Pathology of infectious diseases of the lower respiratory system

Michael A den Bakker

Abstract

Specific texts on infectious diseases and those in textbooks on pulmonary pathology commonly approach the subject of infection in the lung from an etiological microbiological perspective, listing infectious agents by taxonomy followed by associated pathology. However, in practice one is faced with a specimen in which a reaction pattern is seen (usually of inflammatory nature) which may be indicative of a specific type of infection. In these circumstances an approach leading from *reaction pattern* to *specific microbiological* diagnosis is required. This approach will form the basis of this review. General aspects are covered without exhaustive discussion of specific microbiology. For more detailed discussion of specific entities the reader is referred to the excellent textbooks on pulmonary pathology and those on pathology of infectious diseases. The reaction patterns described here are combinations of gross pathology and cellular reactions. The breakdown of these patterns is somewhat arbitrary and artificial. In many cases the pattern will not be absolutely typical and many overlapping features will be present in individual cases.

Keywords Differential diagnosis; histopathology; infection; pulmonary

Introduction

Infections of the lower respiratory tract are extremely common and world-wide are the third leading cause of death, a statistic which is unlikely to change significantly in the next decades. Of all fatal infections, those of the lower respiratory tract are by far the most common and including tuberculosis, account for over half of all infectious deaths world-wide. Many respiratory infections are self-limited and do not require specific medical care. More severe respiratory infections may come to medical attention and are commonly treated empirically with antibiotics, not requiring a specific (microbiological) diagnosis. More extensive analysis may be required in patients with impaired immunity or for patients with a history of travel to destinations in which unusual pathogens are prevalent. Histology is not a typical first-line investigative modality employed in diagnosing respiratory tract infection. However, in some circumstances histology may provide the final diagnosis, because of superior sensitivity, or may provide the fastest route to establish a diagnosis. Furthermore, on occasion infections form tumorous masses with a preoperative diagnosis of neoplasia which are resected and submitted for histology.

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Diagnosing infection through histology can be broadly simplified to two aspects which are commonly combined in one diagnostic process. First, a specific infectious agent may be identified in a sample, or alternatively a specific tissue reaction may be recognized which is highly suggestive of infection, prompting further searching for a specific causative agent (Table 1). Factors which must be taken into account when attempting to diagnose infection through reaction patterns on tissue samples are the integrity of the patients' immune system, the duration of disease before tissue samples were obtained, travel history, co-morbidity and treatment that may already have been given. The usual tissue reaction may be severely influenced by these factors (Figure 1).

Pathological diagnosis

The standard haematoxylin and eosin (HE) stain is sufficient for evaluating the tissue reaction pattern. However, identifying specific micro-organisms (MOs) may require special techniques.

Histological special stains

Classical histochemical stains, such as Gram, Ziehl–Neelsen (ZN) and Grocott–Gomori's methenamine silver stain (GMS), are performed routinely to identify MOs in tissue sections. However, it should be borne in mind that many of these stains were developed for use on direct preparations, such as secretions and are less sensitive when applied to fixed tissue samples. Moreover, the application of several of these stains, in particular those using silver impregnation or decolourization steps, requires optimal histotechnology and familiarity of the staining reaction to be of diagnostic use.[1]

Immunohistochemistry

Antibodies to an increasing number of pathogens are available. However, apart from a limited number of regularly encountered MOs for which immunohistochemical identification may be justified (for instance *Cytomegalovirus*, *Pneumocystis jiroveci*) stocking a battery of rarely used reagents is not efficient.

Nucleic acid based techniques

In situ hybridization offers the advantage of direct visualization of infectious organisms in a tissue background. Although generally considered more sensitive than immunohistochemistry, routine use is fairly limited and few commercial probes are available. PCR amplification of nucleic acid targets of MOs is, at least theoretically, the most sensitive technique to detect an MOs. The inherent sensitivity is also its main drawback; false positives and contaminations are realistic pitfalls.

Reaction patterns

Acute granulocytic – neutrophilic (pyogenic, suppurative) tissue reaction: this pattern is the most common infectious disease reaction pattern encountered in the lung and may be caused by various MOs; by far the most common of these are bacteria (Table 2). Histology of pneumonia with an acute neutrophilic tissue reaction, in which a viral cause is suspected by serology or other means, will, with rare exceptions, have been complicated by secondary bacterial infection. Lung tissue is seldom submitted for histology to diagnose acute pneumonia. Recognition of this

Reaction patterns

Pattern	Typical micro-organism	Pattern in immunosuppressed
• Acute — neutrophilic (pyogenic) inflammation	Bacteria	Neutrophilic dysfunction, change to granulomatous pattern
○ Bronchocentric — Lobular (bronchopneumonia)	Bacteria	More frequently necrotizing
○ Confluent — Lobar (confluent)	Bacteria	
○ Abscess	Bacteria	
○ Necrotizing	Bacteria, virus, fungus	More common
• Diffuse alveolar damage	Virus	No change
• Fibrosing (chronic pneumonia)	Bacteria	Unknown
• Nodular	Fungi, mycobacteria, parasites	Mycobacterial: less cavitation, severe deficiency: no granuloma formation. Fungi: more frequently necrotizing; may be reduced tissue reaction, increased number of MOs
• Cystic	Parasites	No change
• Pseudotumour	Mycobacteria	Typical in severely immunosuppressed
• Specific cell type reaction pattern		
○ Cytopathic changes	Virus	More frequently necrotizing, otherwise similar
○ Eosinophilic inflammation	Parasites (Helminths)	No change; increased severity
○ Histiocytic	Bacterial	
○ Lymphocytic inflammation	Virus	No change
• Others		
Exudative (PCP)	*Pneumocystis jiroveci*	No — change; no reaction in severe immunosuppression
Vascular proliferation (bacillary angiomatosis)	*Bartonella rochalimae*	Typical in immunosuppression
Non-reactive		Typical in severe immunosuppression

Table 1

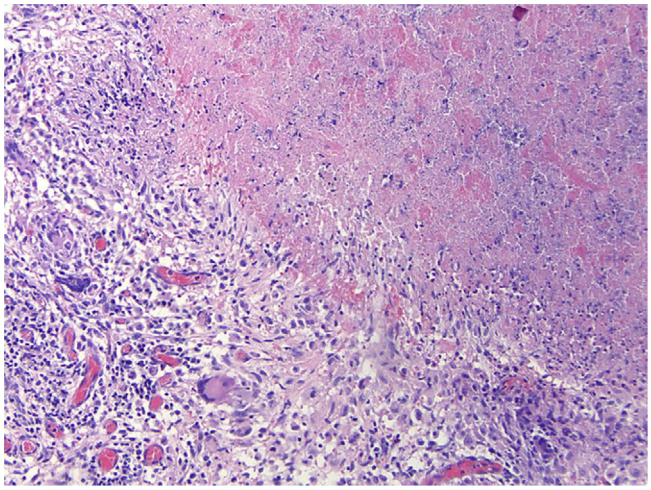

Figure 1 Necrotizing granulomatous inflammation in chronic granulomatous disease (CGD). Pyogenic bacteria, which ordinarily induce a neutrophilic inflammatory response, were cultured from this specimen. CGD is caused by defects in granulocytes which fail to produce an oxidative burst, important in killing pyogenic bacteria.

reaction pattern is straightforward with a neutrophilic infiltrate (variably admixed with other cell types) in the lung parenchyma. Morphological variations of this pattern are well established and depend on the virulence of the causative organism, the integrity of the host's immunity and effects of treatment. Classical morphological patterns of acute pneumonia are lobular pneumonia (bronchopneumonia) and lobar (or diffuse) pneumonia.

Bronchopneumonia is acute neutrophilic inflammation centred on the airway conductive components of the lung with spillover into adjacent lung parenchyma. This type of pneumonia commonly follows previous damage to the airway, which may have been induced by any form of preceding mild airway damage such as inflammation, immunosuppression or debilitation. Primary acute inflammation of the conductive airways (bronchitis and bronchiolitis) soon extends to the parenchyma proper, with a neutrophilic infiltrate filling alveoli, the defining feature of this reaction pattern. Patchy consolidated firm lung tissue is the macroscopic correlate; the parenchyma breaks up easily when pressed, in contrast to spongy normal lung tissue, and pus may be expelled from the tissue. Clearance of the offending MO leads to restoration of the pulmonary architecture through a fibrotic stage in which granulation tissue is formed within air spaces (organizing pneumonia). Scarring may result with loss of lung capacity. However, progression of the inflammation and infection may result in confluent areas of involved lung tissue, leading to a pattern of lobar pneumonia.

Lobar pneumonia is a classical pneumonia pattern, which in its complete form is currently seldom seen. The sequential, macroscopically recognized stages (congestion, red hepatization, grey hepatization and resolution), which were initially described