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Review article

Pathology of pulmonary tuberculosis and non-tuberculous mycobacterial lung disease: Facts, misconceptions, and practical tips for pathologists

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ABSTRACT

Most pathologists are familiar with the microscopic features of tuberculosis and the need to examine special stains for acid-fast bacteria (AFB) in cases of granulomatous lung disease. However, misconceptions do exist, including the concept that finding AFB in "caseating granulomas" confirms the diagnosis of tuberculosis. This dogma is attributable to the high prevalence of tuberculosis in many countries, as well as unfamiliarity with the microscopic spectrum of non-tuberculous mycobacterial lung disease. This review aims to provide surgical pathologists with practical tips to identify AFB, illustrate the histologic overlap between pulmonary tuberculosis and non-tuberculous mycobacterial lung disease, and highlight the importance of cultures in this setting. *M. tuberculosis* and non-tuberculous mycobacteria cannot be reliably differentiated either on the basis of the tissue reaction or by bacterial morphology on acid-fast stains. Although a presumptive clinical diagnosis of tuberculosis can be made without culture-confirmation, the only definitive means to determine the true identity of AFB is by cultures or molecular methods. Making this distinction is most critical when AFB are found in incidentally detected lung nodules in geographic locations where the incidence of tuberculosis is low, because in such settings AFB in necrotizing granulomas of the lung are more likely to be non-tuberculous mycobacteria than *M. tuberculosis*.

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Introduction

Most reviews of mycobacterial lung disease address clinical concerns, and are written from the viewpoint of clinicians. Surgical pathologists enter the diagnostic workflow of mycobacterial lung disease in unique ways, and the issues they face are quite distinct from those encountered by clinicians. Challenges specific to pathologists include: when to suspect that the pathologic findings in a lung specimen might be caused by mycobacterial disease, when to order special stains, which stains to order, how to optimize the search for acid-fast bacteria (AFB), and how to determine whether AFBs in a lung biopsy or resection specimen represent tuberculosis or non-tuberculous mycobacterial (NTM) disease. The goal of this review is to provide practical pointers to pathologists (mainly surgical pathologists/histopathologists) regarding these issues. We also hope to dispel common misconceptions regarding the pathologic features of these diseases.

The two major forms of mycobacterial lung disease are tuberculosis and NTM lung disease. The latter is increasingly recognized as a cause of clinically significant pulmonary infection.[1] The increased clinical recognition of NTM lung disease is slowly but surely being reflected in pathology practice. In a recent international, multicenter study of 500 cases of granulomatous lung disease diagnosed on lung biopsies or resections, NTM lung disease significantly outnumbered tuberculosis in cases contributed from centers in the United States. Specifically, only 1 case (out of 200) in the United States proved to be culture-confirmed tuberculosis, while 13 cases were confirmed by cultures to be NTM lung disease.[2]

NTM lung disease is most commonly caused by *Mycobacterium avium* complex (MAC), formerly known as *M. avium-intracellulare* (MAI). Terms such as “atypical mycobacteria” and “mycobacteria other than tuberculosis” (MOTT) have also been used for these organisms in the past. Other NTM such as *M. kansasii*, *M. fortuitum*, *M. chelonae*, *M. abscessus*, *M. gordonae* and *M. xenopi* can also cause lung disease, but they are far less common than MAC. This review will focus solely on lung infections caused by these organisms, and will not address hypersensitivity phenomena such as hot tub lung.[3,4]

Diagnosis of tuberculosis: are lung biopsies required?

When a diagnosis of pulmonary tuberculosis is entertained clinically, the standard diagnostic approach does not require a lung biopsy. In most cases, the diagnosis is based on a combination of epidemiology, exposure history, symptoms and radiologic findings, ideally supplemented by microscopy of sputum smears stained with an acid-fast stain.[5–8] If possible, the presence of *M. tuberculosis* should be confirmed by microbiologic cultures or nucleic acid amplification testing (NAAT). In many low-resource settings, however, the diagnosis is made without bacteriologic confirmation. The tuberculin skin test (TST) and interferon-γ release assays (IGRA) are useful for the diagnosis of latent tuberculosis.[5,6,8]

In this diagnostic sequence, lung biopsies are seldom indicated unless non-invasive modalities fail to provide a diagnosis,[9] or the clinical setting is atypical, or if rapid diagnosis is essential. Lung biopsies are commonly performed in the evaluation of individuals with lung nodules or masses, since such lesions often raise the possibility of other granulomatous infections or lung cancer (Figs. 1 and 2). In such cases, the identification of granulomas containing AFB is of great value, because it not only excludes malignancy but also re-directs the clinical focus to the evaluation of a specific type of infection. Transbronchial biopsies are particularly useful in the evaluation of suspected miliary tuberculosis,[10] endobronchial biopsies have a high yield in endobronchial tuberculosis,[11] and core needle biopsies are useful for peripheral lung nodules.[12] Necrotizing granulomas are the most common benign finding in core needle biopsies, and mycobacteria can be demonstrated in a subset of these cases.[12,13]

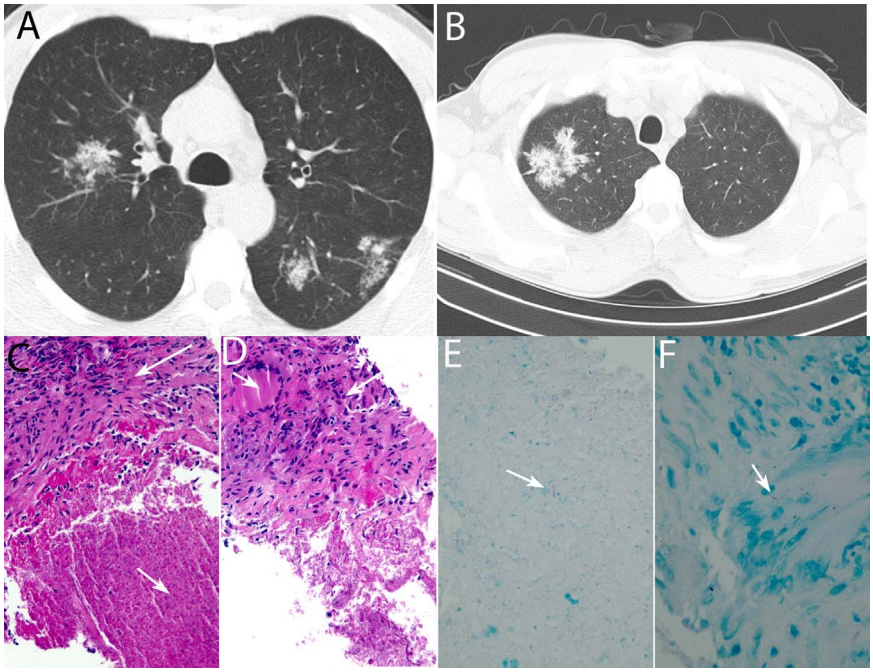

Fig. 1. - Tuberculosis. This 38-year-old Romanian man was found to have abnormal chest imaging after presenting with non-specific musculoskeletal pain. Two TB QuantiFERON tests were negative. A. Axial CT image through the upper lung zones shows coalescence/confluence of multiple tiny clustered centrilobular nodules in the right upper lobe and left lower lobe superior segment. B. Axial CT image through the lung apices shows irregular, mass-like peribronchial consolidation in the right lung apex. C, D. Core needle biopsy of one of the left-sided nodules, showing necrotizing granulomatous inflammation (C, long arrow: granulomatous inflammation, short arrow: necrosis. D, arrow: Langhans-type giant cell). E, F. Ziehl-Neelsen stain, same case. (E, arrow: AFB in necrosis; F, arrow: AFB within a giant cell). PCR for mycobacteria on formalin-fixed paraffin embedded tissue was negative. After the biopsy the patient underwent bronchoalveolar lavage which yielded *M. tuberculosis* on cultures.

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