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CASE STUDY

Acute interstitial pneumonia: report of a series

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Acute interstitial pneumonia: report of a series. A. Bonaccorsi, A. Cancellieri, M. Chilosi, R. Trisolini, M. Boaron, N. Crimi, V. Poletti. ©ERS Journals Ltd 2003.
ABSTRACT: Four cases of acute interstitial pneumonia (AIP) are described with special emphasis on clinical background, lung imaging and bronchoalveolar lavage findings.

A retrospective chart review of four patients with histologically-proven AIP, diagnosed between 1998 and 2000, was carried out. Clinical data, bronchoalveolar lavage (BAL) findings, high-resolution computed tomography (HRCT) and histological features were analysed.

Three patients died and only one is in follow-up. HRCT showed areas of ground glass attenuation and alveolar consolidation in all patients. Histology, documented by open lung biopsy or autopsy specimens, was consistent with the organising form of diffuse alveolar damage pattern.

BAL findings were characteristic, with a huge neutrophilia associated with scattered atypical type II pneumocytes collected in clusters with extracellular amorphous material (fragments of hyaline membranes) observed in two out of three cases.

In this paper, four cases of acute interstitial pneumonia are reported in detail. The poor prognosis associated with this entity has been confirmed and the possible diagnostic role of the bronchoalveolar lavage is emphasised.
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Acute interstitial pneumonia (AIP) is an idiopathic lung disease characterised by rapidly progressive dyspnoea developing over days to weeks [1, 2]. AIP is synonymous with Hamman Rich syndrome. It is defined as rapidly progressive respiratory failure occurring in patients without pre-existing lung disease or extrathoracic disorders known to be associated with lung involvement [3–5]. The outcome is often fatal [1, 3, 4, 6]. The chest radiographic and high-resolution computed tomography (HRCT) scan manifestations of AIP are bilateral and sometimes patchy, and there are alveolar densities associated to areas of ground glass attenuation [7].

AIP radiologically and physiologically resembles acute respiratory distress syndrome (ARDS) [7, 8] and the term idiopathic AIP appears to be quite appropriate. AIP is frequently confused with acute multilobar infectious pneumonia, with other forms of interstitial pneumonia, such as acute exacerbation of idiopathic pulmonary fibrosis, rapidly progressive bronchiolitis obliterans-organising pneumonia [9] or idiopathic acute eosinophilic pneumonia [1, 10, 11], with collagen-vascular diseases involving the lungs and with primary or secondary pulmonary capillaritis [12]. Lung biopsy is confirmatory for AIP and it shows the organising form of diffuse alveolar damage (DAD) pattern [5, 13]. Due to the rarity of this entity, the clinical profile, laboratory data and treatment are not well defined. High-dose corticosteroids and cyclophosphamide are the drugs usually used [14] and recently it has been reported that survivors can experience either recurrences or progressive interstitial lung disease [6].

To widen the knowledge in this field, a series of four cases of AIP is presented in detail here. The possible diagnostic role of bronchoalveolar lavage (BAL) is also emphasised.

Methods

Four patients, three males and one female, constituted the study group. Data were collected from January 1998 to December 2000. All patients presented respiratory symptoms with a duration of $\leqslant 65$ days. None of the patients had any evidence of systemic infection, iatrogenic causes of immunosuppression, toxic exposures, cancer undergoing cytotoxic chemotherapy, pre-existing interstitial lung disease or pre-existing collagen-vascular disease. Collected data included tobacco, history type and duration of symptoms, initial physical examination, laboratory findings, results of microbial cultures, need for mechanical ventilation, corticosteroid or cytotoxic therapy, survival days in hospital and follow-up.

The follow-up information on the only survivor included lung physiological tests and HRCT of the

Table 1. – Clinical data at onset

Case no.	Age	Sex	Smoking	Illness duration days	Respiratory symptoms	Signs	Mechanical ventilation	Outcome
1	52	M	Yes	60	Dyspnoea	Cyanosis	Yes	Died at day 7
2	44	F	No	40	Dyspnoea, cough	None	Yes	Died at day 14
3	66	M	No	17	Dyspnoea, cough	Fever, crackles	Yes	Alive and well
4	67	M	Yes	30	Dyspnoea	Fever, crackles	Yes	Died at day 38

M: male; F: female.

chest. Functional respiratory studies included spirometry (predicted normal values were obtained from standard references and the results were expressed as % pred), carbon monoxide diffusing capacity and arterial blood gases.

All patients were submitted to an HRCT scan of the chest. For this diagnostic investigation, 1 mm thick images obtained at 10 mm intervals through the chest were taken. Scans were reconstructed using a high spatial-frequency algorithm.

All patients were submitted to fibreoptic bronchoscopy (FBS). In three patients BAL was carried out within 2–4 days of hospitalisation. One patient could not be submitted to BAL because of critical conditions. The BAL was performed by instillation of six 25 mL aliquots of sterile saline solution; fluid was aspirated immediately after each aliquot was instilled and collected in a sterile container. After recovery, BAL fluid was filtered through a monolayer of surgical gauze to remove mucus, and immediately centrifuged at 34×*g* for 7 min. Cytospin preparations were stained by both the Diff Quick and the Papanicolaou methods. A BAL specialist (V. Poletti) performed the differential cell count (under light microscopy at ×1000 by counting 300 cells in random fields) and the evaluation of cytological cell characteristics. Total count was obtained by using a haemocytometer.

The infectious aetiology of the respiratory disease was ruled out in all patients with appropriate cultures (bacteria, *Legionella pneumophila*, *Chlamydia pneumoniae*, mycobacteria, fungi, cytomegalovirus, adenovirus, herpes simplex, influenza and parainfluenza) and immunofluorescence tests (syncitial respiratory virus, cytomegalovirus, adenovirus, herpes simplex) of BAL fluid or bronchial washing.

Two patients (no. 2 and no. 3) were submitted to lung biopsy during FBS whilst on mechanical ventilation. One patient (no. 1) was submitted to minithoracotomy whilst on mechanical ventilation. All the patients who died were submitted to autopsy.

Results

The series consisted of three males and one female. Clinical presentation and laboratory data are summarised in table 1 and table 2. The mean age was 57 yrs (range 44–66). The mean duration of symptoms was 37 days. Two out of four complained of cough and all patients had dyspnoea. Two patients presented with fever between 38 and 38.7°C and one patient had cyanosis. In two cases crackles were heard on auscultation. All the patients showed an increase in white blood cells.

Autoantibodies (antinuclear antibodies, anti deoxyribonucleic acid, antineutrophil antibodies, anticardiolipin antibodies, antiphospholipid antibodies) were not detected. With respect to smoking, two patients had never smoked and two patients were current smokers. All four patients needed mechanical ventilation. The mean duration of mechanical ventilation was 10 days (range 6–13). Three patients died and only one is under follow-up.

Lung imaging

The chest radiography showed interstitial shadowing and bilateral parenchymal consolidation predominating at the lung bases in all patients. HRCT of the chest provided suggestive findings in all four patients, such as ground glass areas of attenuation, predominantly involving the lung bases and diffuse alveolar consolidation (fig. 1). Ancillary findings were seen, such as traction bronchioloectasis (n=2), interstitial septal thickening (n=1) and mild bilateral pleural effusion (n=2).

Table 2. – Laboratory data at onset

Case no.	WBC $10^3 \cdot mm^{-3}$	PLT $\cdot mm^{-3}$	Fibrinogen $mg \cdot dL^{-1}$	LDH $U \cdot L^{-1}$	ESR $mm \cdot h^{-1}$	ALT $U \cdot L^{-1}$	AST $U \cdot L^{-1}$	Urea nitrogen $mg \cdot dL^{-1}$	Creatinine $mg \cdot dL^{-1}$	Urine
1	27	48	301	1352	90	73	74	49	0.75	Normal
2	27	351	349	1420	60	15	33	40	0.40	Normal
3	9	380	395	324	18	28	74	38	0.71	Normal
4	11	370	ND	ND	86	34	32	54	0.86	Normal

WBC: white blood cells; PLT: platelets; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ND: not determined.

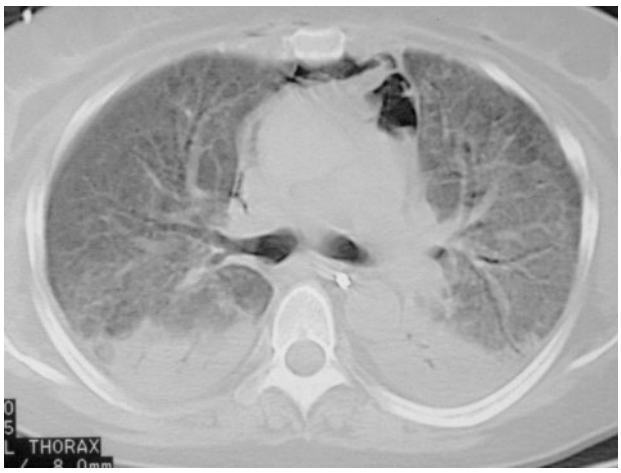

Fig. 1. – High-resolution computed tomography scan performed at the middle level. Bilateral areas of alveolar opacification are evident in the pending areas of the lungs.

Pulmonary functional test

There was a restrictive impairment in one of two patients (table 3). The diffusion of carbon monoxide was reduced in the two patients in whom the test could be performed. Two patients were not able to complete the tests because of their critical conditions. Room air hypoxaemia was found in all patients (mean oxygen tension in arterial blood 8.4 kPa (63 mmHg) and the mean arterial oxygen saturation (S_{a,O_2}) 91%).

Diagnosis

The diagnosis of AIP was achieved by open lung biopsy in one case (no. 3) and autopsy in the other three cases. In two cases the correct diagnosis had been previously suggested by transbronchial biopsy (no. 2 and no. 4). Infectious causes were carefully excluded. In all patients a DAD pattern was present in the exudative and organising phase. In detail, hyaline membranes, type II epithelial cell hyperplasia/dysplasia, interstitial oedema and foci of intra-alveolar organisation were present in a mixture in all above-mentioned specimens (fig. 2).

Table 3. – Pulmonary function tests

Case no.	FVC % pred	FEV1/ FVC ratio	$T_{L,CO_{SB}}$ % pred	$T_{L,CO}$/ VA % pred	P_{a,O_2} mmHg	S_{a,O_2} %
1	NA	NA	NA	NA	55.7	86
2	56	97.5	35.7	57.5	72.0	95
3	75	118.0	58.9	67.0	58.0	91
4	NA	NA	NA	NA	64.0	91

FVC: forced vital capacity; FEV1: forced expiratory volume in one second; $T_{L,CO_{SB}}$: lung transfer for carbon monoxide in single breath; % pred: % predicted normal; VA: alveolar volume; P_{a,O_2}: oxygen tension in arterial blood; S_{a,O_2}: arterial oxygen saturation; NA: not applicable.

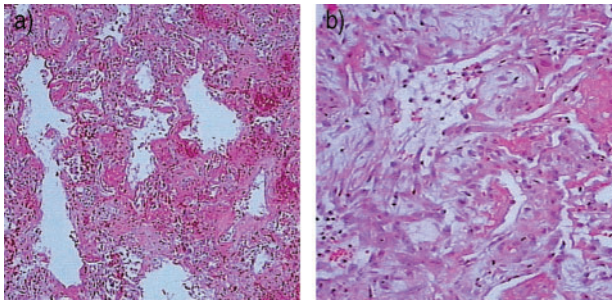

Fig. 2. – Open lung biopsy specimen. a) Widened alveolar septa due to interstitial oedema and numerous hyaline membranes are evident at low magnification. b) Extracellular matrix-containing spindle cells are present in the interstitial and alveolar structures associated with fragments of hyaline membranes in another portion of the specimen (organising phase of diffuse alveolar damage) (haematoxylin and eosin stain).

Bronchoalveolar lavage profile

The BAL cytological profile showed an increased total cell count (560,000 (no. 2), 530,000 (no. 3), 1,230,000 cells·mL^{-1} (no. 4)) and a marked increase in neutrophils in all patients (table 4). The CD4:CD8 ratio was within the normal range. It is noteworthy that in two out of three cases the BAL fluid analysis revealed atypical epithelial cells (fig. 3) with evident

Table 4. – Bronchoalveolar lavage

Case no.	Cellularity 10^3·mL^{-1}	Mac. %	Lymph. %	Neut. %	Eosin. %	CD4: CD8 ratio
1	NA	NA	NA	NA	NA	NA
2	560	50	12	37	1	2.09
3	530	9	20	71		1.54
4	1230	16	5	74		ND

Mac.: macrophages; Lymph.: lymphocytes; Neut.: neutrophils; Eosin.: eosinophil; NA: not applicable; ND: not determined.

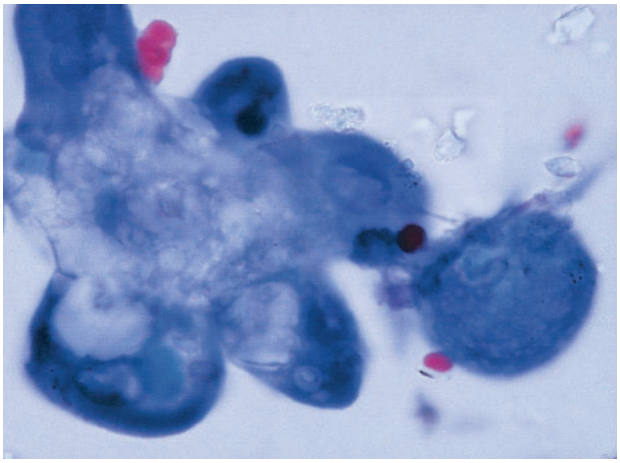

Fig. 3. – Bronchoalveolar lavage. At high magnification a cluster of atypical epithelial cells with wide, vacuolated cytoplasm and amorphous extracellular and intracellular material (fragments of hyaline membranes) are evident (Papanicolaou stain).

nucleoli and wide vacuolated cytoplasm, accumulated in clusters and extracellular amorphous material that was cyanophilic on Papanicolaou-stained preparations (a pattern described previously in ARDS patients and considered to be suggestive of diffuse alveolar damage). Pulmonary pathogens did not grow in BAL cultures.

Therapy and outcome

All four patients received high-dose corticosteroids (40 mg·day^{-1} up to 250 mg·day^{-1} *i.v.* of metylprednisolone). In two cases (no. 1 and 2) cyclophosphamide (500 mg·m^{-2} *i.v.* in bolus) was added.

Three patients died within 7 days, 14 days or 38 days of hospitalisation, respectively, and only one of them has achieved complete remission (table 1).

Follow-up

Nearly 1 yr later, the surviving patient is asymptomatic and has normal pulmonary functional tests (forced expiratory volume in one second (FEV1) 116%, FEV1/forced vital capacity 117.4%, lung transfer for carbon monoxide in single breath 73.4%) and normal gas exchange while breathing room air (S_{a,O_2} 91.9%). HRCT of the chest appears normal. This patient was admitted to the authors' hospital with near normal pulmonary function tests. His pulmonary function deteriorated quickly soon after but this case was probably the only one in which the diagnosis and therapy were carried out in the early phase of the disease.

Discussion

The main clinicopathological characteristics, lung imaging, functional studies and BAL fluid findings of a series of patients with AIP are reported. A male preponderance was evident. Nonspecific findings, such as rapidly progressive dyspnoea (no. 1–4), cough (no. 2 and no. 3), crackles (no. 3 and no. 4), cyanosis (no. 1), restrictive ventilatory impairment, reduction of the diffusion of carbon monoxide and hypoxaemia were found in the patients analysed. The diagnosis was made on the basis of the characteristic histological findings of diffuse alveolar damage.

AIP is an idiopathic clinicopathological condition, characterised by an acute lung injury causing rapid onset of respiratory failure [1]. The diagnosis of AIP is very complex because a long list of disorders needs to be excluded [13]. Recently, some reports have shown that the potential causes of AIP may include environmental exposure to infectious agents or toxins, genetic predisposition or a combination of the two [15, 16]. In a few cases, associations of AIP with rhinovirus or *Streptococcus pneumonia* were found [16]. In the current series, an infectious cause was excluded on the basis of in-depth microbiological investigations. Collagen vascular disorders and capillaritis were also excluded when serological investigations and BAL profiles (BAL fluid was not haemorrhagic) were taken into account. Since interstitial lung disease may sometimes precede the onset of joint disease in patients with rheumatoid arthritis [17, 18], the hypothesis that acute interstitial pneumonitis could be a form fruste of connective tissue disease [17, 18] with isolated lung involvement cannot be excluded from the data in this series.

Since most AIP patients seek medical treatment within 60 days of onset of symptoms this could help to differentiate AIP from other idiopathic interstitial pneumonias in which symptoms duration can be measured in months to years [13]. However, cases of rapidly progressive idiopathic organising pneumonia [19] can show overlapping clinical, radiological and histological findings with those occurring in AIP patients. The boundaries between these two entities are, in a few cases, arbitrary and the absence of an evident lymphocytosis in BAL fluid might be the more important element to distinguish AIP with a prominent intra-alveolar organisation and cryptogenic organising pneumonia [2]. The absence of eosinophils in lung tissue specimens and BAL fluid is evidence against a diagnosis of acute eosinophilic pneumonia.

HRCT [20, 21] proved to be nonspecific, by showing bilateral areas of ground glass attenuation and/or diffuse alveolar consolidation. Bronchioloectasis [22] was found in the two cases with a more prolonged period of mechanical ventilation, probably due to volume reduction and the predominance of organising features. ICHIKADO *et al.* [21] have shown that increased attenuation without traction bronchiectasis are associated with either the exudative or early proliferative phase of diffuse alveolar damage; areas of increased attenuation with traction bronchiectasis are instead associated with either the proliferative or the frankly fibrotic phase.

Histopathological investigation is always necessary for a definitive diagnosis of AIP [23, 24]. The tissue specimens of the cases presented here showed a DAD pattern, in the exudative phase and in the organising phase (that is the organising form of DAD). It is noteworthy that the same lesion was observed on transbronchial lung biopsy specimens obtained during mechanical ventilation in one case. Transbronchial lung biopsy has already been reported as a safe diagnostic tool in mechanically ventilated patients [25, 26]. Generous specimens obtained by transbronchial lung biopsy could substitute a surgical procedure for a definitive diagnosis when clinical, radiographical and microbiological data are consistent with a diagnosis of AIP [27].

BAL, performed in three cases, showed an increased cellularity and a marked increase of the neutrophil percentage. Furthermore, the presence of atypical epithelial cells and extracellular amorphous material was detected in two cases. These features have been suggested by the authors [27] to represent the cytological hallmark of DAD [1, 2]. In AIP the diagnostic value of BAL has never been considered [2], however, negative microbiological data coupled with characteristic cytological findings can underpin the diagnosis of DAD.

Three out of four patients did not achieve remission by corticosteroids, with or without cyclophosphamide, and died on mechanical ventilation. Only one, the patient in which definitive diagnostic investigations

started very early, had a favourable outcome and is in full remission at the time of follow-up.

In conclusion, this study confirms the clinical and radiological profile of acute interstitial pneumonia as reported previously. The diagnostic value of transbronchial lung biopsy and bronchoalveolar lavage is also emphasised. The necessity of open surgical biopsy can therefore be questioned and future prospective, multicentric studies evaluating these aspects seem to be of interest.

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