



Acute Lung Injury and Non-infectious Pneumonias

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Lung injury can occur secondary to a myriad of causes, including infection, immunologic disorders, drug toxicity, or inhalational injury among others. Although the list of causative agents is long, the lung's response to injury is limited resulting in similar patterns of disease irrespective of the cause. From a pathological perspective, acute lung injury refers to a group of entities that present with acute or subacute disease. These conditions are characterized by particular histological patterns including *diffuse alveolar damage*, *acute fibrinous and organizing pneumonia*, *organizing pneumonia*, and *eosinophilic pneumonia* and clinically correspond to the varying degrees of *acute respiratory distress syndrome* [1–5]. All these histological manifestations have in common an acute or subacute clinical course and an association with a wide range of underlying etiologic agents or an idiopathic setting. In most cases, the underlying cause will not be apparent from the histological findings requiring close correlation with clinical history and laboratory findings to determine the etiology. Nevertheless, careful search for infectious organisms with application of histochemical and immunohistochemical stains should be performed in all cases in order to identify cases that benefit from more targeted treatment. In this setting, large biopsy specimens (such as wedge biopsy) offer the best method to confirm the diagnosis as smaller samples may not yield sufficient diagnostic clues. Two other entities included in this chapter are *aspiration pneumonia* and *lipoid pneumonia*, representing pneumonias of non-infectious origin. These conditions develop secondary to aspiration or inhalation of food or particulate matter; however superimposed bacterial infection can occur as a complication in both entities.

2.1 Diffuse Alveolar Damage

Diffuse alveolar damage (DAD) is a response of the lung to acute injury that is characterized by damage to the alveolo-capillary unit and represents the histopathological correlate of *acute respiratory distress syndrome (ARDS)*. There are

numerous etiologic causes that can result in a pattern of DAD (Table 2.1). These include infection, sepsis, shock, trauma, transfusion, inhalational injury, drug reactions, metabolic disorders, and immunologic diseases, although the cause is often multifactorial [3, 6–8]. In cases in which no causative etiology can be elicited, the clinical term *acute interstitial pneumonitis* is applied [9–11]. DAD is generally a diffuse and bilateral process, but a subset of cases may demonstrate localized alveolar damage [12]. Histologically, DAD can be divided into an *acute (exudative)* and an *organizing (proliferative) phase* with some authors also recognizing a final *fibrotic phase* (Table 2.2). These phases are not necessarily progressive, and recovery can occur at any time [13, 14]. Furthermore, although most patients suffer only one episode of DAD, disease recurrence has been reported, especially in the setting of drug reactions [15].

Table 2.1 Common causes of diffuse alveolar damage

Infections	<i>Bacteria:</i> legionella, mycoplasma, rickettsia <i>Fungi:</i> aspergillus, pneumocystis <i>Parasites:</i> malaria, strongyloides, toxoplasma <i>Viruses:</i> influenza virus, hantavirus, herpes virus, adenovirus, cytomegalovirus
Collagen vascular diseases	Rheumatoid arthritis, lupus erythematosus, Sjögren syndrome
Drugs	Cytotoxic: azathioprine, bleomycin, methotrexate Antiretroviral therapy Heroin, methadone Amiodarone, gold, penicillamine
Inhalants	Oxygen, herbicides, chlorine gas, paint remover, smoke, ammonia, nitrogen dioxide
Radiation	Acute radiation pneumonitis
Shock	Traumatic, neurogenic, hemorrhagic, cardiogenic, burns
Sepsis	Gram-positive and negative bacteria
Miscellaneous	Aspiration, altitude sickness, transfusion therapy, organ transplant, intravascular coagulation
Idiopathic	Acute interstitial pneumonia (Hamman-Rich disease)

2.1.1 Clinical Features

Patients with ARDS typically have an acute onset of their disease, characterized by dyspnea, cough, fever, and decreased diffusing capacity for carbon monoxide resulting in hypoxia. Radiographically, ARDS is classically described as showing diffuse bilateral pulmonary infiltrates (white out) in mid- and lower lobe distribution on chest X-ray. High-resolution computed tomography scans show scattered or diffuse areas of ground glass opacities in early ARDS (Fig. 2.1a, b) and marked architectural distortion and honeycombing in the later stages of the disease [16]. Fluid management, mechanical ventilation, corticosteroids, and vasodilators are the mainstay of treatment of ARDS [17–19]. Newer management approaches have reduced the mortality

rate of patients with ARDS from approximately 50% to 35% [15]. While most survivors have no significant residual pulmonary deficits, in others, restrictive pulmonary disease may develop secondary to pulmonary fibrosis [17, 20].

2.1.2 Pathological Features

In the *acute* or *exudative phase* of lung injury in DAD, the lungs will be heavy and rigid with a dusky red-blue surface and hemorrhagic and airless parenchymal cut surface [13]. Histologically, the main findings include capillary congestion, interstitial and intraalveolar edema, and hyaline membranes (Fig. 2.2a, b). These hyaline membranes are composed of plasma proteins, surfactant components, and cellular debris which are condensed into glassy-appearing eosinophilic membranes that line the alveolar septa and alveolar ducts (Fig. 2.3). The alveolar septa are widened by edema and sparse inflammatory cells consisting of lymphocytes, plasma cells, and macrophages (Fig. 2.4). Microthrombi can be present quite extensively, and type II pneumocyte hyperplasia with regenerative cytologic atypia is another common finding (Fig. 2.5a, b). The *proliferative phase* is the phase of organization of the intraalveolar and interstitial exudate acquired in the acute phase [9, 13, 21]. Macroscopically, the lungs are solid and have a diffusely pale gray cut surface [13]. Microscopic examination shows formation of organized granulation tissue characterized by a loose prolifera-

Table 2.2 Phases of diffuse alveolar damage

<i>Acute (exudative) phase</i>	<i>Organizing (proliferative) phase</i>	<i>Fibrotic phase</i>
Day 1–7	Week 1–2	Week 3–4
Capillary congestion, interstitial and intraalveolar edema, hyaline membranes	Proliferation of fibroblasts and myofibroblasts (granulation tissue), type II pneumocyte hyperplasia, squamous metaplasia, vascular thrombi	Dense uniform fibrosis, vascular changes, honeycombing

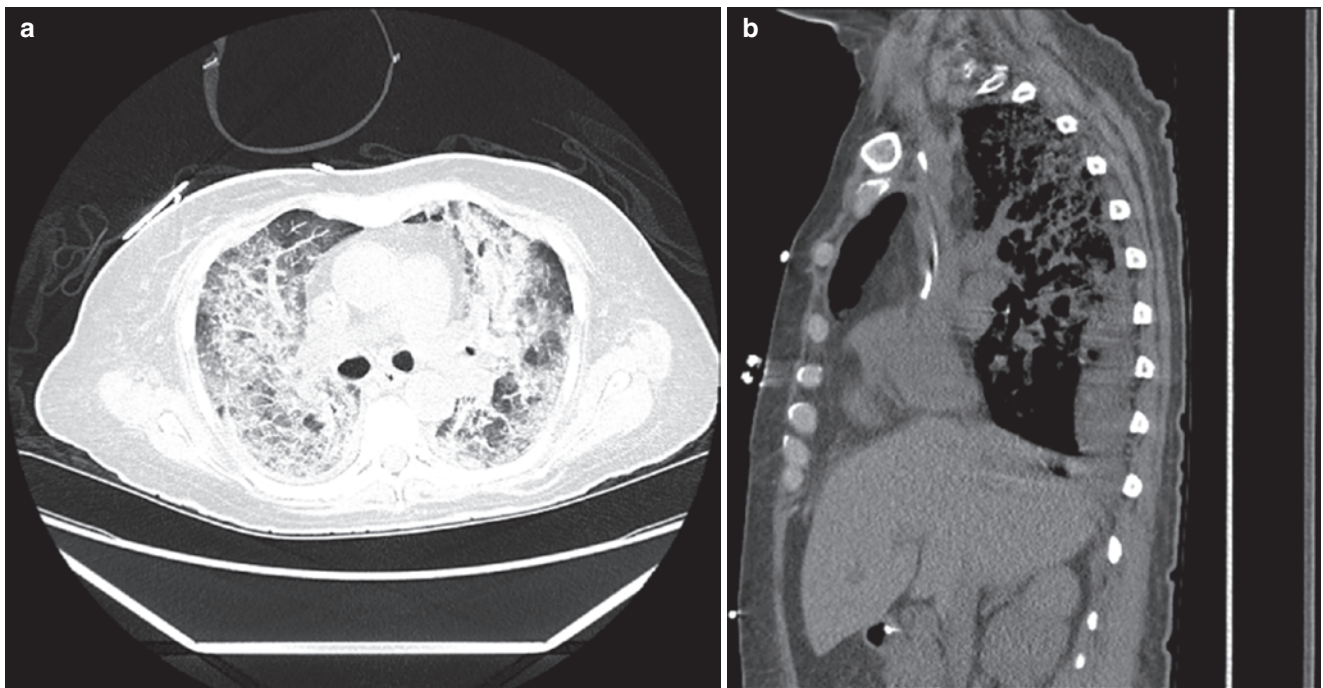


Fig. 2.1 (a) Computed tomography scan of the chest of a patient with acute respiratory distress syndrome demonstrates diffuse bilateral ground glass opacities and consolidation in the lung; (b) sagittal views show the extent of the disease involving all pulmonary lobes

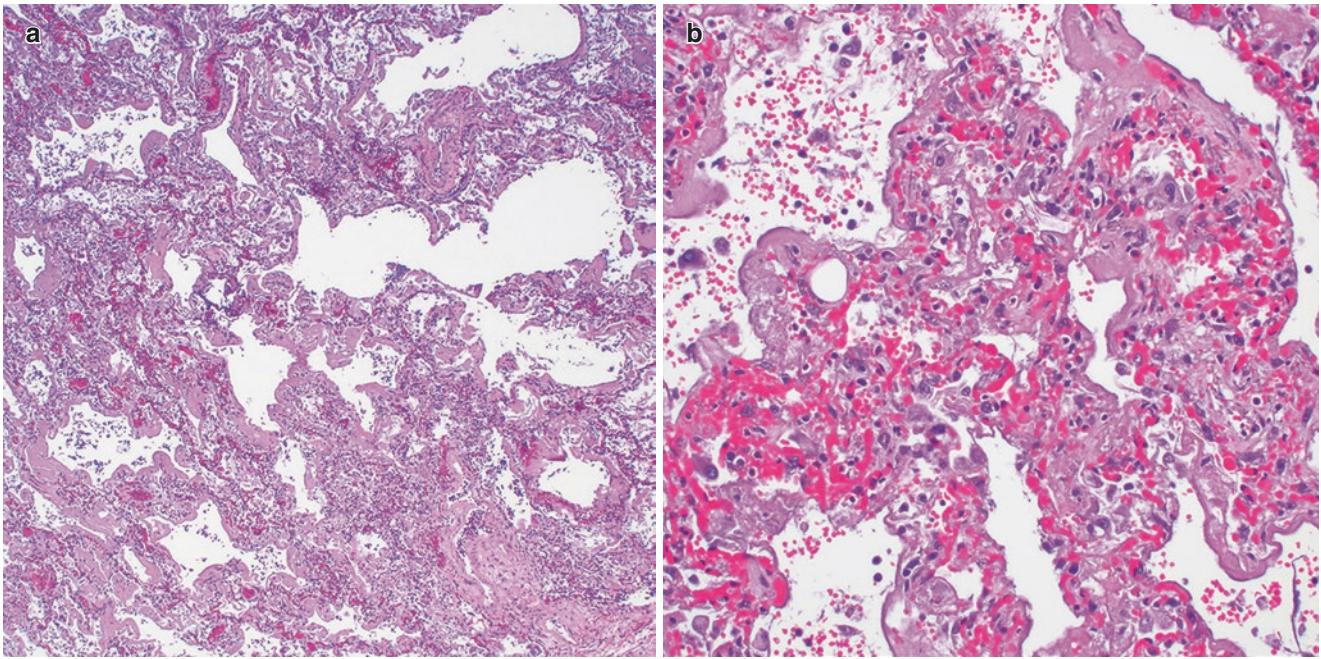


Fig. 2.2 (a) Low power view of the pulmonary parenchyma affected by diffuse alveolar damage in the exudative phase; (b) higher magnification shows prominent capillary congestion and interstitial edema

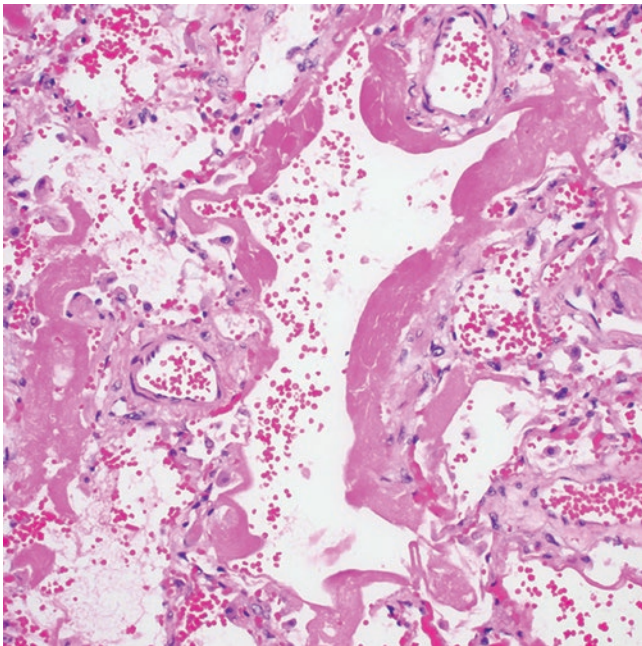


Fig. 2.3 Dense eosinophilic hyaline membranes lining the alveolar spaces are the pathognomonic histological feature of diffuse alveolar damage

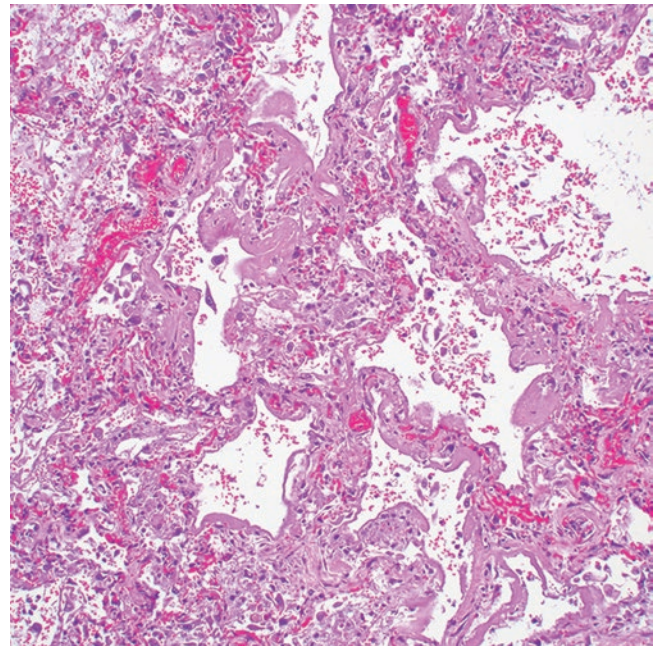


Fig. 2.4 Sparse inflammatory cells can usually be identified in the alveolar septa in diffuse alveolar damage

tion of fibroblasts and myofibroblasts involving the alveolar septa and to a minor degree the alveolar spaces (Fig. 2.6a, b). Further changes include type II pneumocyte hyperplasia and squamous metaplasia, both of which can show striking cytologic atypia which should not be mistaken for malignancy

(Fig. 2.7). Microthrombi, vascular remodeling, and wedge-shaped infarcts are further features, but hyaline membranes are not prominent [9, 13, 21]. In the *fibrotic phase*, gross examination shows a cobblestone appearance of the pleural surface and pale parenchymal cut surface with microcysts

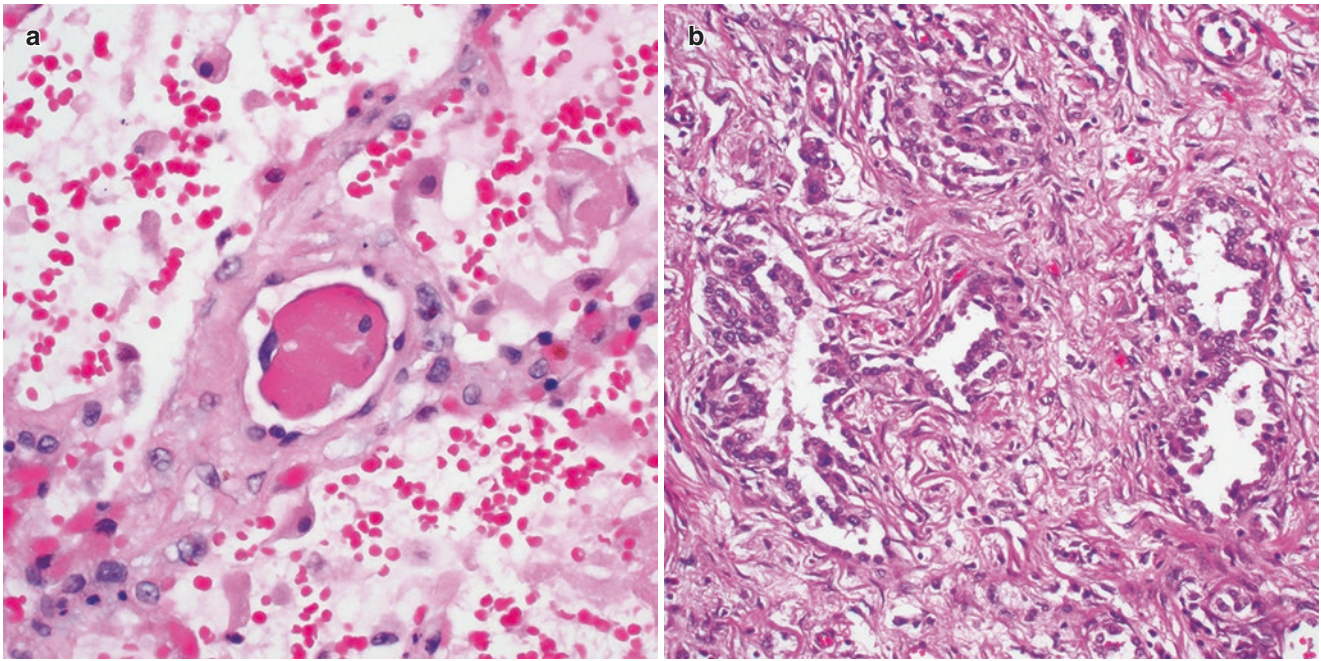


Fig. 2.5 (a) Microthrombi in the vasculature of a lung with diffuse alveolar damage; (b) the lung parenchyma in diffuse alveolar damage can show striking type II pneumocyte hyperplasia

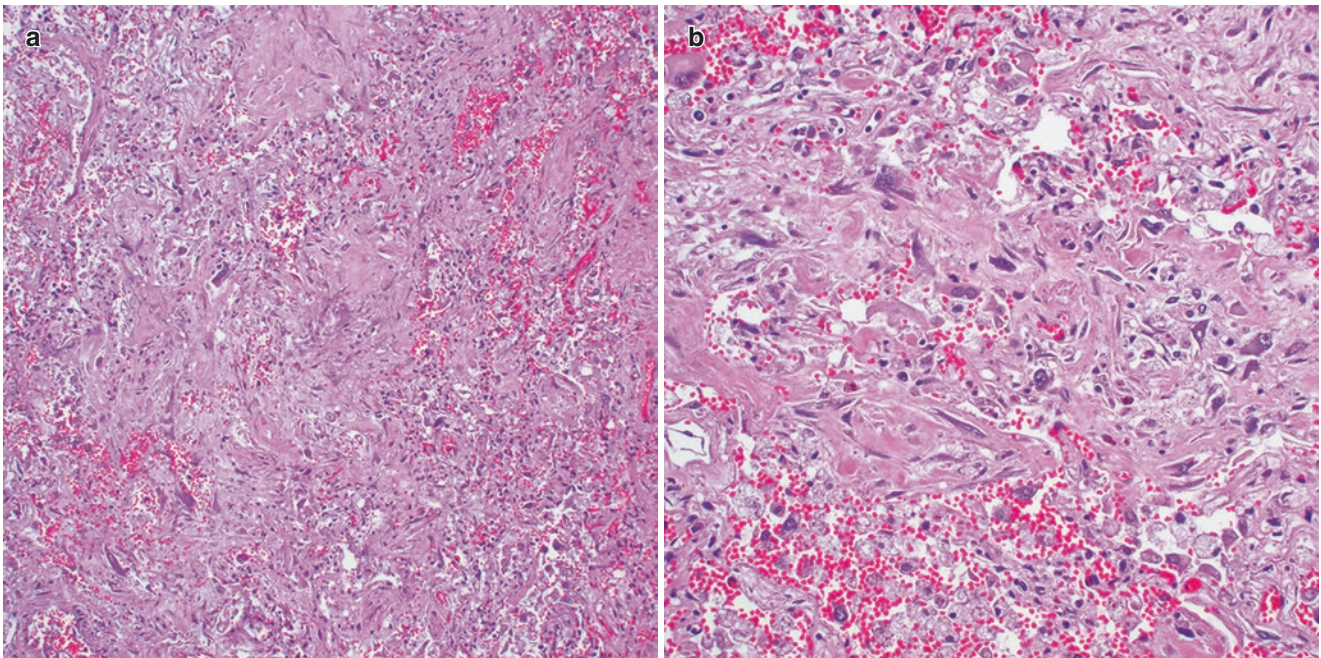


Fig. 2.6 (a) Organizing granulation tissue characterizes the proliferative phase of diffuse alveolar damage; (b) higher power shows a proliferation of loose fibroblasts and myofibroblasts

and scarring [13]. Histologically, the air spaces are enlarged and surrounded by thickened and fibrotic alveolar septa. The fibrosis is uniform and can be associated with areas of honeycombing (Fig. 2.8). Vascular changes in form of intimal or mural fibrosis or arterial muscularization can lead to pulmonary hypertension [9, 13, 21].

2.1.3 Differential Diagnosis

The histological changes of DAD are non-specific and the underlying etiology is often not apparent. Close correlation with clinical history and laboratory findings and application of stains for fungi, mycobacteria, and bacteria or immuno-

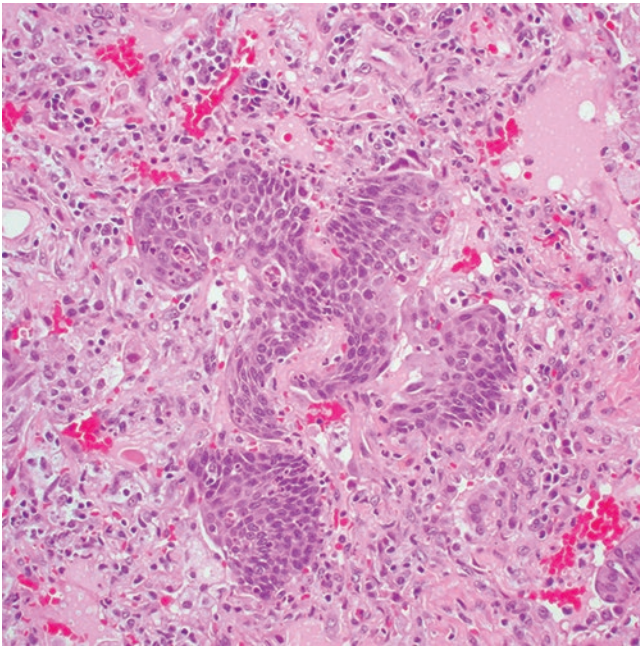


Fig. 2.7 Foci of squamous metaplasia are a common finding in diffuse alveolar damage

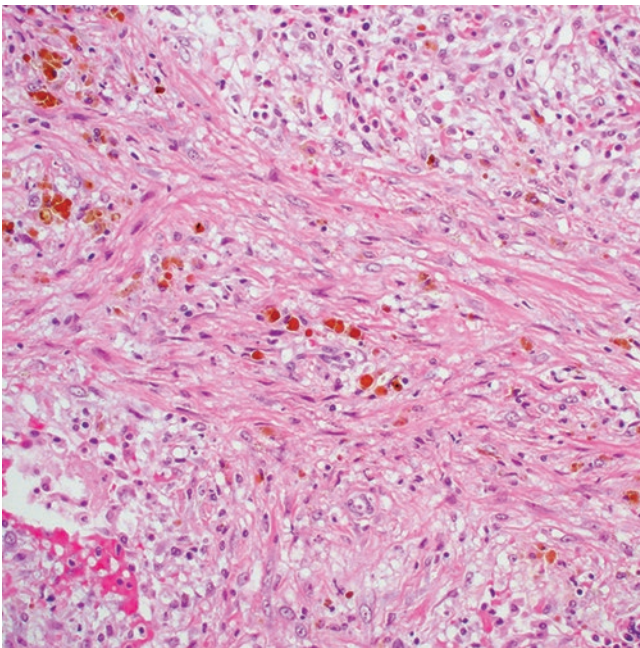


Fig. 2.8 The fibrotic phase of diffuse alveolar damage is characterized by a non-specific uniform fibrotic process

histochemistry for viruses in immunocompromised patients is strongly recommended in the workup of any case of DAD. On a histologic level, the differential diagnosis includes acute fibrinous and organizing pneumonia (AFOP), organizing pneumonia (OP), and non-specific interstitial pneumonia (NSIP). AFOP is characterized by the presence of intraalveolar organizing fibrin balls and organizing fibro-

blastic tissue. Contrary to AFOP, the histologic hallmark of DAD is hyaline membranes, the presence of which is highly suggestive of the condition. Likewise, hyaline membranes are not a feature of OP in which the principal finding is organizing fibrous tissue. The fibrosis occurring in the organizing and fibrotic phases of DAD may be reminiscent of interstitial lung disease, especially NSIP. The fibrosis DAD is usually loose and myxoid and not as dense as that of NSIP. In addition, the striking type II pneumocyte hyperplasia seen in DAD is not as prominent a feature of NSIP.

2.2 Acute Fibrinous and Organizing Pneumonia

The pattern of acute fibrinous and organizing pneumonia (AFOP) was first reported by Beasley et al. in 2002 to describe a histologic pattern of acute lung injury that was distinct from those of diffuse alveolar damage (DAD), eosinophilic pneumonia, or organizing pneumonia [2]. AFOP is an uncommon response to lung injury characterized by intraalveolar fibrin deposition and organizing fibroblastic tissue but without the presence of hyaline membranes. The clinical course ranges from patients that present in a subacute fashion with eventual recovery to those with acute onset of respiratory distress and rapid progression to death. AFOP may be the consequence of a variety of different etiologies, including infection, collagen vascular disease, drug reaction, environmental exposure, and organ transplantation although idiopathic cases have also been described [2, 22–26]. While best treatment of the disease remains under investigation, the mortality rate continues to be high (50%) suggesting that AFOP may clinically and histologically represent a variant of DAD [2]. From a pathologist's perspective, it should be noted that a diagnosis of AFOP requires large biopsy specimens (open lung biopsy or video-assisted thoracoscopic biopsy) as organizing alveolar fibrin may be a non-specific reaction to other processes and bronchoscopy and bronchoalveolar lavage (BAL) usually provide non-specific findings.

2.2.1 Clinical Features

Based on its association with a wide range of clinical conditions, AFOP can affect patients of any age but is most commonly reported in individuals between 50 and 70 years of age. Men are affected slightly more frequently than women [27]. Two different clinical patterns of AFOP have been described. In the acute form, there is rapid onset of the disease with fast development of respiratory failure and death with an average time from onset of symptoms to death of 29 days; in the subacute form, the clinical course is less aggressive with slower progression [2, 22, 28, 29]. Patients commonly present with dyspnea,

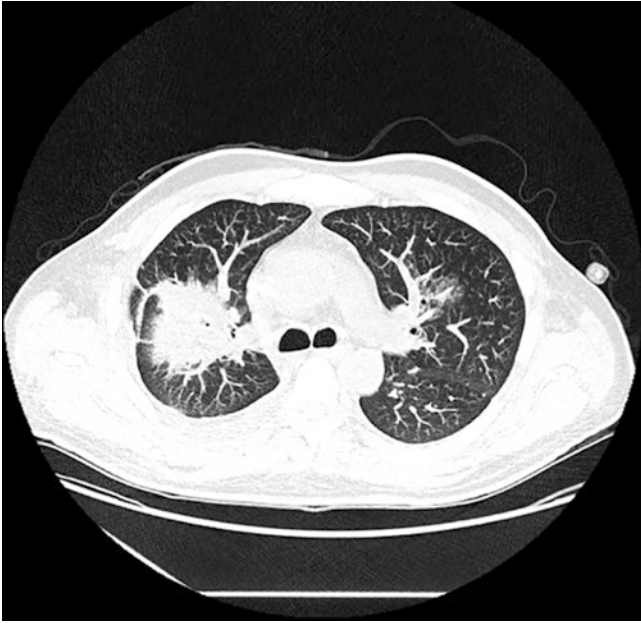


Fig. 2.9 On chest computed tomography, a case of acute fibrinous and organizing pneumonia presents with diffuse consolidation in the right lower lobe of the lung

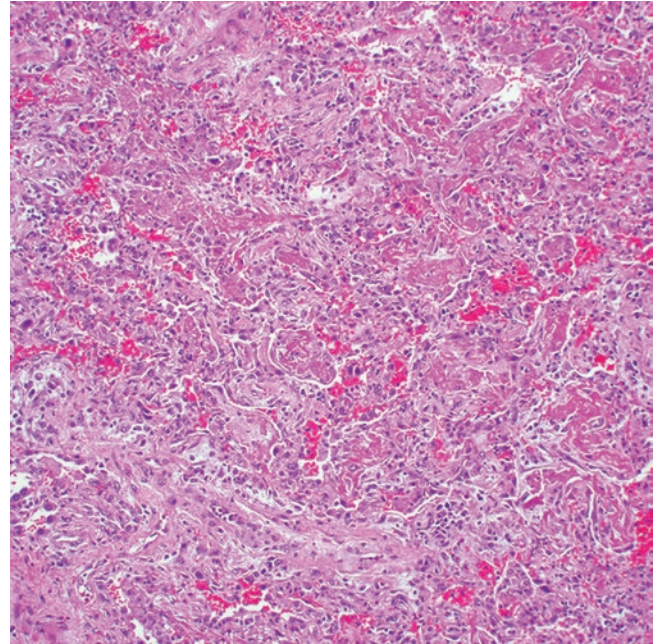


Fig. 2.10 Histologically, acute fibrinous and organizing pneumonia shows areas of intraalveolar fibrin deposition

cough, fever, pleural effusions, and progressive respiratory failure. The radiological findings of AFOP closely resemble those of DAD and comprise diffuse basilar-dependent consolidation, ground glass opacities, and interlobular septal thickening [2, 30] (Fig. 2.9). In the subacute form, imaging findings may be indistinguishable from those of organizing pneumonia and can include focal and diffuse parenchymal abnormalities [2, 31–33]. The treatment of AFOP is largely based on treating the underlying condition and often includes administration of corticosteroids and immunosuppressive therapy [22]. Despite this, patients with fulminant AFOP often succumb to their disease, while patients with subacute AFOP eventually recover [2].

2.2.2 Pathological Features

The dominant finding in specimens with AFOP is the presence of intraalveolar fibrin filling the alveolar spaces (Fig. 2.10). This often takes the form of “fibrin balls” (Fig. 2.11). The distribution of the fibrin is typically patchy with intervening uninvolved lung parenchyma showing minimal interstitial widening or inflammatory cell infiltration (Fig. 2.12). Classic hyaline membranes, however, as seen in DAD are not a feature of AFOP. In addition to the fibrin balls, AFOP will harbor intraluminal loose connective tissue within alveolar ducts and bronchioles (Fig. 2.13a, b). Other associated findings may include type II pneumocyte hyperplasia, alveolar edema, or vascular thrombi (Fig. 2.14). Of note, infiltrates consisting of neutrophils, eosinophils, and macrophages or fibrotic changes are typically absent [2].

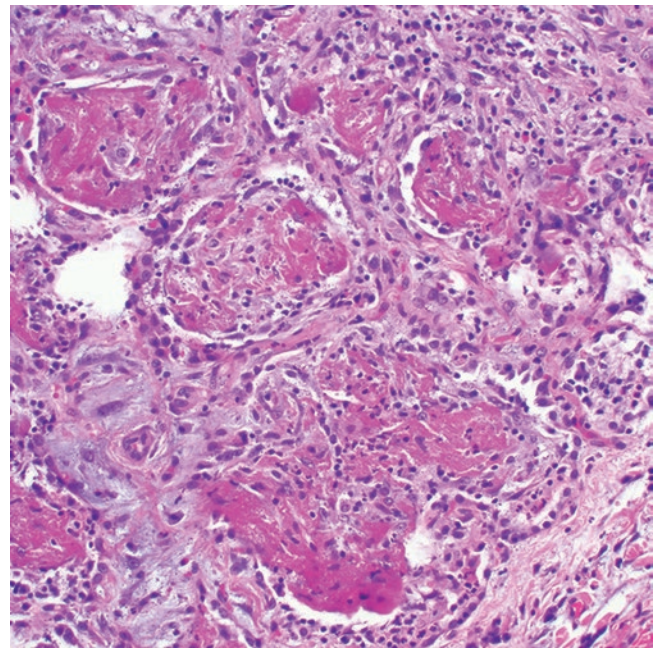


Fig. 2.11 The fibrin often assumes a ball-like configuration in acute fibrinous and organizing pneumonia

2.2.3 Differential Diagnosis

The differential diagnosis of AFOP includes other conditions associated with acute lung injury, including DAD, eosinophilic pneumonia, and organizing pneumonia (Table 2.3). The histopathological hallmark of DAD is the presence of

hyaline membranes, which although they may be focal will invariably have to be present for the diagnosis to be made. Although AFOP is also characterized by organizing fibrin deposition, hyaline membranes are not a feature of this con-

dition, and their presence would rather be indicative of DAD. Intraalveolar fibrin may also be found in eosinophilic pneumonia; however, the latter typically contains abundant eosinophils admixed with macrophages, the presence of

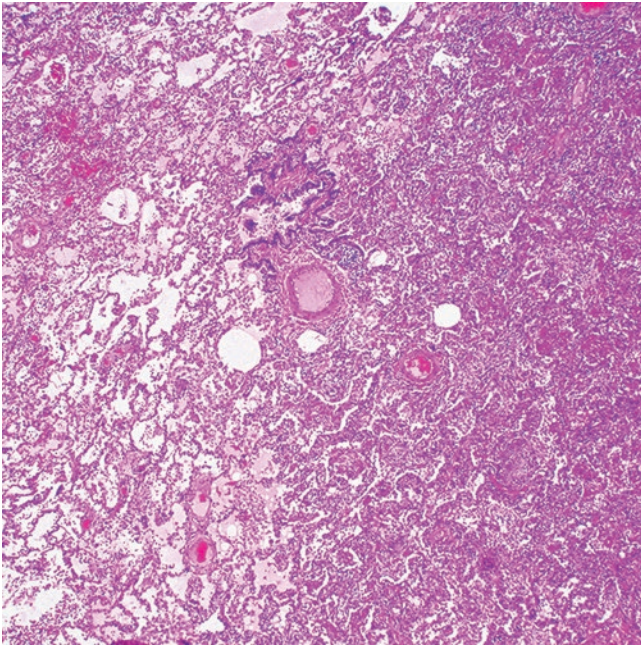


Fig. 2.12 Areas of intervening normal lung parenchyma (left) typically alternate with involved lung (right) in acute fibrinous and organizing pneumonia

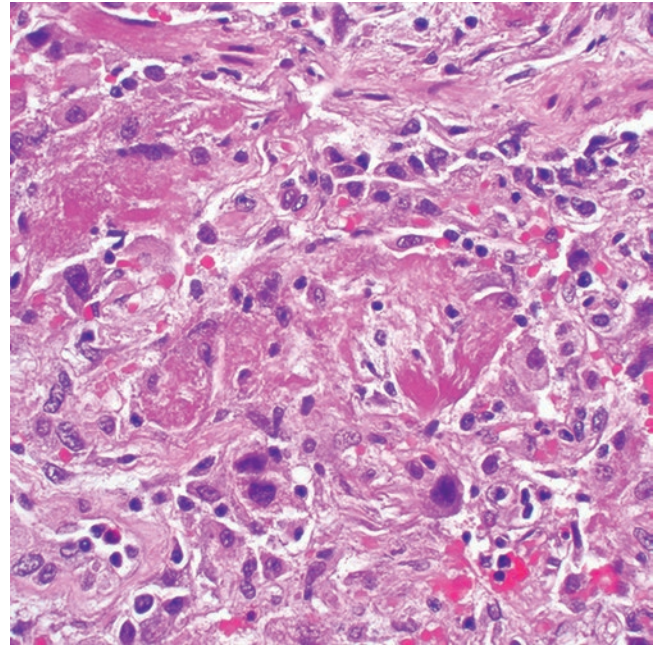


Fig. 2.14 Type II pneumocyte hyperplasia with reactive atypia is typically seen along the alveolar walls in acute fibrinous and organizing pneumonia

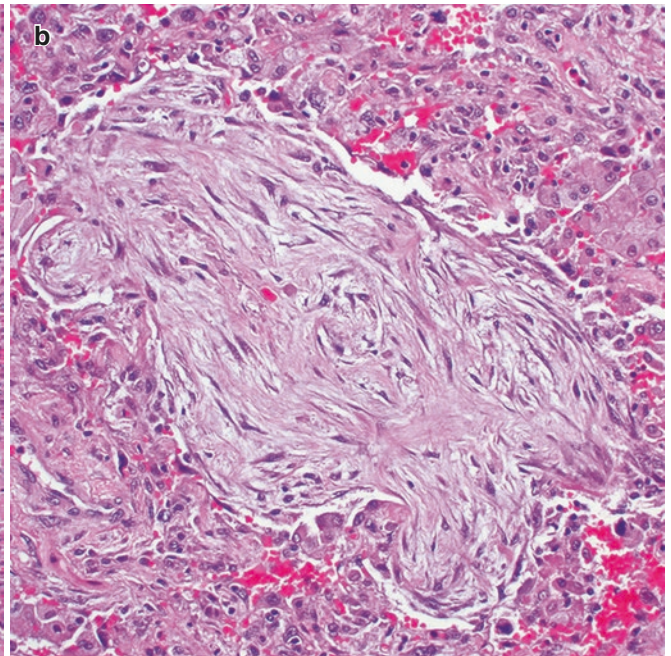
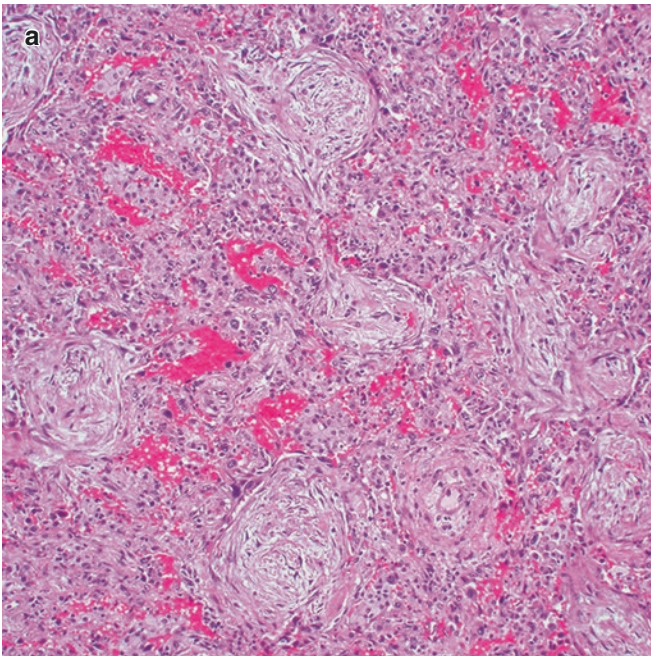


Fig. 2.13 (a) Another characteristic feature of acute fibrinous and organizing pneumonia is the presence of intraluminal loose connective tissue; (b) higher magnification shows the polypoid nature of the fibrous plugs

Table 2.3 Comparison of histological patterns of acute lung injury

Diffuse alveolar damage	Acute fibrinous and organizing pneumonia	Eosinophilic pneumonia	Organizing pneumonia
Interstitial and intraalveolar edema Hyaline membranes Proliferation of fibroblasts and myofibroblasts (granulation tissue)	Intraalveolar organizing fibrin (“fibrin balls”) Proliferation of fibroblasts and myofibroblasts (granulation tissue)	Diffuse infiltrate of eosinophils and macrophages Hyaline membranes Intraalveolar fibrin Intraluminal fibrosis	Polypoid intraluminal plugs of fibroblasts and myofibroblasts

which would preclude a diagnosis of AFOP. The dominant finding in organizing pneumonia is intraluminal fibroblastic plugs. Although organizing fibroblastic tissue is also seen in AFOP, the most striking histologic finding in this condition is the presence of organizing fibrin balls which in turn will be absent in organizing pneumonia.

2.3 Organizing Pneumonia

The term organizing pneumonia (OP), previously referred to as *bronchiolitis obliterans organizing pneumonia (BOOP)*, is used to describe a characteristic histological pattern that is a non-specific response to lung injury. It is composed of polypoid plugs of proliferating fibroblasts and myofibroblasts within the lumen of small airways and alveolar spaces and associated interstitial inflammation [34, 35]. OP may be idiopathic in origin (clinically corresponding to *cryptogenic organizing pneumonia*) or a secondary process due to a wide range of underlying etiologies, such as infection, collagen vascular disease, drug reaction, radiation, environmental or occupational exposure, or organ transplantation [36]. Classically, OP presents in a subacute manner and with diffuse lung disease [37]; however, a rare form of the disease has been reported with an acute onset leading to rapid respiratory failure and need for mechanical ventilation (*rapid progressive OP*) [38, 39]. Another form of the disease presenting as a solitary lung nodule or multiple nodular masses has been termed *localized OP* or *focal nodular OP* [40–43]. This form accounts for 13–14% of all cases of OP and is easily mistaken for primary lung cancer or metastatic disease based on initial clinical and radiological investigations [44, 45]. Furthermore, OP may occur as an integral component of other conditions, such as hypersensitivity pneumonitis, acute and fibrinous organizing pneumonia (AFOP), or organizing diffuse alveolar damage (DAD), or it can be a non-specific reaction to an adjacent unrelated lesion [46].

2.3.1 Clinical Features

Due to the association with a variety of different etiologies, OP can affect patients of any age group. The most common

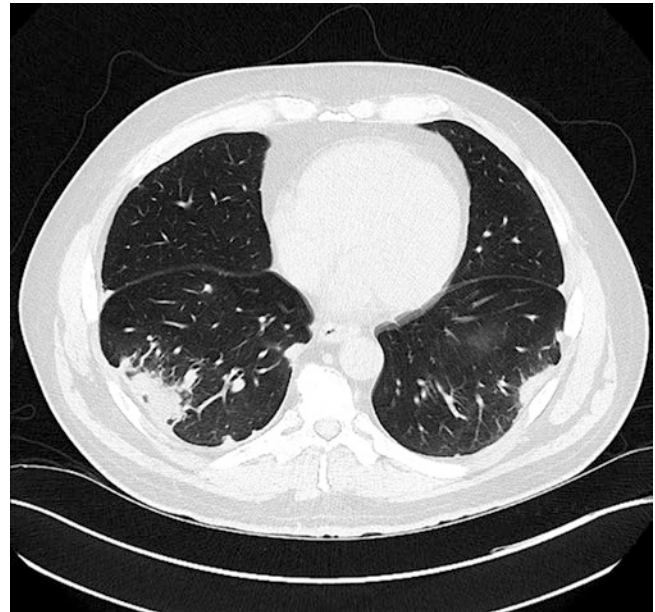


Fig. 2.15 Computed tomography scan of the chest of a patient with organizing pneumonia shows bilateral subpleural areas of consolidation

form of OP however is the idiopathic form which tends to affect men and women equally and with an average age around 50 years. There appears to be no direct relationship with smoking. Presenting symptoms include cough, shortness of breath, or a flu-like illness with fever [38, 45, 47]. Patients with the localized form of the disease are often asymptomatic [41–43, 48, 49] while those with the accelerated form rapidly progress to respiratory failure [38, 39]. Pulmonary function tests often show a decrease in vital capacity and reduced diffusion capacity [38]. Radiologically, most patients present with various patterns of diffuse parenchymal abnormalities. These include bilateral consolidation, especially in a peripheral or peribronchial pattern, triangular-shaped bilateral ground glass opacities, or peribronchial or peribronchiolar nodules [50] (Fig. 2.15). Chest X-ray of *rapid progressive OP* will show a white-out of both lungs and CT findings include ground glass opacities and alveolar consolidation. In *localized OP*, chest radiographs and CT scans will reveal solitary or multiple lung nodules with an average size around 2–3 cm [48, 49]. These nodules are

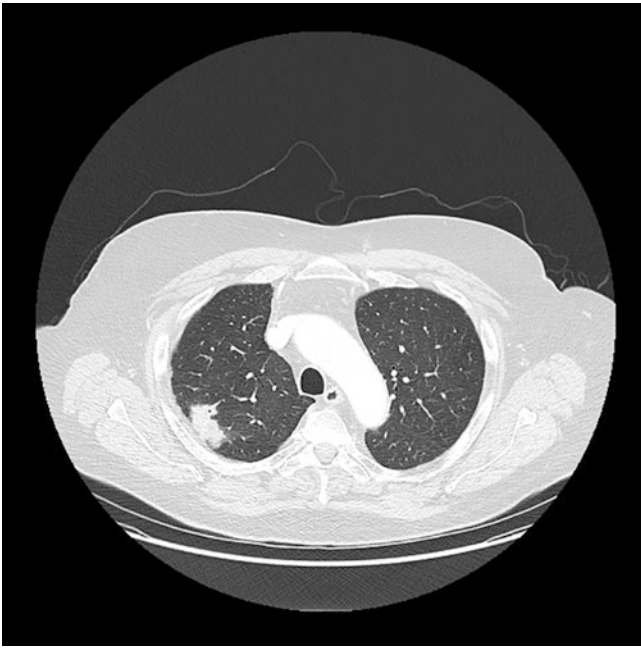


Fig. 2.16 On a computed tomography scan, localized organizing pneumonia may present as a solitary pulmonary nodule closely resembling lung malignancy

round or oval-shaped and have smooth, irregular, or spiculated margins (Fig. 2.16). Of note, fluorodeoxyglucose-positron emission tomography (FDG-PET) is often positive in these lesions making differentiation from primary or metastatic lung tumors even more difficult [48, 49, 51]. Surgery is the treatment of choice and usually curative in cases of *localized OP* while corticosteroids, antibiotics, and immunosuppressive therapy are typically administered in the remaining cases. With appropriate treatment, the prognosis is usually favorable in most cases of OP and the lung will heal without permanent damage [52–54]. However, in severe cases, lung injury can occur and can lead to permanent damage and interstitial fibrosis [44, 52, 53, 55–57].

2.3.2 Pathological Features

Irrespective of the clinical presentation of the disease, the histological hallmark of OP is polypoid intraluminal plugs of fibroblasts and myofibroblasts predominantly within airspaces and with varying degrees of bronchiolar involvement (Fig. 2.17). Their distribution is typically patchy, and on hematoxylin-eosin stains, they have a characteristic gray-blue hue (Fig. 2.18a, b). A mild to moderate interstitial infiltrate may be present in the septa of areas of organization and may lead to associated type II pneumocyte hyperplasia (Fig. 2.19). The general lung architecture, however, remains intact. Neutrophils, eosinophils, granulomas, and significant fibrosis should not be present, but foci of bronchial or squa-

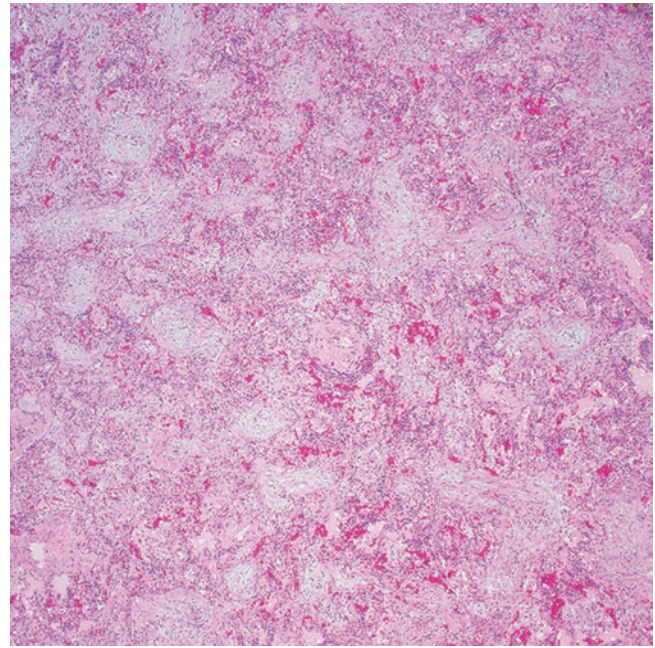


Fig. 2.17 Low power magnification of a case of organizing pneumonia shows scattered intraluminal plugs of granulation tissue

mous metaplasia can sometimes be identified [4, 37, 58–60] (Fig. 2.20).

2.3.3 Differential Diagnosis

Although the histologic pattern of OP is quite distinctive, one needs to remember that an OP-like reaction may form part of other disease entities that need to be excluded before a diagnosis of OP can be established. As mentioned above, hypersensitivity pneumonitis is defined by the histological triad of cellular bronchiolitis, ill-defined non-caseating granulomas, and localized areas of OP. Careful search for additional histologic findings as well as attention to the clinical findings such as antigen exposure and poorly defined centrilobular nodules on high-resolution CT are required to distinguish these entities [61]. Moreover, fibroblastic lesions (*fibroblastic foci*) similar to those seen in OP are commonly associated with usual interstitial pneumonia (UIP) and may be difficult to differentiate especially in small biopsy samples. However, in contrast to OP, UIP shows heterogeneous fibrotic lesions in a spatial distribution, variable degrees of smooth muscle proliferation, and honeycombing. In contrast, OP is more uniform in appearance with more prominent polypoid intraluminal lesions and architectural preservation. Another entity, DAD, may show granulation tissue polyps in bronchioles and alveolar ducts. However, in contrast to OP, DAD typically also contains hyaline membranes with or without organization. When these features are resolving in the later phase of DAD, the differential

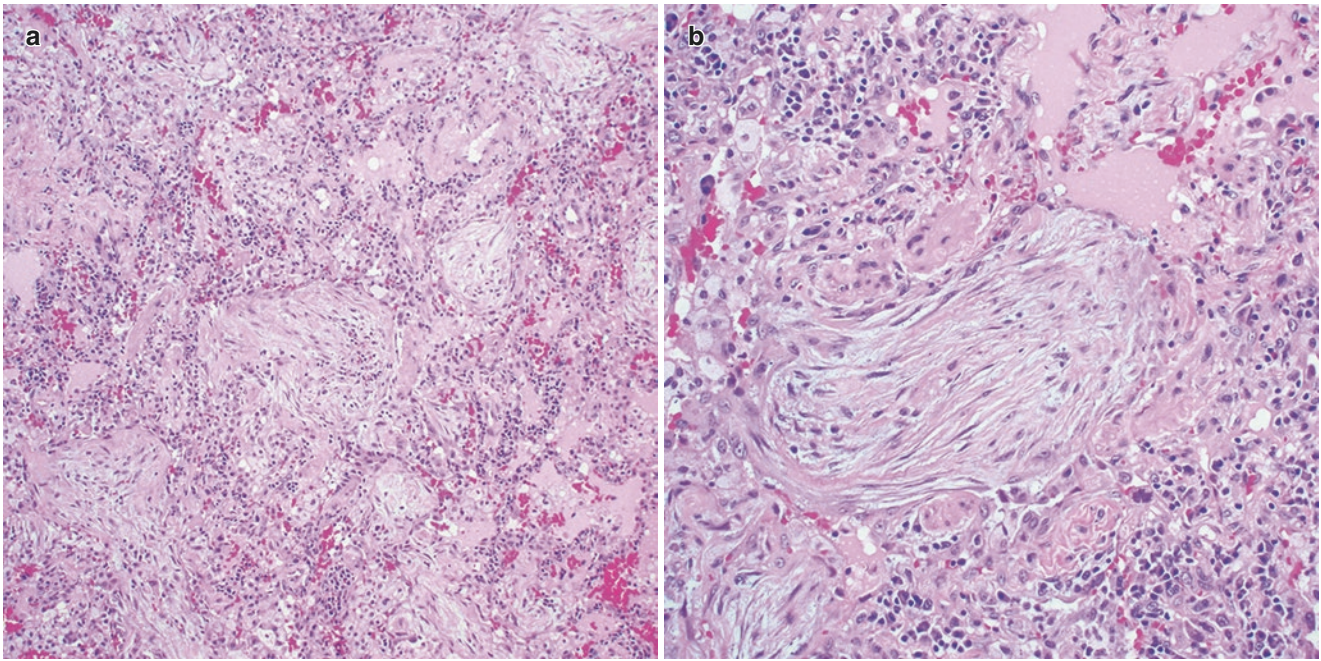


Fig. 2.18 (a) The tissue plugs have a scattered distribution and (b) often have a bluish-gray appearance on hematoxylin-eosin staining

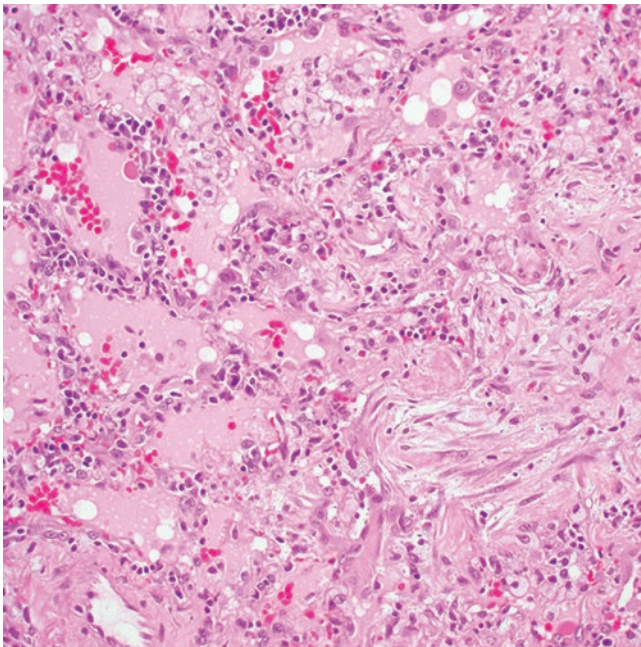


Fig. 2.19 The lung adjacent to organizing pneumonia often shows hyperplastic changes of the alveolar lining cells (left)

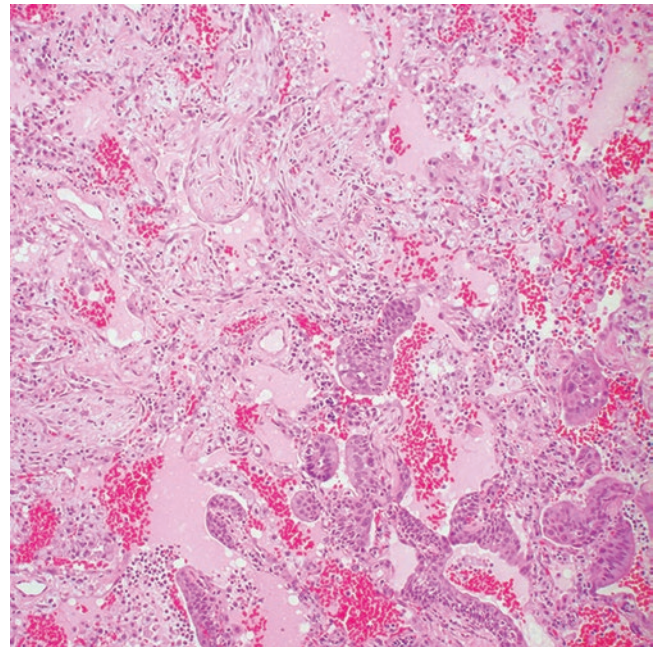


Fig. 2.20 Areas of squamous metaplasia in a case of organizing pneumonia (right lower)

diagnosis on histologic features alone may be difficult and always requires close clinical correlation [62]. OP-like changes are also a component of a pattern of acute lung injury named AFOP. In addition to the OP-like changes, AFOP is defined by the presence of organizing fibrin in the alveolar spaces. While these organizing fibrin balls are the principal finding in AFOP, organizing fibroblastic tissue dominates the histological picture in OP.

2.4 Eosinophilic Pneumonia

Eosinophilic pneumonia, as defined by Liebow and Carrington in 1969 [63], refers to a pneumonic process caused by infiltration of the pulmonary parenchyma by eosinophils that may or may not be accompanied by eosinophilia in the peripheral blood. Eosinophilic pneumonia can

be divided into two forms, *acute eosinophilic pneumonia (AEP)* and *chronic eosinophilic pneumonia (CEP)*, based on clinical parameters and response to therapy [64]. AEP is a clinical entity characterized by an acute febrile illness, normal number of blood eosinophils, and dramatic response to corticosteroid therapy [64], while patients with CEP present with chronic and progressive clinical features, peripheral blood eosinophilia, and frequent relapse after discontinuation of corticosteroids [65]. Both forms of the disease may be the consequence of a range of different etiologies, including inhalation of toxins, drug reaction, or infection or may be idiopathic [66–69]. The development of AEP has also been reported in association with cigarette smoking and exposure to dust or smoke from fireworks [70–72].

2.4.1 Clinical Features

Patients with AEP typically present with an acute onset of respiratory insufficiency, hypoxemia, and fever. Peripheral blood eosinophil percentages are usually normal, but the number of eosinophils in bronchoalveolar lavage (BAL) fluid is increased. Pulmonary function testing during the acute phase often shows a restrictive pattern. In contrast, the onset of CEP is insidious with an average time from onset of symptoms to diagnosis of 7.7 months [65]. Patients are typically middle-aged and women are more commonly affected than men; about half of the patients have a history of asthma. Pulmonary functions tests are mostly normal but can also show restrictive defects [65, 73, 74]. Peripheral blood eosinophilia is typically present and usually mild to moderate and increased IgE levels can be found in two thirds of patients. Analogous to AEP, the percentage of eosinophils in BAL fluid is very high [65, 75, 76]. Radiographic findings in AEP include bilateral reticular densities and pleural effusion, while in CEP non-segmental airspace consolidation in a peripheral and upper lobe distribution is seen [16, 77]. CT scans demonstrate bilateral patchy areas of ground glass opacity, interlobular septal thickening, consolidation and poorly defined nodules in AEP, and areas of airspace consolidation, ground glass opacities, nodules, and reticulation in CEP. Contrary to AEP, pleural effusion is observed in CEP in less than 10% of cases [16, 77]. Both AEP and CEP are highly responsive to treatment with corticosteroids often achieving a rapid clinical response. Unlike patients with CEP who need to be treated with prolonged therapy due to a high short-term relapse rate, those with AEP usually do not experience disease recurrence after discontinuation of corticosteroids [68, 78].

2.4.2 Pathological Features

In general, eosinophilic pneumonia is characterized by diffuse infiltration of varying numbers of eosinophils, macro-

phages, and intraalveolar fibrin (Fig. 2.21). Eosinophils can also be seen in thickened interstitial spaces and the walls of blood vessels, or they can form small microabscesses (Fig. 2.22). Hyaline membranes reminiscent of those seen in diffuse alveolar damage may be seen in cases of AEP [68, 79], while in CEP intraluminal fibrosis is often identified [65, 68, 80, 81]. Additional findings can include type II

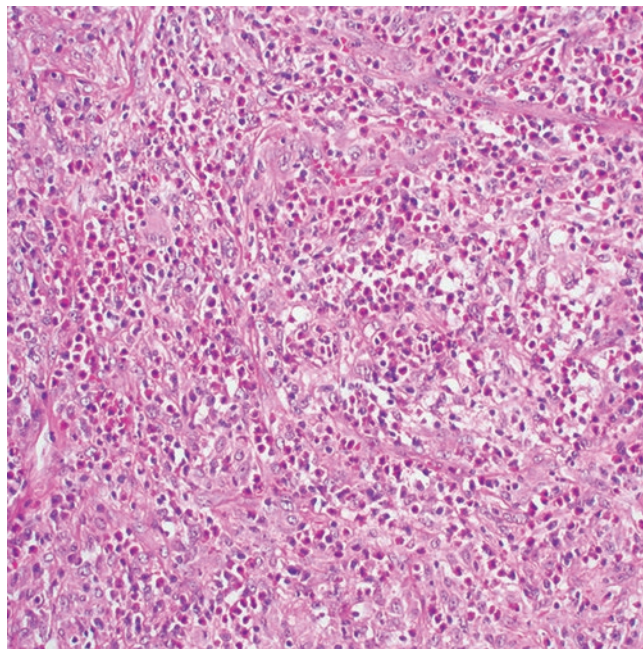


Fig. 2.21 Diffuse tissue infiltration by eosinophils mixed with histiocytes is the histologic hallmark of eosinophilic pneumonia

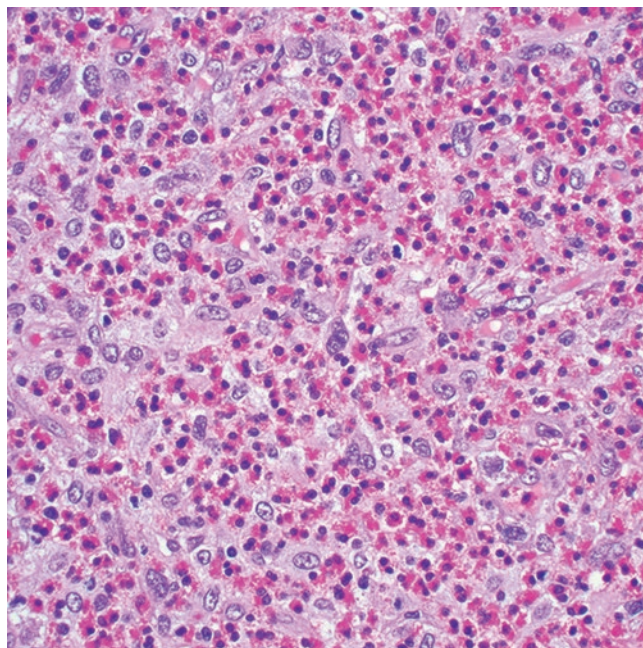


Fig. 2.22 In some areas, the eosinophilic infiltrate in eosinophilic pneumonia can form small microabscesses

pneumocyte hyperplasia, foci of intraalveolar necrosis, and Charcot-Leyden crystals [65, 79].

2.4.3 Differential Diagnosis

The histopathological differential diagnosis of eosinophilic pneumonia primarily includes diffuse alveolar damage (DAD), acute fibrinous and organizing pneumonia (AFOP), and Churg-Strauss syndrome. Distinction from these entities is important due to the dramatic clinical response of patients with eosinophilic pneumonia upon administration of corticosteroid therapy. Cases of DAD and AFOP may share several histological features with eosinophilic pneumonia, such as hyaline membranes or intraalveolar fibrin deposition, respectively. Contrary to eosinophilic pneumonia, however, the presence of numerous eosinophils and macrophages is not characteristic for these entities, and their occurrence would rather point toward a diagnosis of eosinophilic pneumonia. Churg-Strauss syndrome on the other hand typically shows an eosinophilic parenchymal infiltrate coupled with the presence of a necrotizing vasculitis and granulomas; the latter features are not usually seen in cases of eosinophilic pneumonia.

2.5 Aspiration Pneumonia

Aspiration of food or other foreign material can be the cause of a chemical or bacterial pneumonia that most commonly occurs in patients with altered levels of consciousness and subsequent impairment of protective upper and lower airway reflexes. Predisposing factors include chronic debilitation, neurologic disorders, obstetric or emergency surgical intervention, drug overdoses, or syncopal episodes [82–85]. More recently, this disease process has also been described in previously healthy patients, in whom aspiration was unsuspected clinically and pathologically [84]. Most aspirated material is composed of food or other particulate matter such as seeds, vegetable peel or pits, chicken bones, gum, talc, and microcrystalline material among others [84, 86].

2.5.1 Clinical Features

Patients are often in the 6th or 7th decade of life, and males seem to be more frequently affected than females [84, 85]. Common presenting symptoms include dyspnea, fever, cough, weakness, or lethargy. The right lung is involved more commonly, due to the fact that the right main bronchus is wider and enters the lung at a steeper angle than the left one. Radiologically, aspiration pneumonia can manifest as confluent air space opacification in the dependent portions of the

lungs or small nodular and branching opacities (tree-in-bud pattern) centered on the bronchioles [87]. The initial therapy for aspiration pneumonia depends on the rapid recognition of the event and treatment of hypoxemia with supplemental oxygen [88]. Antibiotic treatment is often administered empirically. Pleural drainage may be necessary in patients in whom complications of aspiration pneumonia occur such as lung abscess, empyema, or bronchopleural fistula [88].

2.5.2 Pathological Features

The most common pathological finding in aspiration pneumonia is organizing pneumonia (OP) characterized by intraluminal fibroblast plugs around small bronchioles, alveolar ducts, and peribronchiolar spaces. This OP-like reaction is often accompanied by multinucleate giant cells and/or acute inflammation, foreign body type granulomas engulfing the aspirated material, acute bronchopneumonia or bronchiolitis, and scattered microabscesses (Fig. 2.23a–d). In addition, suppurative granulomas with central necrotic neutrophils or necrosis surrounded by epithelioid histiocytes can be identified [84]. A relatively constant finding is the presence of aspirated foreign material which is usually located in the air-spaces but may occasionally also be seen in the interstitium in which case fibrosis is a common related finding [84] (Fig. 2.24a, b). The particulate matter is often surrounded by giant cells and accompanied by a neutrophilic infiltrate. However, not all cases in which aspiration is clinically documented show the presence of particulate matter in the lung and a granulomatous tissue reaction may be absent [85]. In these cases, the pattern of lung injury can mimic diffuse alveolar damage characterized by fibrin exudation within air spaces leading to the formation of hyaline membranes. The microscopic appearance of the foreign matter depends on the type of aspirated material. Vegetable particles often consist of septate eosinophilic or basophilic structures rimmed by a hyaline cuticle and with a sieve-like inner structure whereas talc or crystalline material presents as refractile yellow-gray sheet-like material or large gray cord-like structures [85] (Fig. 2.25a, b). Hence the importance of examining all cases of suspected aspiration under polarized light in order to identify the potential presence of birefringent material within macrophages or multinucleate giant cells.

2.5.3 Differential Diagnosis

From a histologic point of view, the differential diagnosis includes other disease processes presenting with OP, granulomatous inflammation, multinucleate giant cells, and acute or subacute inflammatory changes. Infections causing a granulomatous response in particular can resemble aspiration pneumo-

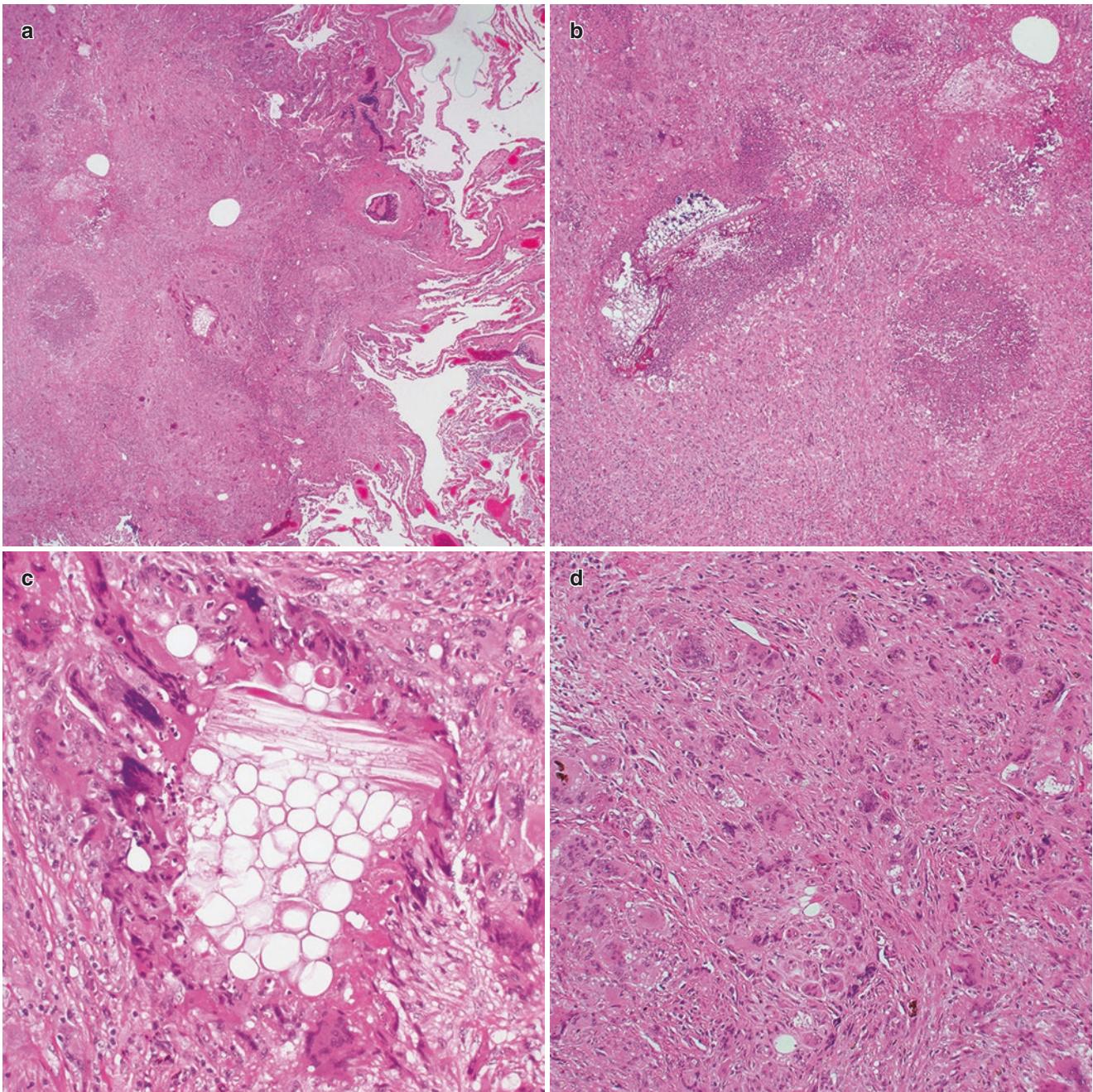


Fig. 2.23 (a) Aspiration pneumonia showing the demarcation between affected and uninvolved lung; (b) the lung is replaced by an inflammatory process composed of aspirated material with associated fibrous

reaction and foci of abscess formation; (c) aspirated vegetable matter surrounded by multinucleate foreign body-type giant cells; (d) granulomatous reaction around small inspissated foreign body material

nia, and special stains and tissue cultures to search for infectious organisms are essential in the work up of such cases. Bronchocentric granulomatosis is another process that may enter the differential diagnosis due to the presence of a granulomatous process surrounding bronchioles. Mucoid impaction, tissue eosinophilia, and the absence of foreign material usually advocates a diagnosis of bronchocentric granulomatosis in this context. Another granulomatous disease, granulomatosis with polyangiitis (Wegener granulomatosis), consists of a combina-

tion of necrotizing granulomas, multinucleate giant cells, and suppuration and may hence mimic aspiration pneumonia. Necrotizing vasculitis, however, another feature that defines granulomatosis with polyangiitis is absent in aspiration pneumonia. Lastly, intravenous drug abuse may result in the deposition of foreign material in the lung. In these cases, however, the material will be deposited within the walls or the lumina of arterial vessels and not in the bronchioles thereby separating this process from aspiration pneumonia [84].

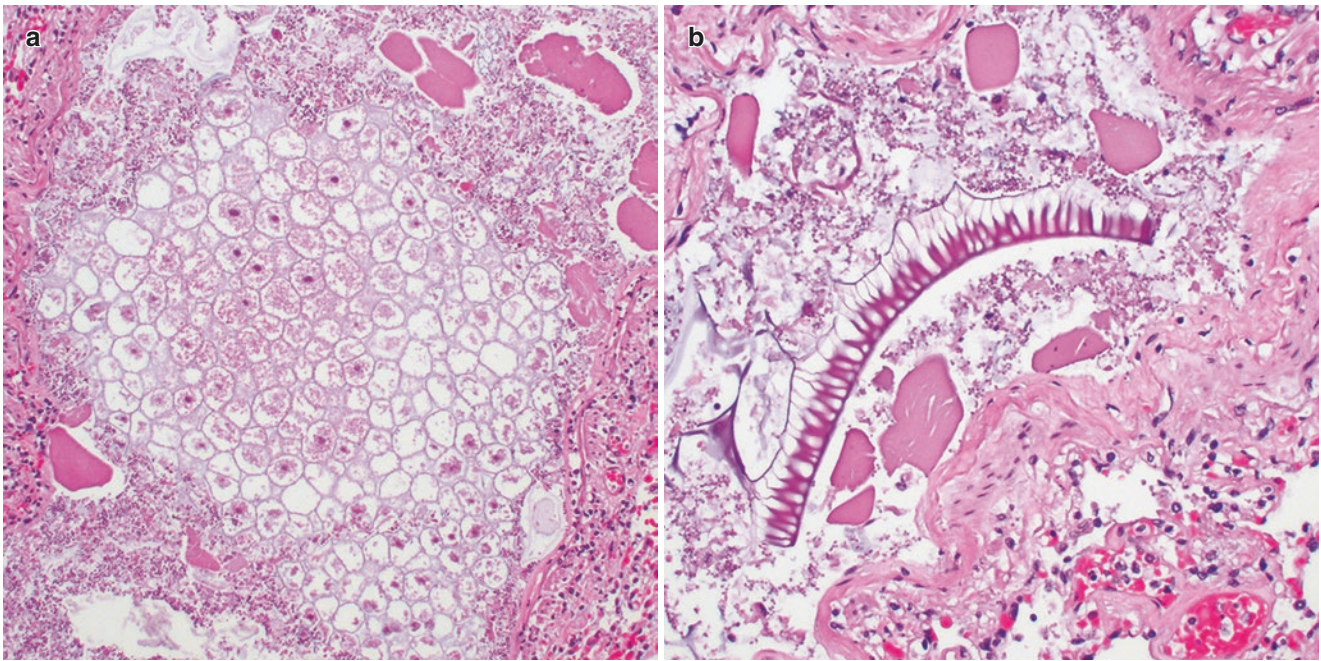


Fig. 2.24 (a) Vegetable matter often has a rigid sieve-like appearance in aspiration pneumonia; (b) aspirated vegetable material in the bronchial lumen of the lung

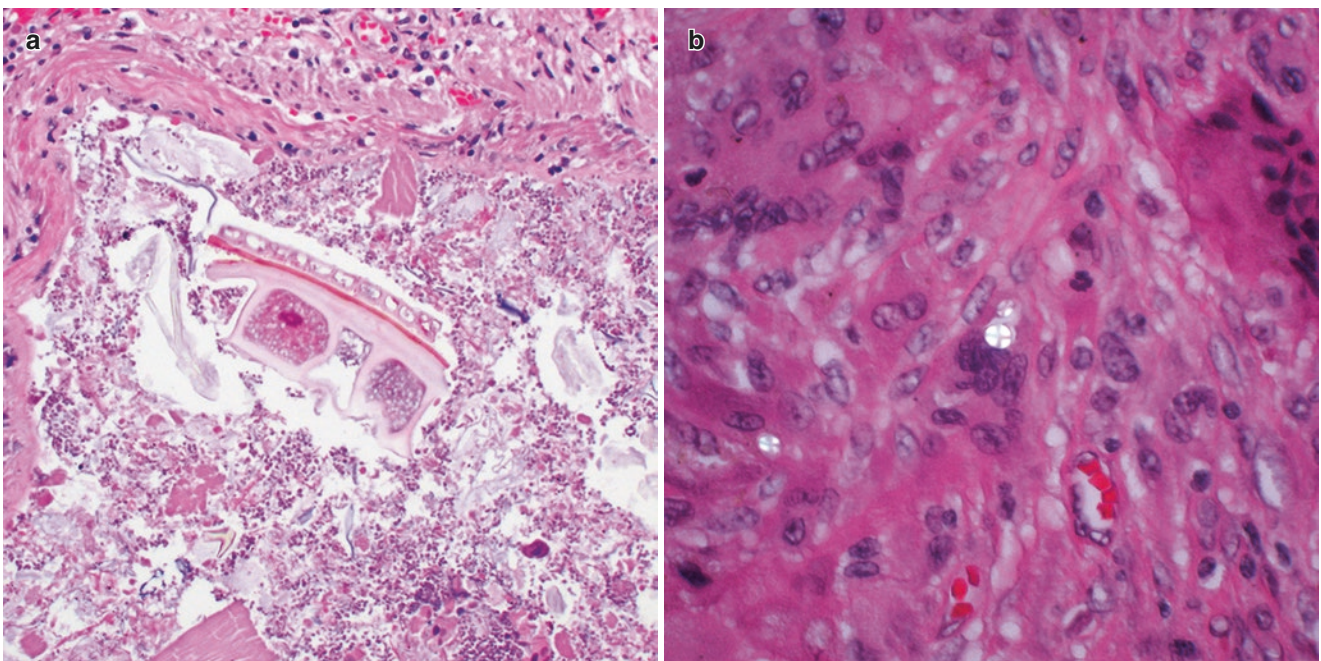


Fig. 2.25 (a) Fragmented vegetable matter in an airway in a case of aspiration pneumonia; (b) birefringent starch particles with characteristic Maltese cross appearance in a case of aspiration pneumonia when viewed under polarized light

2.6 Lipoid Pneumonia

Lipoid pneumonia is an uncommon form of pneumonia that is characterized by the presence of lipid material within alveolar spaces and alveolar macrophages. In the past, lipoid pneumonia has been reported under various different names

such as *paraffinoma*, *cholesterol pneumonia*, *golden pneumonia*, or *lipoid granulomatosis* [89–91]. Lipoid pneumonia can be divided into *exogenous* and *endogenous* types depending on the source of the lipid. Exogenous lipoid pneumonia usually occurs through ingestion or inhalation of vegetable or animal fats or mineral oils whereas endogenous lipid

pneumonia is the result of lipid accumulation within alveolar macrophages in the setting of bronchial obstruction, chronic pulmonary infection, pulmonary alveolar proteinosis, and fat storage diseases [92, 93]. The precise incidence of lipid pneumonia is difficult to determine although an autopsy series reported a frequency of 1.0–2.5% [94].

2.6.1 Clinical Features

Aspiration or inhalation of fatty substances is the causative factor for exogenous lipid pneumonia. Aspiration is often due to abnormality in deglutition or neuromuscular diseases affecting pharyngeal motility or the cough reflex. In healthy individuals, aspiration may be occupation related (fire eaters) or due to use of oil-based laxatives, oil-based nose drops, lip balm, or petroleum jelly among others. Patients most commonly present with dyspnea, cough, and fever. Radiologically, exogenous lipid pneumonia can show airspace consolidation, ground glass attenuation, airspace nodules, and crazy-paving pattern (interlobular septal thickening), preferentially affecting the lower lobes [95]. Endogenous lipid pneumonia is an obstructive type of pneumonitis that was first described in association with lung neoplasms [96]. It can also occur with diseases that are unassociated with bronchial obstruction such as infections, pulmonary alveolar proteinosis, or lipid storage disorders due to physical or chemical effects of airway blockage [97–101]. The clinical and radiological presentation largely depends on

the underlying etiology. Exposure avoidance and supportive care are the treatment of choice for exogenous lipid pneumonia. Systemic corticosteroids or whole-lung lavage may be indicated in more severe cases [102–104]. Surgical resection may be indicated in cases of endogenous lipid pneumonia, especially in cases of suspected lung cancer. Lipoid pneumonia is generally an indolent condition that may regress spontaneously; however, rarely, disease progression is seen leading to superinfection, respiratory insufficiency, or cor pulmonale [105–107].

2.6.2 Pathological Features

Pathologically, the aspirated or inhaled material in exogenous lipid pneumonia accumulates in alveolar macrophages which acquire a foamy or vacuolated look or elicits a foreign body giant cell reaction that can lead to the formation of giant cell granulomas (Fig. 2.26a–d). In addition, there may be varying degrees of inflammation in the alveolar walls and interlobular septa. Interstitial fibrosis with resulting architectural distortion may develop in lesions of longer duration. Lipid-containing vacuoles may be seen in the alveolar spaces or the interstitium especially in older lesions [108] (Fig. 2.27). In endogenous lipid pneumonia, lipid material is derived from breakdown products related to obstruction, cancer cell disintegration, or anoxic tissue injury. Often this results in the formation of low-density lipoprotein cholesterol which is apparent on microscopy as cholesterol crystals [109–112].

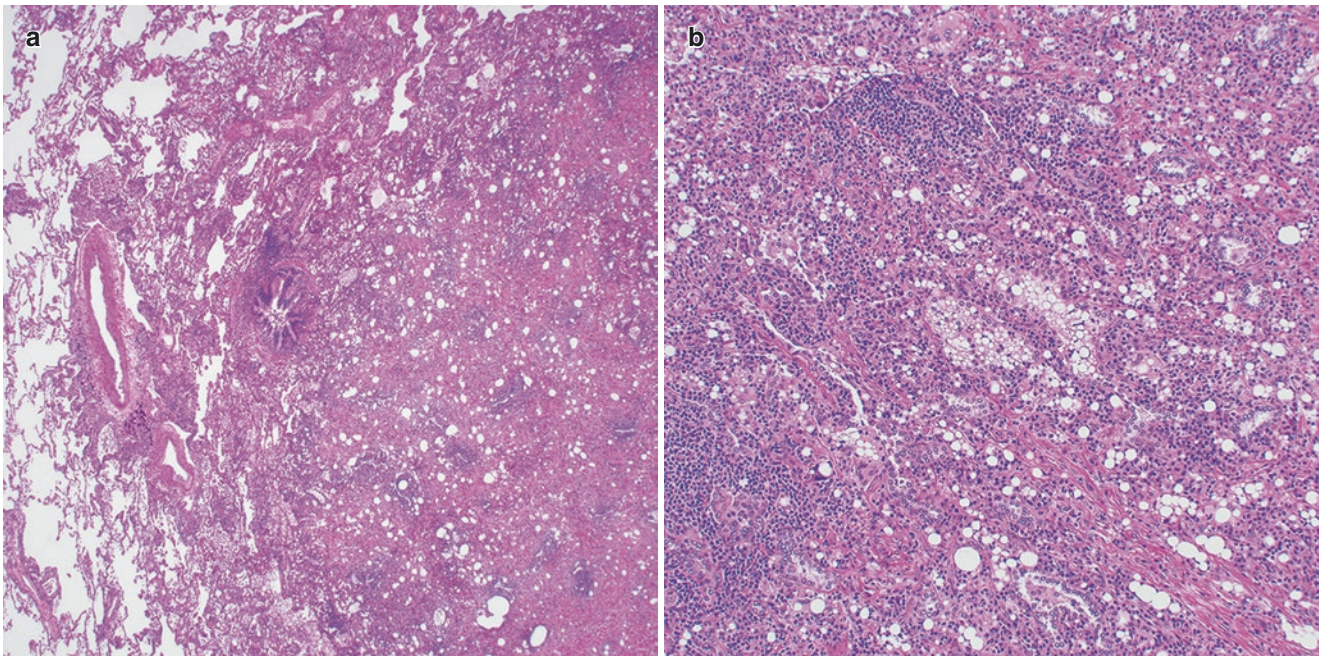


Fig. 2.26 (a) Low power view of lipid pneumonia; (b) numerous lipid vacuoles can be seen in the alveolar spaces; (c) the vacuoles typically elicit a giant cell or granulomatous reaction; (d) high power mag-

nification shows that the vacuoles are often engulfed by foreign body-type giant cells

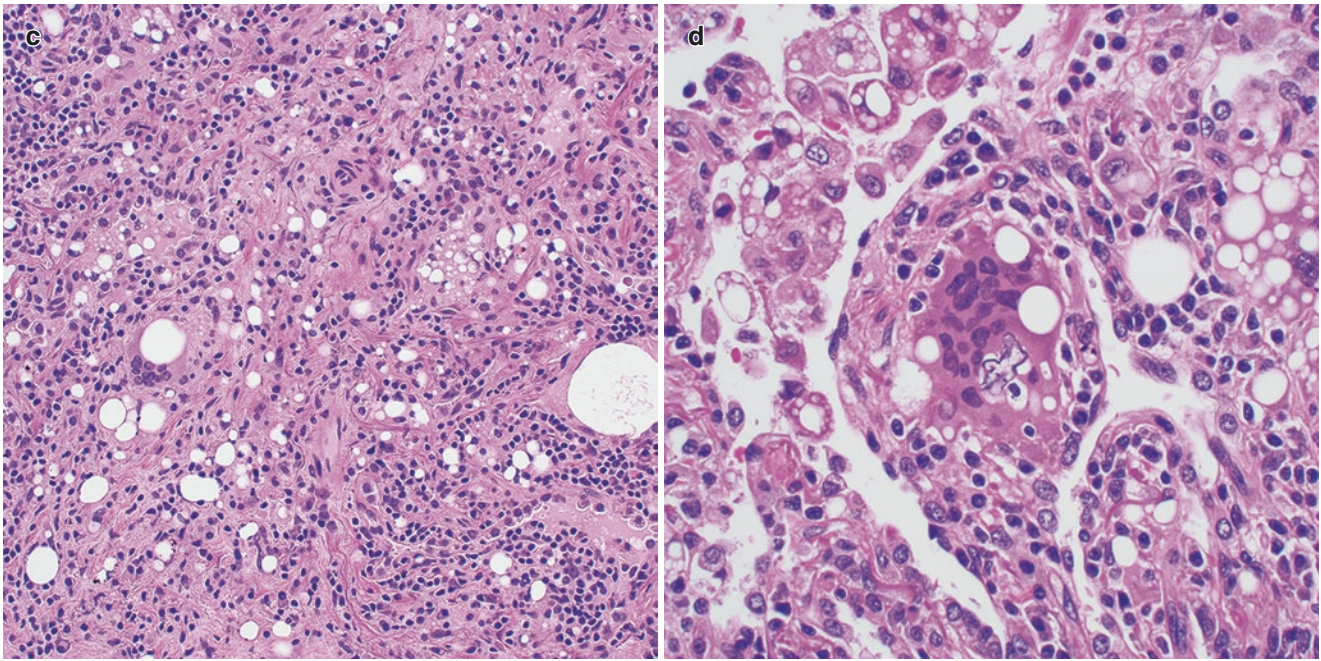


Fig. 2.26 (continued)

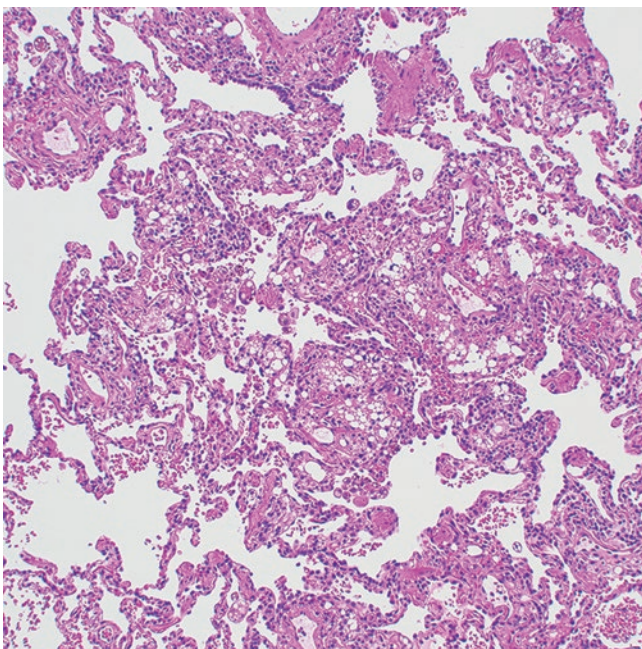


Fig. 2.27 In some cases of lipoid pneumonia, the lipid vacuoles can also be seen expanding the interstitial septa

2.6.3 Histochemical Features

The lipid material in alveolar macrophages or in the interstitial septa can be demonstrated using histochemical stains such as oil red O or Sudan black. Cholesterol crystals in

cases of endogenous lipoid pneumonia can be visualized with a Schultz stain (sulfuric acid and acetic acid).

2.6.4 Differential Diagnosis

The histological pattern of lipoid pneumonia may be confused with other granulomatous or histiocytic conditions, especially infectious diseases. The absence of infectious organisms on special stains or cultures studies in combination with the presence of lipid material and clinical history usually confirm the diagnosis.

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