Acute interstitial pneumonia

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ABSTRACT: The term "acute interstitial pneumonia" (AIP) describes an idiopathic clinicopathological condition, characterized clinically by an interstitial lung disease causing rapid onset of respiratory failure, which is distinguishable from the other more chronic forms of interstitial pneumonia. It is synonymous with Hamman-Rich syndrome, occurring in patients without pre-existing lung disease.

The histopathological findings are those of diffuse alveolar damage. AIP radiologically and physiologically resembles acute respiratory distress syndrome (ARDS) and is considered to represent the small subset of patients with idiopathic ARDS. It is frequently confused with other clinical entities characterized by rapidly progressive interstitial pneumonia, especially secondary acute interstitial pneumonia, acute exacerbations and accelerated forms of cryptogenic fibrosing alveolitis. Furthermore, many authors use the above terms, both erroneously and interchangeably. It has a grave prognosis with >70% mortality in 3 months, despite mechanical ventilation.

This review aims to clarify the relative clinical and pathological issues and terminology.


Histological background and terminology

In 1935 [3] and subsequently in 1944 [4], L. Hamman and A. Rich of the Johns Hopkins Hospitals described four patients who died of a rapidly progressive lung process characterized by the presence of diffuse interstitial pneumonia and fibrosis. The clinical and pathological features of this disorder were considered new and unusual. They termed the condition "acute diffuse interstitial fibrosis of the lungs". The course of the disease was rapidly progressive and the patients died due to respiratory failure and right heart failure within 6 months of onset. On autopsy, the lungs showed diffuse progressive proliferation of the alveolar connective tissue of a type not previously encountered either by them or by other observers. On review of histological material from three of the four original cases described by L. Hamman and A. Rich, the features present were those of organizing or organized DAD, and it is now inferred that AIP represents the same process that was described in the Hamman-Rich report [6].

As well as the term "Hamman-Rich syndrome" [7–9], this clinicopathological process has also been called "accelerated variant of interstitial pneumonitis" [10]. "acute interstitial pneumonia" [1, 2, 7], "fulminant idiopathic pulmonary fibrosis" [11] and "acute diffuse interstitial fibrosis of the lungs" [12]. Unfortunately, the term "Hamman-Rich syndrome" was also considered by some groups to be synonymous with the less fulminant and chronic cases of CFA [9, 11] leading to the inappropriate coalescence of an acute potentially reversible lung injury and a chronic usually progressive fibrotic pulmonary disease. It is now considered that the AIP or "Hamman-Rich syndrome" should be limited to only the former of these two clinicopathological patterns [2, 6, 13–15].

Furthermore, there are papers describing "acute variants of interstitial pneumonitis" [10], in which the majority of patients had either underlying connective tissue diseases or other identifiable aetiologies and "idiopathic pulmonary fibrosis in adult respiratory distress syndrome" [16]. Although all these studies probably have the same...
Histiopathology

It is important to emphasize that the clinicopathological entity of AIP is characterized by the histopathological pattern of DAD. DAD can be found in a number of contexts (table 1). This pattern is more commonly seen in patients with ARDS, and AIP cannot be distinguished from ARDS on the basis of histology alone, the distinction being made purely on there being no identifiable aetiology in cases of AIP after clinical evaluation [1, 2, 6, 14, 15]. The features of DAD are traditionally divided into an early (or exudative) phase that is followed by a late (proliferative or organizing) stage, dependent on the timing of the biopsy in relation to the original lung insult [1, 2]. In practice, combinations of these patterns are often seen throughout the lung. The exudative phase develops during the first week following injury, characterized by interstitial and intra-alveolar oedema, formation of hyaline membranes, hyperplasia of type II pneumocytes, intra-alveolar haemorrhage and an interstitial infiltrate of mononuclear inflammatory cells [1, 2, 8, 14, 15]. However, in cases in which biopsy/autopsy is performed within hours of the insult, no more than an increase in neutrophil numbers within the alveolar capillaries and interstitial oedema may be seen. The proliferative stage usually begins during the second week after lung injury and is characterized by florid fibroblastic proliferation, within both the interstitium and the alveolar spaces. Type 2 cell hyperplasia may be prominent and the nuclear atypia may be sufficient for there to be an erroneous suspicion of malignancy, especially in cytological specimens. Therefore, it is important to be aware of the rapidity of the clinical course [1, 2, 8, 17]. Remnants of hyaline membrane may still be seen within airspaces or sometimes incorporated into the interstitium. Other associated features include thrombi in small pulmonary arteries and squamous metaplasia involving bronchiolar epithelium, the squamous epithelium also sometimes showing cytological atypia [1].

The histological pattern of DAD can usually be distinguished from chronic interstitial pneumonias such as usual interstitial pneumonia (UIP) and desquamative interstitial pneumonia on the basis of temporal uniformity within the fibrosis and a lack of intra-alveolar macrophages respectively, but it may be difficult to differentiate both bronchiolitis obliterans-organizing pneumonia (BOOP) and nonspecific interstitial pneumonia (NSIP) from the proliferative phase of DAD [1, 8]. Also, the type of fibrosis differs from that seen in the chronic interstitial pneumonias [1], with the fibrosis in DAD being characterized by more numerous fibroblasts, a more oedematous-appearing stroma and relatively little collagen deposition, in contrast to that in NSIP in which the fibrotic zones more often contain a greater abundance of collagen [7, 8, 15, 18]. Moreover, at low magnification, the histopathological changes in AIP are relatively uniform from field to field in contrast to those in BOOP, in which the fibroblastic component is more intra-alveolar and patchy, tending to be peribronchiolar in location [7, 17]. However, it is emphasized that there may be considerable histopathological overlap and, in these instances, it is essential to know the clinical history, as a rapid onset of symptoms is not characteristic of either BOOP or NSIP.

Occasionally, the features of DAD may also be seen superimposed on those of a chronic interstitial pneumonia, most commonly those with a pattern of UIP [1, 17]. This may develop if patients receive mechanical ventilation with high concentrations of oxygen or develop either a viral pneumonia or a drug reaction against a background of chronic ILD [1, 17, 18]. However, it may also represent an acute phase in the natural history of patients with CFA, sometimes termed an “acute exacerbation” and this may often go unnoticed as the terminal event, being discounted as a terminal infection [1, 17]. Again, the clinical history is especially helpful in establishing the correct diagnosis [1, 2, 7, 8].

Alveolar haemorrhage syndromes may show histological overlap with DAD, although pulmonary haemorrhage is often recognized as the problem clinically, and recent and old haemorrhages are the most prominent histological features [19].

There are no good series of bronchoalveolar lavage in AIP. It is the experience of the authors, however, that a neutrophil excess is observed, as is the case in ARDS.

Pathogenesis

DAD is a common reaction in the lung and many agents can result in a similar pattern of lung injury to that seen in AIP [20–22]. The acute lung injury is massive, generally involving a large proportion of the parenchyma and occurring as a single event. This differs from that seen in CFA, in which the “acute” injuries are multifocal and recurrent over many years [2]. The difference in patterns of insult goes some way towards explaining the differences in the underlying histopathological patterns of DAD and UIP, and the differences in clinical behaviour between AIP and CFA. CFA manifests chronic and progressive dyspnoea because of continuing and recurring injury with characteristic histopathological heterogeneity [2, 6, 8], whereas in AIP the affected lung area is large and acute respiratory failure ensues. Nevertheless, despite this clinicopathological correlation, the exact pathogenic mechanisms in AIP are not well known, although it has become clear that there are a number of mediators involved in the pathogenesis, including proinflammatory (e.g. cytokines, chemokines, oxygen radicals, eicosanoids and complement products) and anti-inflammatory factors (e.g. interleukin-1 receptor antagonist, interleukin-10 and prostaglandin I2) [21, 22].
Other mechanisms that may have some relevance to AIP include metalloproteinases and their tissue inhibitors [23], and proteins regulating apoptosis of type II pneumocytes. In this regard, p53, WAF1 and BAX (a homologue of Bcl-2 and induced by P53), have all been found to be up-regulated in DAD, reflecting a response to cellular and deoxyribonucleic acid damage [24, 25]. Bcl-2, another protein that regulates apoptosis, is also seen in DAD but only in myofibroblasts and not in type II cells [25]. Histochemical evaluation using lectins and monoclonal antibodies directed against surfactant apoprotein and collagen type IV is helpful in the evaluation of hyperplastic type II pneumocytes in DAD [26].

Clinical features

The clinical presentation and course of AIP are similar to ARDS other than that no identifiable predisposing factor is identified [1, 2, 8]. The onset is acute (1–3 weeks), with dyspnoea and cough followed by rapid development of respiratory failure and the need for mechanical ventilation in the vast majority of the patients. As such, the patients meet the criteria for acute lung injury/ARDS [27, 28]. A history of viral-like symptomatology exists in most cases. Fever is present in almost half of the patients on presentation, but extensive investigations for bacterial and viral agents are negative.

This is mirrored by the original cases of L. Hamman and A. Rich, which occurred in previously healthy individuals who presented with symptoms of dyspnoea, fever, cough and mucopurulent sputum 10–20 days following a “flu-like” syndrome. There is no apparent sex predilection in the cases of AIP reported to date and the mean age at onset of all reported cases is 49 yrs (range 7–83 yrs). Patient characteristics in the published series of AIP are shown in table 2. This table, however, includes series in which patients had recognized DAD aetiologies and, therefore, should not have been originally classified as AIP.

Table 2. – Patient characteristics in the published series of acute interstitial pneumonia

<table>
<thead>
<tr>
<th>First author</th>
<th>[Ref]</th>
<th>Cases (n)</th>
<th>Sex</th>
<th>Age yrs</th>
<th>Duration of symptoms days</th>
<th>Biopsy type</th>
<th>Outcome length of survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamman</td>
<td>[4]</td>
<td>4</td>
<td>1/3</td>
<td>43</td>
<td>21–68</td>
<td>0/8</td>
<td>All died/1.7 months (20 days–3 months)</td>
<td>First description</td>
</tr>
<tr>
<td>Katzstein</td>
<td>[1]</td>
<td>8</td>
<td>3/5</td>
<td>28</td>
<td>13–50</td>
<td>8–17</td>
<td>7 died/5 at 23 days–2 months, 2 at 3.5 and 6 months; 1 survivor/recovered after 35 days</td>
<td>Original description</td>
</tr>
<tr>
<td>Olson</td>
<td>[6]</td>
<td>29</td>
<td>14/15</td>
<td>50</td>
<td>18 (&lt;7 in 14 patients)</td>
<td>24/5</td>
<td>12/29 survived/discharged from hospital after 48 (11–104) days</td>
<td>Retrospective review of previously diagnosed cases</td>
</tr>
<tr>
<td>Primack</td>
<td>[29]</td>
<td>9*</td>
<td>7/2</td>
<td>65</td>
<td>46–83</td>
<td>NA</td>
<td>7/2</td>
<td>CT study</td>
</tr>
<tr>
<td>Ichiado</td>
<td>[30]</td>
<td>14</td>
<td>8/6</td>
<td>53</td>
<td>40–66</td>
<td>&lt;30</td>
<td>3/11</td>
<td>Retrospective HRCT study (only 7 examined PM)</td>
</tr>
</tbody>
</table>

Data are presented as mean and/or range or as absolute numbers. *: two patients had cryptogenic fibrosing alveolitis, one systemic lupus erythematosus, one asbestos exposure and one cirrhosis. M: male; F: female; OLB: open lung biopsy; PM: post mortem; MV: mechanical ventilation; CT: computed tomography; HRCT: high-resolution CT.
predominant consolidation. Ichikado et al. [30], in a retrospective review of 14 AIP cases (three with open lung biopsy and 11 cases at autopsy) correlated high-resolution computed tomographic findings with histopathological appearances. They employed post mortem HRCT in 27 selected areas of the lung and attempted to establish a detailed correlation with the pathological stages (acute exudative, subacute proliferative and chronic fibrotic phases) of AIP. In the exudative phase, they found increased attenuation without traction bronchiectasis and spared areas within or adjacent to areas of increased attenuation; in the proliferative phase, they found increased attenuation with or without traction bronchiectasis; and, in the fibrotic phase, increased attenuation with traction bronchiectasis and honeycombing. Although the high-resolution computed tomographic findings were not specific to the pathological phase, traction bronchiectasis in areas of increased attenuation suggested a late-phase. They concluded that histological HRCT-assisted assessment of “active” lesions might be important in management decisions regarding patients with AIP.

Recently, Akira [31] described the computed tomographic features in seven patients with AIP, two patients with an accelerated form of CFA and 10 with an acute exacerbation of CFA. All patients showed progressive ground-glass attenuation, consolidation or both on initial examination. In the seven patients with AIP, none had predominant subpleural ground-glass attenuation. Distortion and traction bronchiectasis were observed if CT was performed >7 days after the onset. On late follow-up examination (after 105 and 114 days of onset), traction bronchiectasis and cystic airspaces had become apparent. The computed tomographic features of the two patients with the accelerated form of CFA included bilateral areas of ground-glass opacity, consolidation or both on initial and follow-up CT. On follow-up examination, traction bronchiectasis and cystic airspaces were seen in one patient after 37 days, and were associated with consolidation. Post mortem CT revealed extensive subpleural honeycombing, which was not seen on initial computed tomographic examination. In the 10 patients with acute exacerbation of CFA, bilateral multifocal or diffuse areas of ground-glass attenuation and subpleural honeycombing were seen. Follow-up CT showed a change from ground-glass attenuation to consolidation with distortion.

Architectural distortion and traction bronchiectasis were seen after 1 week from the onset, cystic lesions within 1 month and extensive honeycombing within 3 months. The authors conclude that early computed tomographic examination at the onset of acute symptoms may help to differentiate the fulminant forms of idiopathic interstitial pneumonia.

Mimics of acute interstitial pneumonia

Infectious pneumonia should be rigorously excluded from the outset by means of an extensive laboratory work-up. Serological and other biological samples should be stored for future epidemiological research given the idiopathic nature of the disease and the viral-like symptomatology on presentation. The clinical history and investigation should identify ARDS of known aetiology (e.g. sepsis, drug reaction and transfusion) as well as underlying systemic diseases (e.g. connective tissue disease and vasculitis) that may cause DAD. Patients may have underlying lone CFA, which has gone unnoticed or has suffered an acute exacerbation [33]. However, certain histological and radiological features can help in the differential diagnosis (table 3).

Acute exacerbation/acceleration of cryptogenic fibrosing alveolitis

Most patients with CFA show a slowly progressive deterioration characterized by progressive parenchymal lung injury and fibrosis leading to restrictive lung disease, decreased diffusing capacity and, ultimately, cor pulmonale. The mean survival is 4 yrs [33–36]. However, an accelerated phase may occur at some point during the chronic course of the disease [31, 33], which may be misinterpreted as infection. It still remains uncertain what causes acute exacerbation, which may occur at any stage in the history of CFA.

Clinical data are summarized in table 4. Kondoh et al. [37] reported a series of three patients with acute exacerbation of known CFA, with a duration of exacerbation of 3–20 days and a duration of disease before exacerbation of 6–24 months. They defined acute exacerbation

| Table 3. – Distinguishing characteristics among fulminant forms of idiopathic interstitial pneumonia |
|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| AIP | CFA | Acute exacerbation of CFA |
| Onset | Acute (1–2 weeks) | Chronic (>6 months) | Acute on chronic |
| Chest radiography | Bilateral airspace opacity | Bilateral reticular opacities in lower zones/honeycombing | New areas of ground glass on a diffuse reticular pattern; progress to consolidation |
| HRCT | Bilateral ground-glass opacities and/or airspace consolidation | Irregular lines, traction bronchi(ol)ectasis, honeycombing, patchy subpleural and lower zone predominance | New areas of ground glass on a diffusely reticular pattern without distortion or traction bronchiectasis; progress to consolidation |
| Pathology | Homogeneous organizing DAD, focal hyaline membranes | UIP: heterogeneous patchy subpleural fibrosis, honeycombing, fibroblast foci | DAD and UIP |
| Treatment | MV, antivirals, CS, IMS | CS±IMS | CS±IMS; institute or increase dose/combination |
| Prognosis | 75% mortality in 6 months | 50% mortality in 5 yrs | 50% mortality in 1 month |

AIP: acute interstitial pneumonia; CFA: cryptogenic fibrosing alveolitis; HRCT: high-resolution computed tomography; DAD: diffuse alveolar damage; MV: mechanical ventilation; CS: corticosteroids; IMS: immunosuppressive drugs; UIP: usual interstitial pneumonia.
in their patients with known CFA as follows: 1) exacerbation of dyspnoea over a few weeks; 2) newly developing diffuse pulmonary infiltrates on chest radiography; 3) deterioration of hypoxaemia (arterial oxygen tension \( P_a,O_2 \)/inspiratory oxygen fraction \( F_i,O_2 \) <225), and 4) absence of infectious agents. All patients’ conditions deteriorated, and their lung injury score reached the state of severe lung injury. The initial symptoms were influenza-like illness or cough with fever. All patients exhibited leukocytosis and elevation of C-reactive protein concentration. Infectious events were excluded by extensive bacteriological and serological examination. Findings from bronchoalveolar lavage showed marked neutrophilia and elevation of albumin concentrations. Open lung biopsy, performed within 2 weeks after the exacerbation, confirmed an acute DAD pattern without hyaline membrane formation together with a chronic interstitial pneumonia of UIP type. However, there had been no historical confirmation of UIP before the acute exacerbation. The condition of the patients improved after corticosteroid treatment. One patient died after 5 months of superimposed methicillin-resistant \( Staphylococcus aureus \) infection; the other two were alive at 10 and 30 months of follow-up, respectively.

Akiyama et al. [38] described 17 patients who fulfilled the following criteria for acceleration of CFA: exacerbation of dyspnoea within 1 month; new diffuse pulmonary opacities on chest radiography, a decrease in \( P_a,O_2 \) of >1.33 kPa (10 mmHg); and absence of an infectious agent or heart failure. Seven patients underwent sequential computed tomographic examination and pathological examination was performed in nine patients. High-resolution computed tomographic findings during phases of accelerated deterioration were classified as peripheral \( n=6 \), multifocal \( n=6 \) and diffuse \( n=5 \) parenchymal opacification. A response to corticosteroid treatment occurred in three of six patients with a multifocal pattern and all patients with a peripheral pattern. Eight patients with either a diffuse \( n=5 \) or multifocal \( n=3 \) pattern died within 3 months of presentation. The multifocal pattern thus carries a variable prognosis. The diffuse pattern was universally fatal and the majority of those with a peripheral pattern improved sustainedly. Multifocal and diffuse opacifications corresponded pathologically to acute DAD. Peripheral opacifications corresponded to active fibroblastic foci. The authors conclude that computed tomographic patterns during the rapid deterioration of CFA may be of prognostic and therapeutic significance (table 4). No survivors of AIP have been reported to progress or convert to CFA [6].

**Diffuse alveolar damage associated with systemic disease**

The term AIP has been used in patients having a number of underlying systemic diseases, especially connective tissue diseases and vasculitis. The reason for using the term AIP in these rare cases is that the patients develop rapidly progressive interstitial pneumonia with acute respiratory failure and DAD on histology. Only a few reports involving small series or case reports describe the development of AIP in systemic diseases, and many of these studies report the condition as “AIP associated with the relevant connective tissue disorder”. Patients with dermatomyositis, polymyositis, scleroderma and rheumatoid arthritis may present with a pattern of DAD [39–43]. Acute lupus pneumonitis also probably equates to DAD as a complication of systemic lupus erythematosus [39], and sporadic cases of acute progressive ILD with a clinical picture similar to AIP have been described in patients with Takayasu’s arteritis [44], polyarteritis nodosa [45], Behçet’s disease [46] and microscopic polyarteritis [47]. It is important to maintain a distinction between “lone” AIP and DAD occurring in the context of (chronic) systemic disease. It could be argued that it is not yet justifiable to separate out DAD occurring in the context of chronic systemic disease from AIP occurring in the absence of such associations. However, it is clear that the diffuse lung disease manifestations of systemic disease should not be lumped together with diffuse disease occurring alone in the lung and the authors would prefer to consider them separately until studies of cause, response to treatment and outcome in systemic disease have been described.

**Treatment**

This is largely supportive and initially consists of oxygen supplementation and noninvasive mechanical ventilation,
but mechanical ventilation with positive end-expiratory pressure is required in most patients. Patients are often treated with various antibiotics, antiviral agents and steroids.

Some authors stress the importance of early treatment with corticosteroids [9], which may improve outcome as in patients with ARDS [28]. The degree of the initial host defense response may determine the progression of DAD. A combination of intravenous prednisolone (250 mg-day−1) and intravenous cyclophosphamide (1.5 g) with intravenous vincristine (2 mg) has been reported to be effective in halting the rapid progression of the disease [9, 10]. Treatment with newer agents, such as surfactant, anticytokine antibodies and inhaled nitric oxide traditionally used for ARDS, might be beneficial but are largely untested [27, 28].

Robinson et al. [48] described a case of AIP who required single-lung transplantation. There was improvement in the native lung post-transplantation, presumably in response to post-transplantation immunosuppression. The patient showed a rather slower progression of AIP than the cases reviewed by Olson et al. [6] and similar to the cases described by Hamman and Rich [3, 4]. Improvement in a native lung has never been recognized in 28 patients with CFA (with UIP) who required transplantation [49].

Outcome

The mean 6-month mortality of patients with AIP is 78% (range 60–100%) (table 2). In the Mayo Clinic series [6], only 12 of 29 patients survived after long and complicated hospitalization, the mean duration of hospitalization was 33 days. This survival was similar to that of ARDS in the same era. No histopathological feature was predictive of survival. Surprisingly, many survivors showed severe architectural destruction of lung parenchyma, whereas several nonsurvivors had much less impressive parenchymal destruction. Follow-up spirometry undertaken in six patients showed either mild abnormalities (n=2) or normal lung function (n=4) within 1–2 yrs. In the series of Katzenstein et al. [1] only one patient survived; all the others died within 6 months. In the series of Primack et al. [29], eight of nine patients died within 3 months of presentation. There was a striking difference in the survival of patients described by Olson et al. [6] by comparison with other series. This probably reflects the severity of the patients at presentation. The overwhelming majority of patients in the series of Olson et al. [6] were well enough to undergo diagnostic biopsy and had less severe disease as evidenced by the $P_aO_2/F_iO_2$ ratio. Finally, this series was originally compiled from pathological records which may not be a true reflection of the severity of the disease as a whole, i.e. for those patients not well enough to undergo biopsy.

Today acute respiratory distress syndrome has a better prognosis than previously with <50% mortality [27, 28]. The extent to which experimental therapies or other changes in treatment contributed to this decline in mortality rates is not known. Future investigation will show whether this trend is followed in patients with acute interstitial pneumonia.

References