Recent Advances in
Histopathology 24

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It is with pleasure that I introduce volume 24 of *Recent Advances in Histopathology*.

The publication of the human genome sequence in 2001, and the technological advances that made it feasible and that have developed as a consequence of this milestone, have already impacted many areas of diagnostic histopathology, none more so than in cancer. The pathologist is no longer solely reliant on microscopic features for the classification of a disease, and can now provide more robust diagnoses by complementing a histological phenotype with molecular profiles. The spectrum of morphological features that have long been appreciated by pathologists can now be explained through DNA sequencing, opening up new avenues of research.

A number of chapters in this book capture the transformational changes that are occurring in our discipline, and will therefore be of interest to the pathologist, the generalist, the specialist who wishes to remain abreast of recent changes in the field, and those preparing for their postgraduate exams. There are also two chapters covering postmortem pathology, which demonstrate how the study of the cause of death remains a much needed and valuable resource.

If the technological advances in biomedical science that have taken place over the last two decades are to be exploited effectively, change is required in medical education. It was with this in mind that Professor Davinder Sandhu was commissioned to provide a comprehensive overview of postgraduate education in the UK.

I wish to thank all of the contributors who kindly gave up their time, and I am grateful to Steffan Clements, the commissioning editor, for his support throughout the project.

Adrienne Flanagan
August 2016
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INTRODUCTION

The term acute lung injury (ALI) means different things to different specialist groups. In respiratory medicine and intensive care, ALI is part of a clinical spectrum of lung injury up to and including the adult respiratory distress syndrome (ARDS). This was defined in 1994 by a joint American and European Consensus Conference [1] as a condition with acute onset, bilateral pulmonary infiltrates on chest X-ray/CT, impaired oxygenation and the absence of left atrial hypertension. Oxygenation was assessed as the ratio between $P_{\text{ao}2}$ (the partial pressure of oxygen in arterial blood) and $F_{\text{io}2}$ (the fraction of oxygen in the inspired air), and in a clinical setting a ratio of <300 mmHg was consistent with a diagnosis of ARDS, while less severe injury with a ratio of <200 mmHg was termed ALI. In 2012, a revision of this was published by the ARDS Definition Task Force [2]. This defined ARDS as having onset within 1 week of a clinical insult, bilateral radiological opacities and an objective demonstration that lung oedema was not hydrostatic in nature. They divided cases into mild, moderate or severe ARDS on the basis of the $P_{\text{ao}2}/F_{\text{io}2}$ ratio with the term ALI no longer being used.

In the pathology literature, the term ‘acute lung injury’ was also put forward by Katzenstein to describe inflammatory/fibroblastic processes in lungs that are felt to be of acute onset with temporal homogeneity, usually characterised by loose oedematous ‘granulation tissue’ like stroma reflecting response to an insult occurring at one point in time [3]. The aim was to differentiate these conditions from the chronic interstitial pneumonias that had a longer time course and showed mature fibrosis. This pathological definition is broader than the clinical definition and includes a range of patterns of lung remodelling including diffuse alveolar damage syndrome (DADS) as seen in patients with ALI/ARDS, as well as some other patterns of lung injury such as cryptogenic organising pneumonia (COP) and eosinophilic pneumonia. In addition, the recent American Thoracic Society/European Respiratory Society consensus statement on the classification of idiopathic interstitial pneumonias has suggested that the clinical term ‘acute interstitial pneumonitis’ (AIP) should be adopted in cases of idiopathic lung injury with a DADS pattern on histology [4] adding yet another layer to the terminology.

This chapter will focus on the pathology of the clinical syndrome of ALI/ARDS looking at the aetiology, the pathological features and the pathogenesis, as currently understood. The potential issues to be considered, difficulties and differential diagnoses that may be...
encountered when these patients undergo lung biopsy for histological evaluation or come to autopsy will then be discussed.

**AETIOLOGY**

ALI/ARDS may be idiopathic (AIP) or arise in the context of a wide range of primary pulmonary conditions as well as representing a complication of numerous extra-pulmonary insults [5] (Table 1.1). Although subtle differences exist between cases associated with pulmonary and non-pulmonary causes [6], the pathological features, at least at the level we currently understand them, are sufficiently uniform that this can be regarded as a stereotypical pattern of lung injury. What is very clear, however, is the importance of both pulmonary and systemic sepsis as a trigger. Clinical studies have indicated that this is the pre-eminent risk factor and prompt and early recognition of this is essential in reducing the incidence of ALI/ARDS [7].

It is, however, important to acknowledge that the development of ALI/ARDS is not inevitable, even in patients with recognised risk factors, suggesting that there are 'host factors' that predispose some patients to develop the syndrome. This has led to searches for genetic factors and biomarkers that predict both susceptibility and severity of lung injury [8,9]. It is also becoming increasingly recognised that DADS can present as an acute exacerbation with respiratory failure on a background of idiopathic pulmonary fibrosis/ usual interstitial pneumonitis (IPF/UIP) [10].

**THE HISTOLOGICAL FEATURES OF ALI/ARDS**

The pathological pattern of lung abnormality encountered in patients with ALI/ARDS is termed DADS [11–13]. Traditionally, this is divided into three phases, but it is important

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ALI/ARDS can be associated with a wide range of pulmonary and non-pulmonary conditions. It is important, however, to realise that it may be a rare complication in many of these situations suggesting that other contributing factors, including host factors, may be important in the development of lung injury. In some instances, similar clinical features with pathological evidence of diffuse alveolar damage syndrome may be seen that appears idiopathic. In this instance, the clinical term ‘acute interstitial pneumonitis’ (AIP) is preferred.

Reprinted with permission from Hasleton et al [11].
to recognise that these represent a continuous process rather than distinct steps. The early events comprise an ‘exudative’ phase that is followed by a ‘proliferative’ phase. In some patients, this is followed by resolution of the fibroproliferative process with the lung architecture returning to normal or near normal but in many patients the process is progressive with the development of fibrosis. As would be expected each ‘phase’ is complex and our understanding in many ways remains limited but as will be discussed later, we are gaining some understanding of the cellular and inflammatory mediators involved.

Exudative phase

In the early stage of the exudative phase, the lungs appear macroscopically normal but as the process develops the lungs become oedematous. Autopsy examination of patients dying at this stage characteristically show lungs that are heavy (>1 kg) with a red, beefy appearance, and are firm on palpation (Figure 1.1). The earliest changes are not seen by light microscopy but electron microscopic studies demonstrate necrosis of type I alveolar epithelial cells with a denuded basement membrane, increased numbers of marginated neutrophils in the alveolar capillaries with, in some cases, fibrin thrombi and interstitial oedema.

Two to three days from the onset of injury, oedema becomes apparent at the light microscopic level. This exudative oedema fluid, often with associated haemorrhage, is rich in fibrin and fills the alveolar spaces becoming mixed with necrotic debris. The fibrin condenses to form the characteristic histological feature of the exudative phase - a hyaline membrane (Figure 1.2). Initially, these may be relatively localised but as the injury develops they become more widely seen. The hyaline membranes appear on haematoxylin and eosin staining as intensely eosinophilic bands of proteinaceous material lining the alveolar airspaces and ducts. Significant numbers of inflammatory cells within the interstitium or alveolar spaces are not a conspicuous feature although neutrophils are believed to have a critical role in the pathogenesis of ALI/ARDS. In cases where significant numbers of neutrophils are evident, particularly in the alveolar spaces associated with fibrinous exudates, the possibility of pneumonia needs to be considered recognising that both can coexist.

Figure 1.1  Macroscopic appearance of a fixed lung slice demonstrating the appearance of the lung in the exudative phase of diffuse alveolar damage syndrome. The cut surface of the lung is red, congested and firm. The process is generally diffuse but in some cases can be more localised. By courtesy of Prof DB Fleider, Philadelphia, USA. Reprinted with permission from Hasleton et al [11].
Pathology of acute lung injury

Proliferative phase
Histological features in keeping with the development of the proliferative phase are usually seen 5–7 days from the onset of lung injury. Macroscopically the lungs remain heavy but show a grey, consolidated firm appearance (Figure 1.3). The characteristic feature of the proliferative phase is the progression to organisation of the exudate. Ultrastructural studies have demonstrated that the basement membrane is further disrupted. Myofibroblasts proliferate both within the interstitium and also migrate through the breaks in the basement membrane into the exudates, giving rise to the development of granulation tissue within alveolar spaces and ducts (Figure 1.4). In the early stages, this may be patchy in its distribution and coexist with persisting hyaline membranes in keeping with the concept that this is an evolving process. The organisation of the luminal exudates is accompanied by prominent proliferation of type II alveolar cells along the alveolar walls. These have a cuboidal, 'hob-nail' appearance and may show significant cytological atypia with pleomorphic nuclei and large punctuate nucleoli.

Fibrotic phase
In most cases, the proliferative stage is followed by organisation with progressive interstitial fibrosis, collapse of the alveolar architecture and distortion of the lung architecture. Examination of the lungs at autopsy from patients with DADS who survive several weeks following onset of ALI/ARDS can show various patterns of established fibrosis. In some cases, the lungs may show extensive sheets of fibrosis, occasionally with honeycombing. Other areas of fibrosis may be more nodular with entrapped cleft-like spaces lined by alveolar epithelial cells, while in some instances a more diffuse, less destructive pattern of alveolar wall thickening that resembles fibrotic nonspecific interstitial pneumonitis may be apparent. It is important to realise that different patterns may be observed in sections taken from different areas of the same lung. In cases with prominent honeycomb or subpleural fibrosis, the possibility that this represents DADS superimposed on a background of IPF needs to be considered (see below). In addition to the fibrosis, there is often evidence of extensive squamous metaplasia, secondary inflammatory changes and evidence of

Figure 1.2  Histologically the exudative phase is characterised by the presence of hyaline membranes. These are dense eosinophilic bands that line the alveolar space and represent condensed proteinaceous fluid. Small numbers of neutrophils and other inflammatory cells may be seen but if large numbers are present the possibility of pneumonia should be considered. Reprinted with permission from Hasleton et al [11].
vascular remodelling with extensive hypertrophy of the media and irregular intimal fibrosis.

While the majority of patients with ALI/ARDS who survive long enough show evidence of fibrosis, there are a group of patients in which the proliferative phase undergoes resolution, either in part or in some cases, totally. These patients may be left with minimal respiratory symptoms although some impairment in lung function can be seen, particularly in carbon monoxide diffusing capacity, suggesting that even in these patients some degree of alveolar fibrosis has occurred.

**PATHOGENESIS OF ALI/ARDS**

Traditionally the pathogenetic processes that are associated with the development of ALI/ARDS are divided into the same phases as the histological changes. This, however, represents an over simplification, and there is evidence that fibroproliferation and attempts at healing occur simultaneously with the injurious processes that characterise the early exudative phase [14]. The following represents an overview of the pathogenesis and further more detailed information is available in reviews of the subject [11,15–19].
Exudative phase

A sustained inflammatory insult principally mediated by neutrophils and characterised by pulmonary capillary endothelial and alveolar epithelial cell injury is believed to be the hallmark of ALI. There is evidence to indicate neutrophil trapping in the pulmonary circulation at an early stage in the disease process and increased numbers can be recovered in bronchoalveolar lavage fluid supporting a central role for these cells in the injury phase. It is, however, important to note that ALI can also occur in neutropaenic patients.

IL-8, other members of the chemokine family, pro-inflammatory mediators such as C5a and leukotrienes, as well as bacterial endotoxin, have all been identified as being important in the recruitment, activation and retention of neutrophils in the pulmonary circulation. The mechanism whereby this occurs is thought to be by a combination of passive and active events. There is decreased neutrophil deformability resulting in an impaired ability of these cells to pass through the capillary bed of the lung. In addition, neutrophils are actively retained following activation of the pulmonary endothelial cells, an event that occurs early in the process. This is driven by IL-1 and TNFα and results in increased expression of endothelial adhesion molecules such as selectins and intercellular adhesion molecule 1 allowing neutrophil attachment and margination via β2 integrins expressed on their cell surface.

Simultaneously chemokines, such as IL-8 and other pro-inflammatory cytokines, including IL-1, IL-6 and macrophage migration inhibitory factor (MIF), are released further promoting recruitment and retention of inflammatory cells. In addition, neutrophil turnover and survival in the lung also appears to be dysregulated. The normal mechanism whereby neutrophils recruited by inflammatory signals undergo apoptosis appears disrupted, and it is believed that neutrophils recruited to the lung in ALI are more resistant to apoptosis, thereby potentiating the tissue damage.

Resident tissue macrophages in the lung tissue can be activated by exposure to bacterial products such as lipopolysaccharide (LPS) and by cytokines such as MIF. These cells are important sources of primary inflammatory cytokines such as IL-1 TNFα, IL-8 and MIF that means they may have a role in amplifying the inflammatory processes as well as contributing directly to tissue damage that may in part explain why ALI can occur in neutropenic patients. The activation of neutrophils and resident macrophages results in release of a wide range of biologically active molecules including proteolytic enzymes (neutrophil elastase, collagenases and gelatinases), reactive oxygen species, leukotrienes and platelet activating factor that damage the overlying alveolar epithelial cells and the basement membrane.

Endothelial cell injury is mediated by a wide range of potential triggers. Among the most important are cytokines, especially TNFα and IL-1, vascular endothelial growth factor (VEGF), bacterial products, such as LPS, immune complexes, radiation and ischaemia/reperfusion. This promotes changes in cell morphology as well as potentiating a proinflammatory, prothrombotic environment with increased production of thromboxane A2, platelet activating factor and endothelin-1 as well as a reduction in prostaglandin I2.

The change in endothelial cell morphology is brought about by cellular contraction and results in a permissive fluid shift between the circulation and the extravascular space via gaps which develop between the endothelial cells, through which fluid and macromolecules can escape. This increase in lung vascular permeability results in the movement of fluid with a high protein content into the alveolar interstitium. Type I pneumocytes on the other side of the alveolar basement membrane form a tight barrier, which in health prevents the passive movement of fluid from the interstitium into the alveolar space. In addition to
this passive role in maintaining the integrity of the alveolar space, these cells also play an active role in preventing fluid accumulation in the lung via Na⁺/K⁺ ion transport channels and aquaporins. The latter are believed to allow movement of water across these cells in a manner independent of ionic pumping. In ALI, there is damage to this alveolar epithelial barrier with cellular necrosis and denudation of the basement membrane such that this barrier is lost.

From the discussion above, a sequence of events can be postulated to explain the exudative phase. Neutrophil activation and retention in the lung occurs in tandem with endothelial injury/activation promoting a proinflammatory environment as well as allowing fluid and inflammatory cells to move into the interstitium. Associated epithelial injury allows this fluid into the alveolar spaces. This increase in fluid within the alveoli may initially be counteracted by an increase in fluid transport out of the alveoli via the Na⁺/K⁺ pumps and the aquaporins, but this requires functional epithelium. As the degree of epithelial injury increases, this capacity is degraded and the alveoli become flooded with the protein-rich oedema fluid.

**Fibroproliferative phase**

As has been discussed above this phase is characterised by the migration of myofibroblasts into the exudate fluid in alveolar spaces, with subsequent proliferation, deposition of extracellular matrix proteins and angiogenesis, giving rise to loose granulation tissue formation. This is associated with prominent type II pneumocyte proliferation. These are believed to represent the alveolar epithelial stem cell population and this represents evidence for an attempt at alveolar healing.

Although this process is usually regarded as following on from the exudative phase, it may in fact start early in the process as BAL fluid obtained from patients even in the earliest stages of ALI shows increased mitogenic activity for fibroblasts in vitro. This process is believed to be mediated principally by macrophage-derived factors such as platelet-derived growth factor, insulin-like growth factor-1, basic fibroblast growth factor and TGFβ1. The recruitment of myofibroblasts into the alveolar space is associated with secretion of extracellular matrix proteins including fibronectin, tenascin and collagen III. This is associated with accumulation of mucopolysaccharides, such as hyaluronic acid, giving rise to the loose myxoid appearance that characterises the plugs of material forming in the alveolar sacs. Regulation of the angiogenesis that accompanies this process is less well understood. Possible roles for IL-8, monocyte-derived CXC chemokines, VEGF and procollagens have all been suggested.

Regulation of the epithelial proliferation appears to involve signalling between epithelial cells in autocrine and paracrine fashions as well as through direct interaction between these cells and elements in the extracellular matrix. BAL fluid from patients even in the early phase of ALI promotes epithelial proliferation in vivo. A variety of epithelial mitogens including by IL-1β, TGFα, keratinocyte growth factor and hepatocyte growth factor have been implicated as having a possible role in this. One important function of re-epithelialisation is that the presence of epithelial cells on the basement membrane appears to inhibit fibroblast proliferation, although the mechanism of this is unclear.

**Fibrosis versus resolution**

The regulation of wound healing in other tissues has been extensively studied. In dermal wounds, the granulation tissue undergoes organisation with the development of
increasingly mature fibrous tissue that remodels eventually forming a scar predominantly composed of collagen I. In many patients with ALI/ARDS, an analogous process occurs with deposition of collagen resulting in the lungs becoming scarred with impaired function. In some cases, the pre-existing architecture may still be recognisable but the individual alveolar walls are diffusely thickened giving rise to a nonspecific interstitial pneumonia like pattern. In other cases, the lung architecture appears to collapse entirely and is replaced by sheets of fibrous tissue.

The process described above could be regarded as the expected outcome, given the normal progression of granulation tissue to scar formation that occurs at sites of tissue injury but intriguingly in some patients with ALI the fibro-proliferative component may either, in part, or more rarely wholly resolve. In these instances the lung architecture returns to a normal or near normal appearance. The regulation of this process is very poorly understood, but it must involve cessation of the process that initiated ALI, removal of oedema fluid and fibroproliferative granulation tissue from the alveolar spaces as well as re-epithelialisation of the alveoli and repair of endothelial damage. Cessation of the inflammatory process by removal of the triggering event is likely to reduce neutrophil and macrophage activation as well as decreasing endothelial and epithelial injury. This may be associated with increased neutrophil apoptosis in the lung. In addition, many of the pro-inflammatory agents discussed above have natural tissue inhibitors and the environment in the tissues may shift from being pro-injury and fibrosis to pro-resolution. Oedema fluid may be cleared by the proliferating alveolar epithelial cells while the granulation tissue may be removed by a combination of myofibroblast apoptosis and metalloproteinase (MMP) digestion of the extracellular matrix. BAL fluid from patients with resolving ALI has been shown to initiate apoptosis in fibroblasts in vitro and MMP-2 and MMP-9 are increased in the lungs of patients with ALI. Epithelial proliferation has been discussed above and as this progresses the type II cells differentiate and flatten out to form new type I cells. Very little is known about repair of the capillaries, but it is assumed that there is endothelial proliferation and that fibrin thrombi are removed by the fibrinolytic system.

In this context, it is important to acknowledge that unlike the liver there is no evidence the lung can reconstitute itself following extensive tissue destruction. This means that for resolution to occur the elastic and collagen scaffolding of the lung remain must remain intact so that healing of individual alveolar spaces can occur. If severe tissue injury occurs and the alveolar structure is destroyed then fibrosis may be the inevitable outcome [20]. This concept would fit with clinical studies that have found that markers of inflammatory damage to the lung correlate with clinical outcome.

THE ROLE OF PATHOLOGICAL DIAGNOSIS IN ALI/ARDS

As has been discussed above, ALI/ARDS is essentially a clinical diagnosis and pathological assessment is not usually required. The most common specimens likely to be encountered from these patients are bronchoscopic lavage samples that have been taken to identify potential infective organisms in the lung and these are frequently also submitted for diagnostic cytology [21]. As has been discussed above, the regenerating alveolar epithelial cells present in the distal lung can show severe reactive cytological atypia and great care needs to be taken to avoid an erroneous diagnosis of malignancy.

Surgical lung biopsies are not frequently performed but may be done when there is clinical uncertainty around the diagnosis [22,23]. The histological features will clearly
The role of pathological diagnosis in ALI/ARDS

depend on the stage of the process at which the biopsy is taken. The principal differential diagnoses to consider histologically are those which may show some morphological overlap with DADS. These include organising pneumonia, eosinophillic pneumonia, acute hypersensitivity pneumonitis and occasionally vasculitis (polyangiitis with granulomatosis/Wegener’s granulomatosis when this is associated with a prominent organising pneumonic component and microscopic polyangiitis with extensive lung haemorrhage) [12]. In more chronic cases with established fibrosis variable patterns of remodelling may be seen and the possibility of fibrotic nonspecific interstitial pneumonitis or UIP may need to be considered. It is critical in these cases to have good clinical-radiological-pathological correlation with multidisciplinary discussion in order to establish a diagnosis especially as some of these may be amenable to specific therapeutic interventions with a better outlook than DADS.

More recently a further pattern of ALI, acute fibrinous organising pneumonia (AFOP) has been described [24]. This pattern may be idiopathic but can be seen in association with connective tissue disorders, infection, drug reactions and in patients with malignancy. Patients typically present with a short history of increasing breathlessness and cough and may have respiratory failure requiring ventilation. Histologically, the lung shows the presence of fibrinous balls within the alveolar spaces with variable evidence of organisation. Hyaline membranes are however not seen (Figure 1.5). The process is patchy in the lung and inflammatory cells are usually sparse. Some of these patients show a rapid progression to death, while others have a more subacute course and survive.

The commonest situation in which ALI/ARDS is encountered in routine diagnostic practice is, however, in the hospital autopsy [25,26]. The patient typically has been admitted to ITU in respiratory failure, where a clinical diagnosis has been made and the patient has then died some hours, days or even weeks later. Frustratingly in these cases the autopsy often adds very little other than confirming the presence of DADS with variable evidence of fibrosis. Tissue should be submitted for bacterial, fungal and viral cultures but these are often negative and the significance of any positive results may be unclear given that these patients are at risk of secondary ventilator associated pneumonias.

Figure 1.5 Acute fibrinous organising pneumonia is characterised by the accumulation of fibrin within alveolar spaces without hyaline membrane formation.
As has been discussed already DADS can be seen as an acute complication of IPF/UIP [4,10] (Figure 1.6). In many instances, there is a clinical history of this, but in some cases, this may be the first presentation with the underlying IPF/UIP having been unrecognised. It is important to examine such lungs carefully looking for any macroscopic and microscopic evidence of more established mature, honeycomb pattern of fibrosis with a subpleural and basal distribution. This usually involves taking multiple blocks from each lobe remembering to include the subpleural region. In some cases, underlying UIP may be relatively easy to differentiate from the more acute superimposed DADS but in others, particularly when the DADS is becoming more fibrotic this may be very difficult. Careful review of radiology at the time of first presentation may help as the finding of established fibrosis at that time would suggest an underlying more chronic condition.

SUMMARY

ALI/ARDS represents a complex clinical problem, and while there has been some improvement in survival, it still has a 40–50% mortality although this is showing some improvement [27,28]. Clinical management remains supportive; treating the underlying cause, often sepsis, and attempting to optimise oxygenation without inducing further ventilator associated injury to the lung. It does, however, represent an interesting ‘model’ of lung injury and remodelling in that the fibrotic process appears to be subject to factors that induce resolution rather than progression. While we have only a very superficial understanding of this currently, further elucidation of these mechanisms may provide therapeutic targets relevant to a broad range of progressive fibrotic lung diseases and not just ALI/ARDS.

Figure 1.6 Macroscopic appearance of diffuse alveolar damage syndrome (DADS) that has developed on a background of known idiopathic pulmonary fibrosis. Most of the cut lung surface shows the typical red, beefy pattern typical of the exudative phase of DADS. In addition, however, there is evidence of pale subpleural fibrous tissue that represents the previous established fibrosis of usual interstitial pneumonitis. By courtesy of Prof KM Kerr, Aberdeen, UK. Reprinted with permission from Hasleton et al [11].
Key points for clinical practice

- ALI/ARDS is a clinically defined condition that represents a broadly stereotypical pattern of lung injury secondary to a wide range of pulmonary and extrapulmonary insults that is associated with around a 40–50% mortality.
- DADS represents the pathological pattern of injury most commonly seen in patients with ALI/ARDS.
- Although advances have been made in understanding the pathogenesis of ALI/ARDS, particularly the injury phase, much remains unclear especially in relation to the regulation of progressive fibrosis versus resolution. An improved understanding of how immature fibroblastic remodelling in the lung can be reversed may have importance in other progressive fibrotic lung conditions.

REFERENCES