, within the secondary lobule include the airways and their paired pulmonary arteries in the centrilobular bronchovascular bundles; the alveolar parenchyma; the veins in the pleura and interlobular septa; and the lymphatics in the bronchovascular bundles, pleura, and interlobular septa.

What Type of Process Is Present?

In nonneoplastic lung disease, this question specifically addresses

- whether there is fibrosis and how it is distributed;
- whether an inflammatory cell infiltrate is present and what constituent cell types are present; and
- whether there are diagnostic/pathognomonic findings, such as asbestos bodies, viral cytopathic effects, or aspirated foreign materials.

Can the Duration of the Process Be Determined?

Pathologists use clues such as the composition of inflammatory cell infiltrates and the presence of fibrosis to determine, in general terms, whether a disease process is acute (of recent onset), subacute (longer onset), or chronic (longstanding). CB is a disease that is usually diagnosed histopathologically after fibrous tissue has been deposited in the walls of bronchioles in a circumferential manner, constricting and obliterating the bronchiolar lumen. Because this process develops over time, it is therefore generally considered to be a chronic process.

How Is the Process Distributed Anatomically and Chronologically?

After the site and duration of a disease process have been determined, ascertaining whether these facets are heterogenous or homogeneous among biopsies from different lung lobes—or even within the same open lung biopsy—can be diagnostically important. For example, a single episode of exposure to an infectious microorganism or toxic fumes may result in lesions of the same type, location, and age, whereas repeated episodes of aspiration pneumonia may show a variety of lesions of different ages.

Can Additional Tests Performed on the Tissue Specimen Confirm the Cause of the Process?

In the field of infectious diseases, there are histochemical stains that can rapidly confirm the presence of fungal, bacterial, and mycobacterial infections, although they cannot speciate microorganisms as a microbiological culture can. Immunohistochemical stains, such as those for cytomegalovirus, can be performed on sections from a biopsy specimen to specifically identify the presence of a microorganism. Histochemical stains, such as Masson's trichrome stain, are useful in highlighting collagen deposition in areas of fibrosis and can be helpful in recognizing the pattern of fibrosis typical of CB. Elastin stains are particularly useful in diagnosing CB because they help to identify residual bronchiolar elastic tissue encircling fibrous scar tissue and to highlight the presence of pulmonary arteries without adjacent patent bronchioles.[4] CB is a pattern of histopathological change that has been associated with a variety of distinctly different causes and clinical scenarios. There is no single specific stain or test for CB, and establishing the diagnosis typically requires examination of several tissue sections from biopsies from more than one lung lobe. In addition, in most cases, the underlying cause of CB is not identified by routine tests that can be performed on the formalin-fixed, paraffin-embedded lung tissue, but rather are determined by correlation with patients' clinical and occupational histories, laboratory findings, and radiological findings.

WHAT IS THE REPERTOIRE OF HISTOLOGICAL RESPONSES OF HUMAN LUNG TISSUE?

The human lung has a limited repertoire of responses to injury. In nonneoplastic lung disease injury, the response is most commonly expressed as variable amounts of fibrosis and inflammatory cell infiltrates. Responses that are more specific, such as sarcoidosis and the granulomas (seen secondary to infection), can help narrow the etiological differential diagnosis. Pathognomonic tissue reactions do occur and are often diagnosed because of the presence of identifiable objects within the lesions of interest (eg, asbestos bodies associated with airway and alveolar wall fibrosis or cytomegalovirus cytopathic changes). Conversely, findings such as asbestos bodies, in the absence of histopathological lesions, are evidence of exposure, but not necessarily of disease causation.

Similarly, both carbon and silicate deposits are common findings in lung tissue from adult, urban-dwelling patients, but the presence of deposits alone does not establish a silicate-related lung disease.

Patterns of lung injury in nonneoplastic lung disease are generally not specific for a single etiology and may be associated with a wide spectrum of both inhalational and noninhalational clinical settings. For example, CB is most commonly seen in lung and bone marrow transplant recipients where it is regarded to be a manifestation of chronic rejection in the former and graft-versus-host disease in the latter.[4] In most of these instances, the histopathology alone does not indicate which of these possible causes is

responsible for the pathological changes seen. It is usually only by correlating the histopathology with clinical, laboratory, and radiological data (and exposure histories where appropriate) that a likely cause can be identified.

It has also been well documented that single materials are capable of eliciting different patterns of histopathological response in lung tissue; inhaled silica (silicon dioxide) is a good example. Fibrotic nodules appearing after prolonged exposure to crystalline silica are seen in silicosis, but a histopathological picture of pulmonary alveolar proteinosis associated with acute silicosis can also develop, usually after heavy exposure to small silica particles over a short time period.[4]

HOW DO PARTICLE SIZE AND COMPOSITION AFFECT THE DISTRIBUTION OF INHALED MATERIALS?

The part of the lung involved is influenced by particle characteristics, including size. In general, particles >10 μm in greatest dimension usually deposit in the upper aerodigestive tract and large airways where they are removed by the mucociliary escalator. In this case, there may be no histopathological response visible on the lung biopsy. Particles 1 to 3 μm in size are small enough to reach respiratory bronchioles and alveoli where they may deposit.[5]

Solubility is among the factors that influence whether irritant gases affect upper/larger airways or peripheral airspaces. Sulfur dioxide, for example, is an irritant gas that is readily soluble in the aqueous milieu of the upper airways, causing inflammatory or corrosive structural changes. Nitrogen oxides, however, are relatively insoluble and tend to injure respiratory bronchioles and alveoli.[5]

WHAT IS CONSTRICTIVE BRONCHIOLITIS?

There is a problem of inconsistency in the terminology that has been used to describe the histopathological lesion referred to as CB. A clear understanding of what is meant by this pathological term is central to much of the debate surrounding respiratory illnesses among previously deployed military service members.

The term bronchiolitis denotes inflammatory injury to the small airways which, by definition, lack cartilage and submucosal glands and have an internal diameter of <2 mm. However, bronchiolitis is often confusing because it encompasses a group of clinically, etiologically, and pathologically divergent lesions.[6] Bronchiolar disorders have historically been difficult to classify; clinical, pathological, and radiological schemes have all been offered. However, classification into primary bronchiolar disorders (eg, CB), interstitial lung diseases with a prominent bronchiolar involvement (eg, hypersensitivity pneumonitis), and bronchiolar involvement in large airway diseases (eg, chronic bronchitis) highlights the necessity of assessing the distribution of disease both radiologically and histologically so that involvement of parts of the lungs other than the small airways is not overlooked, thus resulting in an erroneous diagnosis.[6]

CB is a pattern of injury rather than a specific disease entity and is characterized histologically by circumferential submucosal deposition of fibrous tissue that leads to extrinsic, concentric compression of the airway rather than filling the airway lumen, which may result in obliteration of the bronchiolar lumen.[3,7] Obliteration of the bronchiolar lumen has led some authors to use the term "constrictive bronchiolitis obliterans,"[4] and has led clinicians to use "bronchiolitis obliterans" or "obliterative bronchiolitis" for the same diagnosis.[2] This terminology may be confused with the more common condition of cryptogenic organizing pneumonia (COP), formerly termed bronchiolitis obliterans organizing pneumonia. COP differs from CB in its clinical course, radiological appearance, histological findings, treatment, and more favorable prognosis. In contrast to CB, COP demonstrates plugs of granulation tissue most commonly distributed in airspaces and, to a lesser degree, in the lumens of small airways. Additionally, CB is considered to be a diffuse progressive process resistant to medical treatment, whereas COP is most often patchy and bilateral in distribution and typically responds to steroid therapy.[8]

In practice, mixed histopathological features may be present, and the confidence with which a pathologist can make a diagnosis of CB is influenced by other features that may be present in the biopsy. Peribronchiolar fibrosis and chronic inflammation are not specific findings because they have been noted in many settings; in particular, they are common findings in cigarette smokers[9] and are seen in a minority of cases of chronic pulmonary aspiration.[10]

Pathological diagnosis of CB is generally made when CB is recognized as a predominant pattern rather than merely as a focal feature within other histopathological processes. Pathological changes may be subtle, and, as previously noted, CB can be patchy in distribution. Sampling issues may also lead to underdiagnosis.

CB is a histopathological pattern of injury rather than an etiologically specific diagnosis. The rate at which CB lesions will progress to the point of becoming symptomatic will vary among individuals and among different etiologies. However, the process is progressive and considered to be irreversible.

WHAT ARE THE KNOWN ASSOCIATIONS OF CONSTRICTIVE BRONCHIOLITIS?

Although CB is a relatively rare pulmonary diagnosis, it has been associated with the following:

- organ transplant recipients (bone marrow, heart-lung, and lung);
- autoimmune disease (rheumatoid arthritis, eosinophilic fasciitis, systemic lupus erythematosus, psoriatic arthritis, pemphigus vulgaris, and ulcerative colitis);
- postinfections, mainly in childhood (viral and mycoplasmal);
- inhaled or ingested toxins (nitrous oxides, sulfur dioxide, sulfur mustard**,** ammonia, chlorine, phosgene, and *Sauropus androgynus*);
- drugs (penicillamine and lomustine);
- peripheral carcinoids/neuroendocrine cell hyperplasia; and
- occupations (microwave popcorn manufacturers and possibly fiberglass workers).

Some cases are idiopathic/cryptogenic.[3,8,11–13]

WHAT ARE THE LIMITS OF HISTOPATHOLOGY?

Intra- and interobserver variabilities have been documented for many histopathological diagnoses, and even among experts in specific fields, the rate at which universal diagnostic agreement can be attained is in some instances surprisingly low.[14,15] A study of open lung biopsies for the histological classification of patients with clinical cryptogenic fibrosing alveolitis documented a kappa value of 0.49 between two expert lung pathologists.[16] We are not aware of large studies examining intra- and interobserver variabilities among lung pathologists examining open lung biopsies for the diagnosis of CB. One study reporting poor agreement in the presence of CB in transplant recipients between two lung pathologists was published in 2005, but was based on transbronchial biopsies that are generally considered to be suboptimal specimens for diagnosing CB.[17]

In addition to specimen adequacy, there are (as previously noted) sampling issues that may prevent the recognition of CB. As with histopathology specimens in general, the preservation, fixation, and staining of tissue sections can influence the diagnostic yield.

Even in situations where there is well-documented exposure (ie, to diacetyl in popcorn workers and sulfur mustard exposure during the Iran-Iraq War), expert pulmonary pathologists have made the diagnosis of CB in only approximately 50% of cases or less in open lung biopsies.[18,19] This outcome may be partially explained by a lack of classic morphological findings, but it is also influenced by the presence of other processes that may either obscure or serve as alternative explanations for bronchiolar fibrosis and inflammation.

WHAT IS THE ROLE OF RADIOLOGY?

The utility of functional imaging is based on the seminal work by Hogg et al,[20] demonstrating that small airways with an internal diameter of <2 mm contributed <25% of total airflow resistance.[21] Damage to these peripheral, noncartilagenous airways can be substantial and yet can remain undetected by standard pulmonary function tests because of the relatively high resistance to airflow normally presented by the central bronchi.

Typical findings of CB on HRCT cross-sectional imaging include large airway thickening and multilobular regions of decreased lung attenuation.[6,22,23] This lobular pattern of alternating high and low attenuation has been termed either "mosaic attenuation" or "mosaic perfusion" (Figure 15-1). The extent of decreased lung attenuation on expiratory HRCT, obtained with the patient at residual volume, has the strongest correlation with physiological tests of small airway function.[23] Mosaic attenuation on expiratory CT is a consistent finding in patients with both dyspnea and a clinical diagnosis of CB. A substantial minority of these patients (approximately 15%) will not demonstrate obstruction on the pulmonary function test.[24] As such, screening with expiratory HRCT provides the most sensitive and easily obtained objective indicator of small airway disease.[6]

A number of areas related to the accuracy of expiratory HRCT will require further clarification. It is important to confirm that a normal expiratory HRCT precludes the diagnosis of CB. Although highly sensitive to the presence of small airway dysfunction, the exact correlation between findings of expiratory mosaic attenuation on imaging and pathological specimens is unknown because the majority of patients who carry the clinical diagnosis of CB are not subjected to open lung biopsy.[6] It is also important to recognize that minimal change of lobular mosaic attenuation can be identified in apparently normal individuals.[25,26]

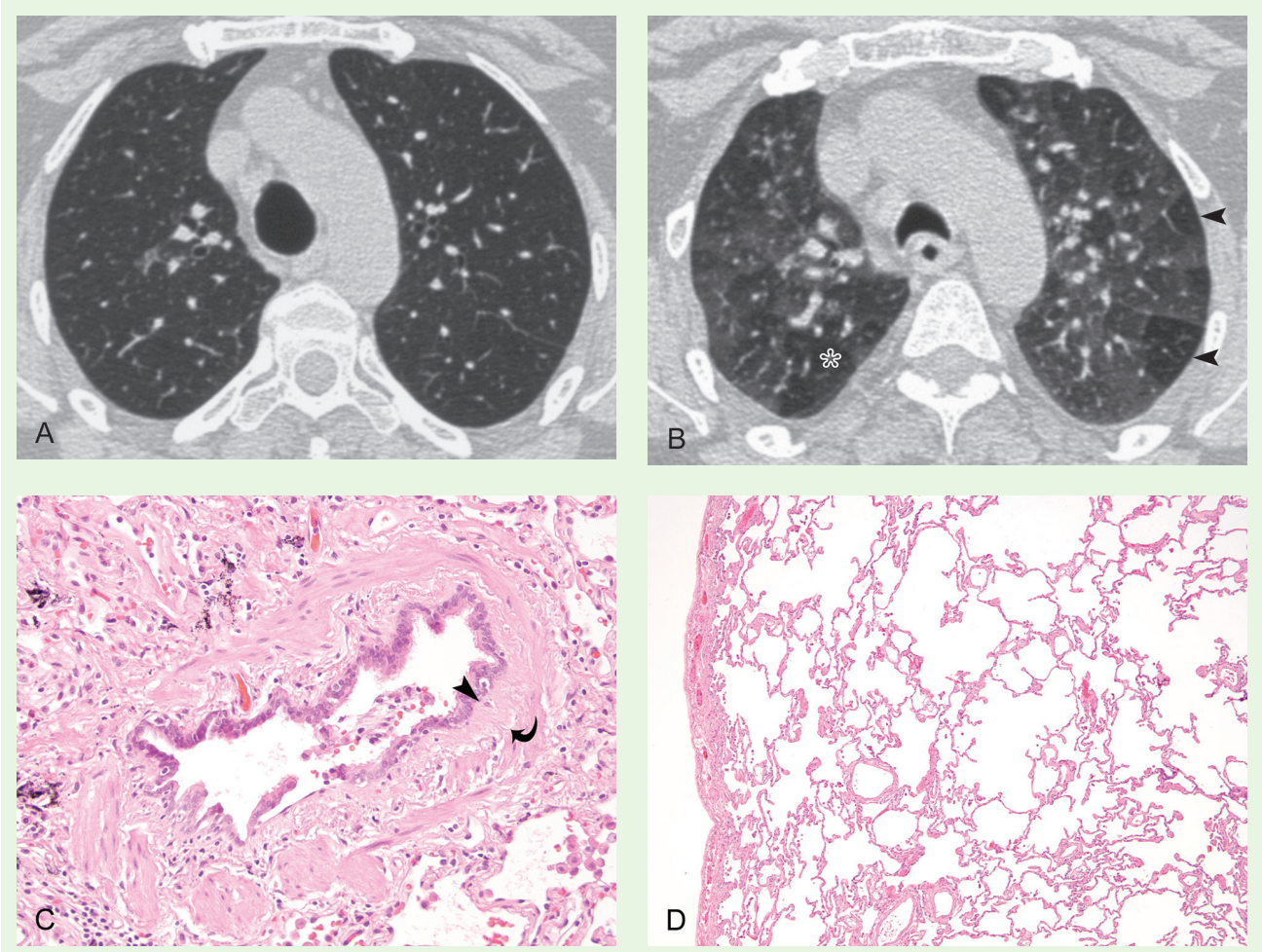

Figure 15-1. Mosaic attenuation. This 38-year-old female with dyspnea on exertion and normal pulmonary functions demonstrates normal lung parenchyma on this axial high-resolution computed tomographic image (**A**) acquired through the upper lobes at full inspiration. The expiratory phase image (**B**) at the same level demonstrates multiple, lobular (*arrowheads*), and larger (*asterisk*) regions of low attenuation consistent with air-trapping. In the same patient, the open lung biopsy demonstrates a prominent layer of fibrous tissue (**C**) between the bronchiolar epithelium (*arrowhead*) and the smooth muscle layer (*curved arrow*); normally, the bronchiolar epithelium rests directly on the smooth muscle layer. Airway fibrosis in constrictive bronchiolitis is typically present in a background of essentially normal lung parenchyma (**D**).

WHAT OTHER INFLUENCES IMPACT THE DIAGNOSIS OF CONSTRICTIVE BRONCHIOLITIS?

In as much as the timing of biopsy is influenced by clinical suspicion of CB, documentation of exposure history is likely to influence the rate at which CB is detected pathologically. The deployment history of military patients, occupational history, and inclusion in groups exposed to known hazards—such as the 2003 Mishraq Sulfur Mine fire—are factors that may lead to greater clinical suspicion of CB and, if supported by additional findings, greater likelihood of lung biopsy.

In the study by King et al,[1] reduced performance in physical fitness tests was a principal presenting feature of the patients studied. In a relatively young military population that includes individuals who have undergone medical screening upon joining the military and who are more physically fit than age- and gender-matched members of the general US population, one might expect to see the "healthy warrior effect." This phenomenon is considered to confer lower incidences of many medical conditions on the active duty military population than the general US population. Military personnel may also be reluctant to present with respiratory symptoms for fear of being prevented from remaining in their current military occupational specialty.

The impact of cigarette smoking on the interpretation of lung biopsies cannot be overemphasized. The US military still includes a relatively high number of tobacco smokers, with more smoking reported among the deployed.[27–29] The group of patients reported by King et al[1] to have CB had a relatively high reported proportion of lifelong nonsmokers for a previously deployed US military population.

Another issue that influences assessment of pulmonary function is body mass index. The diagnosis of overweight/obesity tripled in the active component of the US armed forces between 1998 to 2010.[30] Reduced performance in respiratory function testing has been associated with increases in body mass index and age.[31] Age is inevitably a factor not only in the histopathological diagnosis of CB, but also in clinical assessment parameters.

The impacts of other clinical findings are also likely to influence the ability of pathologists to diagnose CB. In particular, gastrointestinal reflux disease can lead to CB through aspiration of gastric contents and has been particularly associated with postlung transplant bronchiolitis obliterans syndrome.[32] Upper airway lesions, including laryngeal dysfunction, may also lead to aspiration and fibrosis.

SUMMARY

CB is a pattern of histopathological findings that have been associated with a wide variety of clinical scenarios. A rare diagnosis associated with specific inhaled toxic exposures, CB is not likely to be present in a large population of deployed veterans, but is possible in subgroups (eg, specific units or occupational groups). The histopathological diagnosis of CB should be reserved for cases with recognizable and broadly accepted pathological features to retain the utility of this diagnosis and preclude overdiagnosing CB as a focal finding in the presence of other lung pathology. Clinically, in the absence of objective findings, such as changes in pulmonary function tests and abnormal expiratory phase HRCT, it is difficult to classify patients as candidates for invasive open lung biopsies as the next step in their diagnostic evaluation. In the large military population with prior deployment histories to Iraq and Afghanistan, it is likely that a spectrum of pulmonary pathology will arise, as with any large population followed over time. However, CB described in a small cohort with a large proportion of patients who reported to have been exposed to the 2003 Mishraq Sulfur Mine fire is not likely to comprise such a large proportion of the pulmonary disease burden of the entire deployed military cohort. Although it is important for pathologists to recognize CB, it is equally important that they do not underdiagnose other (treatable) conditions among active duty military service members and retirees who were previously deployed to Iraq and Afghanistan.

REFERENCES

1. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med*. 2011;365:22–30.

2. Epler GR. Diagnosis and treatment of constrictive bronchiolitis. *F1000 Med Rep*. 2010;2:ii, 32.

3. Schlesinger C, Meyer CA, Veeraraghavan S, Koss MN. Constrictive (obliterative) bronchiolitis: diagnosis, etiology, and a critical review of the literature. *Ann Diagn Pathol*. 1998;2:321–334.

4. Katzenstein A-LA. *Katzenstein and Askin's Surgical Pathology of Non-neoplastic Lung Disease; Major Problems in Pathology*. 4th ed. Philadelphia, PA: Saunders Elsevier; 2006: 459–461.

5. Ziskind MM. Occupational pulmonary disease. *CIBA Clin Symp*. 1978;30:1–32.

6. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med*. 2003;168:1277–1292.

7. Myers JL, Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. *Clin Chest Med*. 1993;14:611–622.

8. Visscher DW, Myers JL. Bronchiolitis: the pathologist's perspective. *Proc Am Thorac Soc*. 2006;3:41–47.

9. Adesina AM, Vallyathan V, McQuillen EN, et al. Bronchiolar inflammation and fibrosis associated with smoking. A morphologic cross-sectional population analysis. *Am Rev Respir Dis*. 1991;143:144–149.

10. Mukhopadhyay S, Katzenstein AL. Pulmonary disease due to aspiration of food and other particulate matter: a clinicopathologic study of 59 cases diagnosed on biopsy or resection specimens. *Am J Surg Pathol.* 2007;31:752–759.

11. Kreiss K, Gomaa A, Kullman G, et al. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med*. 2002;347:330–338.

12. Rowell M, Kehe K, Balszuweit F, Thiermann H. The chronic effects of sulfur mustard exposure. *Toxicology*. 2009;263:9–11.

13. Cullinan P, McGavin CR, Kreiss K, et al. Obliterative bronchiolitis in fiberglass workers: a new occupational disease? *Occup Environ Med*. 2013;70:357–359.

14. Rosai J. Borderline epithelial lesions of the breast. *Am J Surg Pathol.* 1991;15:209–221.

15. Jain RK, Mehta R, Dimitrov R, et al. Atypical ductal hyperplasia: interobserver and intraobserver variability. *Mod Pathol*. 2011;24:917–923.

16. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med.* 2000;162:2213–2217.

17. Stephenson A, Flint J, English J, et al. Interpretation of transbronchial lung biopsies from lung transplant recipients: inter- and intraobserver agreement. *Can Respir J*. 2005;12:75–77.

18. Akpinar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J.* 2004;24:298–302.

19. Ghanei M, Tazelaar HD, Chilosi M, et al. An international collaborative pathology study of surgical lung biopsies from mustard gas-exposed patients. *Respir Med*. 2008;102:825–830.

20. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med*. 1968;278:1355–1360.

21. Macklem PT. The physiology of small airways. *Am J Respir Crit Care Med*. 1998;157(5 Pt 2):S181–S183.

22. Desai SR, Hansell DM. Small airways disease: expiratory computed tomography comes of age. *Clin Radiol.* 1997;52:332–337.

23. Hansell DM, Rubens MB, Padley SP, Wells AU. Obliterative bronchiolitis: individual CT signs of small airways disease and functional correlation. *Radiology.* 1997;203:721–726.

24. Parambil JG, Yi ES, Ryu JH. Obstructive bronchiolar disease identified by CT in the non-transplant population: analysis of 29 consecutive cases. *Respirology.* 2008;14:443–448.

25. Stern EJ, Webb WR. Dynamic imaging of lung morphology with ultrafast high-resolution computed tomography. *J Thoracic Imaging.* 1993;8:273–282.

26. Webb WR, Stern EJ, Kanth N, Gamsu G. Dynamic pulmonary CT: findings in healthy adult men. *Radiology.* 1993;186:117–124.

27. Ornelas S, Benne PD, Rosenkranz RR. Tobacco use at Fort Riley: a study of the prevalence of tobacco use among active duty soldiers assigned to Fort Riley, Kansas. *Mil Med*. 2012;177:780–785.

28. Smith B, Ryan MA, Wingard DL, et al. Cigarette smoking and military deployment: a prospective evaluation. *Am J Prev Med*. 2008;35:539–546.

29. Talcott GW, Cigrang J, Sherrill-Mittleman D, et al. Tobacco use during military deployment. *Nicotine Tob Res.* 2013;15:1348–1354.

30. US Armed Forces Health Surveillance Center. Diagnosis of overweight/obesity, active component, U.S. Armed Forces, 1998–2010. *MSMR.* 2011;18:7–11.

31. Thyagarajan B, Jacobs DR Jr, Apostol GG, et al. Longitudinal association of body mass index with lung function: the CARDIA study. *Respir Res*. 2008;9:31.

32. Morehead RS. Gastro-oesophageal reflux disease and non-asthma lung disease. *Eur Respir Rev*. 2009;18:233–243.