Acute Lung Injury

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Venerino Poletti, Giovanni Poletti,
Christian Gurioli, Carlo Gurioli,
and Alessandra Dubini

16.1 Introduction

Rapidly progressive respiratory failure (from days to a few weeks) with diffuse parenchymal lung infiltrates in CT scan is a clinical setting that may be determined by a variety of clinical and pathologic conditions [1]. The term acute lung injury may be used to define this setting. CT scan features are usually characterized by alveolar consolidation and/or ground glass attenuation [2]. Some peculiar aspects may address a specific diagnosis: alveolar consolidation surrounded by ground glass attenuation (the "halo sign") is seen mainly in infections and in organizing pneumonia; the reversed "halo sign" (atoll sign) is more typically observed in cases with organizing pneumonia; and the perilobular sign may suggest the diagnosis of antisynthetase syndrome manifesting mainly as lung involvement or a diagnosis of Niemann-Pick disease. The pathologic background is highly heterogenous. Usually however this background may be identified without the need of biopsies because bronchoalveolar lavage (BAL) is diagnostic. Atypical type II pneumocytes with evident nucleoli and with finely textured cyanophilic cytoplasm and frequently fine or large cytoplasmic vacuoles appearing singly in flat plaques or in rosettes or pseupapillae are grouped around extracellular amorphic and metachromatic material and are the cytological hallmark of the histopathologic patterns called "diffuse alveolar damage" [3]. Inflammatory cells may consist of neutrophils (in classical diffuse alveolar damage pattern), eosinophils (in acute eosinophilic pneumonia), or even lymphocytes with a "Lutzner-like" appearance (in explosive organizing pneumonia or in a minority of cases of the yet not well-known idiopathic entity labeled by the morphological term "acute fibrinous and organizing pneumonia," in cases of antisynthetase syndrome, in drug-induced lung injury) [4–8]. The coexistence of hemosiderin-laden macrophages and red cells is diagnostic of alveolar hemorrhage/capillaritis (typically observed in ANCA-associated vasculitis or systemic lupus erythematosus). Infectious causes

V. Poletti (✉)
Department of Diseases of the Thorax,
Ospedale Morgagni-Pierantoni, Forlì, Italy

Department of Respiratory Diseases and Allergy,
Aarhus University Hospital, Aarhus, Denmark

G. Poletti
Hematologic Section, Corelab, Azienda USL
Romagna, Pievesestina, Cesena, Italy

C. Gurioli · C. Gurioli
Department of Diseases of the Thorax,
Ospedale Morgagni-Pierantoni, Forlì, Italy

A. Dubini
Department of Diseases of the Thorax-Pulmonology
Unit, Azienda Usl della Romagna, Ospedale GB
Morgagni, Forlì, Italy

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(from bacteria to DNA viruses) may be detected also. Finally microbiological investigation in BAL fluid, including molecular biological tests, is very sensitive and specific for identification of causative agents. Rarely rapidly progressive respiratory failure may be due to lung neoplasms (carcinomatous lymphangitis or neoplastic thrombotic microangiopathy, acute myeloid leukemia, metastatic melanoma) or to fat embolism. In this context however BAL may again contribute significantly to the final diagnostic [9].

Therefore lung biopsy is indicated only when BAL result to be inconclusive [10].

16.2 Case Series

Case 1

A 48-year-old male, non-smoker, truck-driver, was admitted to the hospital for acute dyspnea. Physical examination was not relevant. Gas analysis documented a severe hypoxemia (PaO_2 while breathing room air at rest = 54 mmHg) and hypocapnia. Pulmonary function tests were not performed due to the severe dyspnea. Routine laboratory tests were not relevant except a significant reduction of absolute lymphocyte count (lymphocytes = 385 × 10^9/L). High-resolution CT scan documented diffuse ground glass attenuation with superimposed interlobular septal thickening and intralobular reticular thickening ("crazy paving" pattern) (Fig. 16.1a). BAL was diagnostic of *Pneumocystis jiroveci* and *Cytomegalovirus* pneumonia (Fig. 16.1b, c). Further investigations documented an HIV infection and a marked CD4+ lymphopenia.

Case 2

A 54 year-old, housewife, non-smoker female was admitted to the hospital for low-grade fever since 1 month and rapidly progressive dyspnea in the last week. Family history was not relevant. Pulmonary function tests documented a restrictive defect with FVC = 58% of predicted and DLCO = 35% of predicted. Gas analysis, while breathing room air at rest, showed a PaO_2 of 59 mmHg and $PaCO_2$ of 31 mmHg. Physical examination showed only inspiratory rales and a high-pitched, mid-systolic crescendo-decrescendo murmur at the apex of the heart (mitral valve prolapse). CT scan showed alveolar consolidations and ground glass opacities distributed in the upper and lower parts of the lung with a gradient and mainly in the subpleural regions with a perilobular pattern (Fig. 16.2a).

Bronchoalveolar lavage fluid cell count documented an increase of total cells (450,000/mm^3) and an increase of lymphocytes (39%, in the great majority CD3+, with a CD4/CD8 ratio of 0.7) and of neutrophils (19%) with scattered eosinophils and mast cells. Some reactive type II pneumocytes singly or in small cluster were also present. Transbronchial cryobiopsies were taken from the lateral segment of the lower right lobe and the dorsal segment of the upper right lobe (Fig. 16.2b, c).

Autoimmune tests were not relevant except positivity for autoantibodies against PL-7 (threonyl-tRNA synthetase).

A diagnosis of idiopathic organizing pneumonia (with fibrin) and nonspecific interstitial pneumonia with an autoimmune background was rendered. This case has all the characteristics to be classified as idiopathic interstitial pneumonia with autoimmune features (IPAF). This is not a diagnosis but a heterogenous category. The morphologic features (perilobular pattern in CT scan and a mixed pattern in histology-organizing pneumonia with fibrin and nonspecific interstitial pneumonia) predict a good response to steroids and immunosuppressors. In fact the patient improved significantly after treatment with steroids (high doses at the beginning) and mycophenolate.

Case 3

A 37-year-old male, bank employee and smoker (11 packs/year), was admitted to intensive care unit for rapidly progressive respiratory failure. He had two previous episodes of acute dyspnea in the last 2 years diagnosed as community-acquired pneumonia and treated with a short course of antibiotics and steroids. CT scan showed a diffuse "crazy paving" pattern (Fig. 16.3a).

Laboratory tests documented normal functional renal indexes and a significant increase of

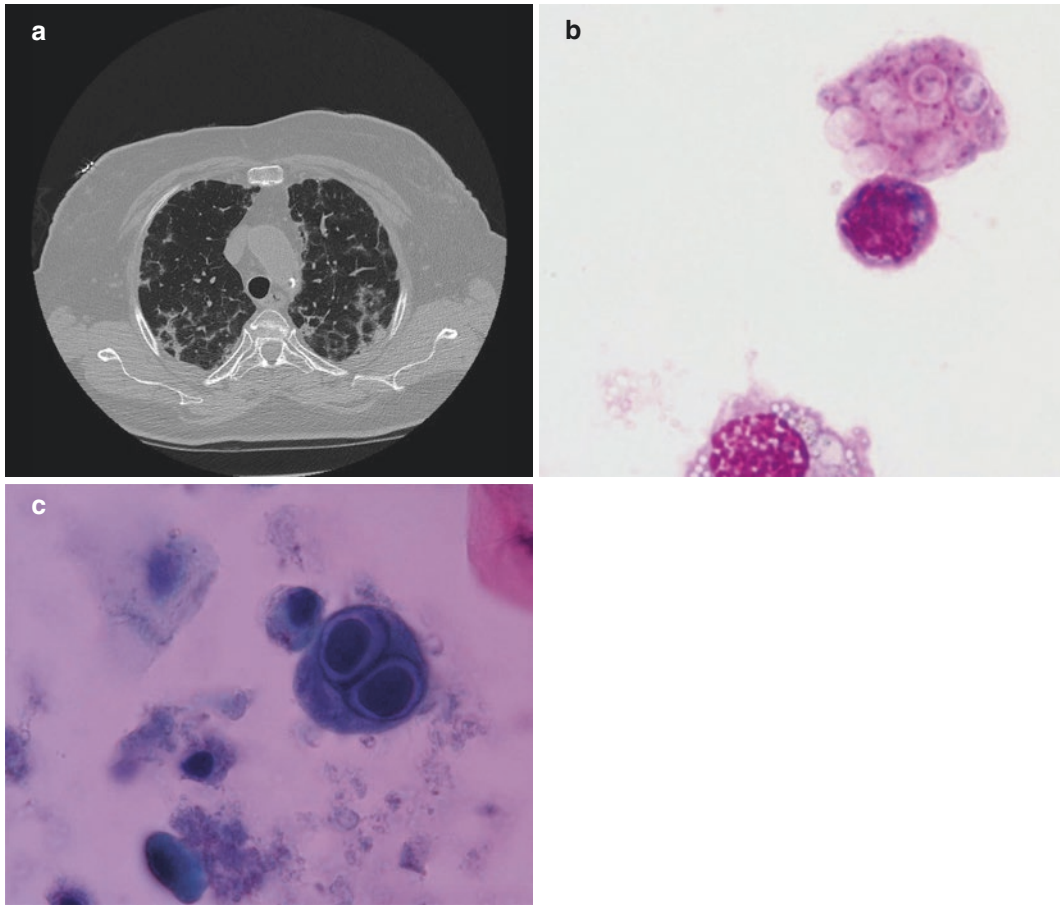

Fig. 16.1 (**a**) HRCT: crazy paving pattern and some alveolar consolidations in the upper lobes. (**b**) A cluster of extracellular foamy material consisting of spherical "cysts" with a thin wall containing one or two dot-like trophozoites. These casts are essentially diagnostic of *Pneumocystis jiroveci* (May Grunwald Giemsa). (**c**) A markedly enlarged cell with large, basophilic intranuclear inclusions surrounded by a clear halo and tiny satellite basophilic inclusions in the cytoplasm. Extracellular foamy exudate is also present. These cytological aspects are typically due to *Cytomegalovirus*. The foamy exudate represents casts of *Pneumocystis* (Papanicolaou)

C-reactive protein and of LDH and a slight increase of neutrophils. Autoimmunity tests, including ANCA autoantibodies, were negative.

Bloody lavage (increase on sequential aliquots of bloody fluid) was macroscopically evident, and the microscopic analysis documented fresh red cells, neutrophils, and siderophages.

Transbronchial cryobiopsy samples showed typical features of neutrophilic capillaritis (Fig. 16.3b). Because of the primary lung involvement, negative autoimmunity tests, negative tests for cocaine abuse, and a clinical history excluding use of drugs known to elicit an alveolar hemorrhage, a diagnosis of idiopathic pulmonary capillaritis was done. The patient was treated with steroids and cyclophosphamide.

16.3 Discussion

Lung biopsy is rarely useful in patients with acute lung failure and bilateral lung infiltrates, mainly when they are in noninvasive or mechanical ventilation. In fact in the majority of cases, blood laboratory tests are pivotal for a definite diagnosis. BAL may support the diagnosis in

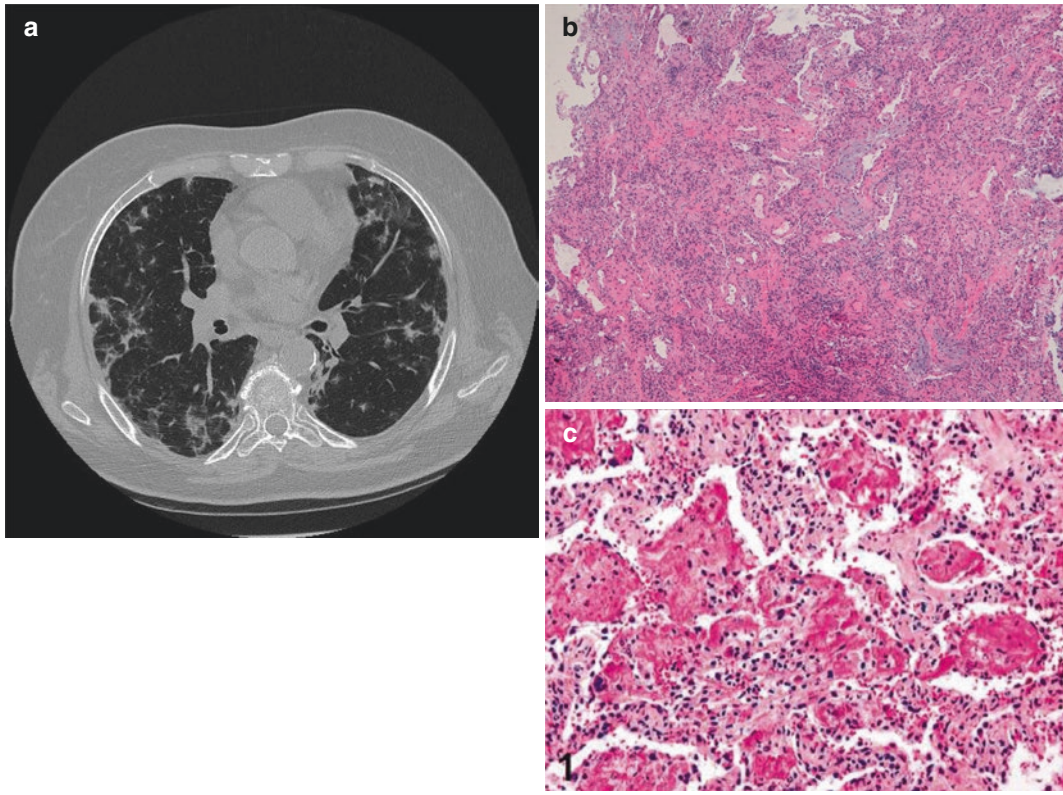

Fig. 16.2 (**a**) Peripheral alveolar consolidation and ground glass opacities predominantly located at the bounderies of the lobules with a poorly defined arcadelike or polygonal appearance (perilobular pattern) in the upper and lower parts of both lungs. (**b**) Nonspecific interstitial pneumonia. Preserved alveolar lung architecture with widened alveolar septa for fibrosis and chronic inflammatory cells infiltration. Ellipsoidal intra-alveolar buds of granulation tissue—pale in H and E—rich in extracellular matrix are also present (hematoxylin-eosin, low power). (**c**) In some areas intra-alveolar ball of fibrin with embedded inflammatory cells are also present (hematoxylin-eosin, mid power)

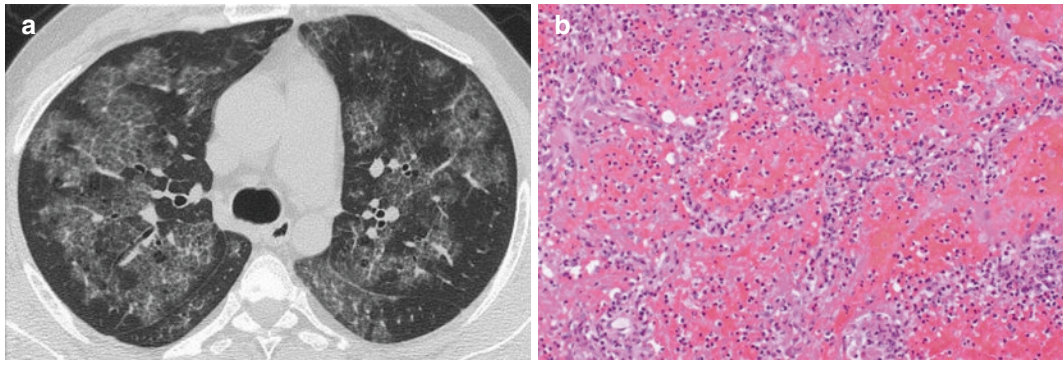

Fig. 16.3 (**a**) CT scan. Ground glass opacities and superimposed reticulation with sparing of the subpleural regions. (**b**) Alveolar walls are infiltrated and partly destroyed by neutrophils that spill into the adjacent alveolar spaces. Alveolar spaces contain also numerous red blood cells and fibrin (hematoxylin-eosin, mid power)

cases in which these tests will not be conclusive. Recent papers considering the role of surgical lung biopsy in this context did not explore the role of BAL and mainly they did not investigate the diagnostic value of cytological analysis of BAL fluid [10, 11]. Transbronchial forceps biopsy in combination with BAL was shown to increase the diagnostic confidence with no associated important complications [12]. The potential role of transbronchial cryobiopsy in acute respiratory distress syndrome has been recently addressed [13]. Transbronchial cryobiopsy in ventilated patients is done without the use of fluoroscopic guide, and an increase of pneumothorax rate or even bleeding is expected. This last complication may be reduced using bronchial blockers and stopping immediately the retrieval of the bronchoscope—after having frozen the probe—when resistance is felt. Transbronchial cryobiopsy may provide with large and well-preserved samples to have a diagnosis of organizing pneumonia (with or without fibrin), diffuse alveolar damage, or pulmonary capillaritis or confirm the histopathologic background in subjects with acute-subacute disease that may be categorized as IPAF [14].

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