Early Intervention Can Improve Clinical Outcome of Acute Interstitial Pneumonia*

Gee Young Suh, MD;† Eun Hae Kang, MD;† Man Pyo Chung, MD; Kyung Soo Lee, MD; Joungho Han, MD; Masanori Kitaichi, MD; and O Jung Kwon, MD

Study objectives: To report on our experience with acute interstitial pneumonia (AIP) in which patients underwent early diagnostic procedures and received mechanical ventilation with a "lung-protective" strategy and early institution of immunosuppressive therapy.
Design: A retrospective chart review.
Setting: A tertiary referral hospital.
Participants: Ten patients with AIP who presented with idiopathic ARDS and showed diffuse alveolar damage on surgical lung biopsy specimens from July 1995 to March 2004.
Measurements and results: The median age of patients was 65.5 years (age range, 38 to 73 years). Patients presented with a median duration of severe dyspnea of 9.5 days (range, 2 to 34 days) at the hospital visit. All patients required mechanical ventilation beginning at median time of hospital day 1 (range, hospital day 0 to 5), which continued for a median duration of 9.5 days (range, 4 to 98 days). Patients received ventilation in the pressure assist-control mode with a median tidal volume of 6.97 mL/kg (range, 6.05 to 8.86 mL/kg) and median positive end-expiratory pressure of 11 cm H_2O (range, 8 to 16 cm H_2O). An aggressive diagnostic workup for respiratory infection, including BAL at a median time of hospital day 2 (range, hospital day 1 to 5) was performed. High-dose steroid pulse therapy was initiated on median hospital day 3.5 (range, hospital day 1 to 8), while surgical lung biopsy was performed on median hospital day 4 (range, hospital day 2 to 7). Eight patients (80%) survived to hospital discharge.
Conclusion: Earlier intervention, such as an aggressive diagnostic approach, mechanical ventilation with lung-protective strategy, and the early institution of immunosuppressive may improve clinical outcome in patients with AIP. *(CHEST 2006; 129:753–761)*

Key words: acute interstitial pneumonia; ARDS; corticosteroids; diffuse alveolar damage

Abbreviations: AIP = acute interstitial pneumonia; APACHE = acute physiology and chronic health evaluation; DAD = diffuse alveolar damage; F_{IO_2} = fraction of inspired oxygen; HRCT = high-resolution CT; PEEP = positive end-expiratory pressure

Acute interstitial pneumonia (AIP) is a distinct clinicopathologic entity, which is diagnosed by clinical features of ARDS of unknown etiology and a pathologic finding of diffuse alveolar damage (DAD) on lung biopsy specimens.[1] Since first reported by Hamman and Rich in 1935,[2] several case series of AIP have been published in the literature.[3–10] Ac-

cording to these reports, this uncommon disease is characterized by the rapid development of acute respiratory failure in a previously healthy individual and high mortality despite intensive treatment, including mechanical ventilation. However, some reports on AIP[10–13] showing higher survival rates have suggested that AIP might not be a fatal disease. To date, no guideline on the management of AIP has been published. Patients with AIP usually require mechanical ventilation and some receive therapy with corticosteroids, but it is unclear whether this treatment is effective in patients with AIP.

At our institution, we have been taking an aggressive diagnostic and therapeutic approach to patients who are suspected of having AIP. It includes prompt investigation for respiratory infection as a potential etiology for ARDS, the application of mechanical ventilation with a "lung-protective strategy", a rapid confirmatory diagnosis of DAD by surgical lung biopsy, and the early initiation of high-dose pulse steroid therapy. This approach has resulted in a surprisingly high survival rate in our patients with AIP. Here we report on our experience.

Materials and Methods

Between July 1995 and March 2004, surgical lung biopsy was performed for diagnostic purpose in 269 patients with interstitial lung diseases or unexplained bilateral lung infiltrates at Samsung Medical Center. Among them, 42 patients were found to have a pathologic diagnosis of DAD. Internal review board approval for chart review was obtained, and informed consent was waived due to the retrospective nature of the study. Medical records and pathologic findings for these 42 patients were reviewed to diagnose AIP. Our diagnostic criteria for AIP were as follows: (1) acute respiratory failure developing within 2 months; (2) the presence of DAD on surgical lung biopsy specimens; (3) the absence of underlying chronic pulmonary disease or previously abnormal chest radiograph findings; (4) the absence of any known inciting event or predisposing condition for ARDS such as respiratory infection, collagen vascular disease, exposure to environmental or occupational toxic agents, drugs, or radiation, and prior interstitial lung disease; and (5) no recent history of shock or use of vasopressors prior to hospital admission.[1,3,7,8]

Following a review of the medical records for each case, 29 patients were excluded from the study because they had known causes of DAD. Their etiologies for DAD were infections (n = 13), drugs (n = 7), collagen vascular diseases (n = 4), acute exacerbation of usual interstitial pneumonia (n = 2), and others (n = 3). Then, pathology slides for the remaining 13 patients with DAD were further reviewed by two experienced lung pathologists (J.H. and M.K.). When the lung pathologists did not concur on the diagnosis, the case was excluded from the analysis. An alternative histopathologic diagnosis was suggested by one of the pathologist in three cases (bronchiolitis obliterans organizing pneumonia in two patients and nonspecific interstitial pneumonia in one patient). Thus, of the initial 42 patients who showed the presence of DAD on surgical lung biopsy specimens, 10 patients were determined to be definitive AIP cases and were included in the final analysis.

Clinical and laboratory parameters such as age, sex, duration of symptoms, respiration rate, body temperature, acute physiologic and chronic health evaluation (APACHE) II score,[14] arterial blood gas analysis, and the presence of other organ failure[15] were retrospectively obtained. An expert chest radiologist analyzed high-resolution CT (HRCT) scans of the chest for the extent of ground-glass opacity, consolidation, reticulation, and nodules. The distribution of these conditions was classified into a *diffuse pattern* or a *patchy pattern*. The extent of each pattern of parenchymal abnormalities was estimated to the nearest 10% of lung volume. Then the differences between the pattern and distribution of abnormalities between survivors and nonsurvivors were compared.

Lung specimens were classified as exudative, proliferative, or mixed exudative and proliferative phases of DAD.[16] The presence of marked architectural distortion was also evaluated.

The data are shown as the median value (range), unless otherwise indicated. The difference in clinical parameters between survivors and nonsurvivors was compared by the Fisher exact test or the Wilcoxon rank sum test, as appropriate.

Results

Clinical Findings at Presentation

The median age of 10 patients was 65.5 years (range, 38 to 73 years) [Table 1]. There were four female patients and six male patients. All patients presented with severe dyspnea. Most of them had fever (9 of 10 patients), cough (8 of 10 patients), and whitish sputum (8 of 10 patients). The duration of symptoms prior to the hospital visit was 9.5 days (range, 2 to 34 days). The patients had been treated with empirical antibiotics with the idea that they had community-acquired pneumonia but had failed to respond to therapy. At the time of their visit to our hospital, patients were tachypneic with a respiration rate of 37 breaths/min (range, 32 to 44 breaths/min). The APACHE II score was 11.5 (range, 9 to 18), and no patient had evidence of other organ failure except for the respiratory system. The PaO_2/fraction of inspired oxygen (FIO_2) ratio was 130.6 (range, 82.6 to 287.3) on positive end-expiratory pressure (PEEP) of 10 cm H_2O (range, 8 to 16 cm H_2O) on the day of the surgical lung biopsy was performed.

Diagnostic Workup and Management

All patients were immediately admitted to the medical ICU. Therapy with IV empirical antibiotics was administered, consistent with the American Thoracic Society guideline for the management of severe community-acquired pneumonia.[17] Blood and sputum cultures, serology for atypical pneumonia, and BAL on hospital day 2 (range, hospital day 1 to 5) to exclude respiratory infection were performed in all patients.

Mechanical ventilation was started on day 1 (range, day 0 to 5) and was continued for 9.5 days (range, 4 to 98 days) until weaning from the venti-

Table 1—Clinical Characteristics of 10 Patients With AIP*

Patient/ Sex/Age, yr	Smoking Status	Fever	RR, breaths/ min	APACHE II Score	PaO$_2$/FIO$_2$ at SLBs	Sx-Adm, d	Adm-MV, d	Adm-SLBx, d	Adm-Steroid, d	PEEP, cm H$_2$O	VT/kg, mL	Outcome (F/U Duration)
1/F/68	NS	+	42	12	126.9	25	0	2	0	12	7.6	Died at 32 d
2/F/68	NS	−	32	9	93.3	21	5	7	7	10	8.9	Survived (75 mo)†
3/M/60	CS	+	32	13	287.3	2	1	3	1	8	7.7	Survived (78 mo)
4/M/70	ES	+	36	10	196.2	4	0	4	3	8	7.4	Survived (62 mo)
5/M/57	CS	+	36	18	147.0	4	1	6	8	16	6.4	Survived (60 mo)
6/M/38	CS	+	44	10	100.5	9	4	5	4	12	7.9	Survived (59 mo)
7/M/63	CS	+	40	11	231.2	5	1	2	4	10	6.0	Survived (48 mo)
8/F/70	CS	+	38	12	82.6	21	1	3	3	14	6.1	Died at 18 d
9/F/73	NS	+	40	11	134.2	10	0	3	3	10	6.1	Survived (28 mo)
10/M/51	CS	+	34	15	116.0	34	3	9	10	12	6.6	Survived (12 mo)

*M = male; F = female; NS = never smoker; ES = ex-smoker; CS = current smoker; RR = respiration rate; Sx-Adm = time interval from the onset of symptom to hospital admission; Adm-MV = time interval from admission to initiation of mechanical ventilation; Adm-SLBx = time interval from admission to surgical lung biopsy; Adm-Steroid = time interval from admission to the initiation of high-dose steroid therapy; MV = mechanical ventilation; F/U = follow up; VT = tidal volume; + = yes; − = no.
†Died due to progression of lung fibrosis 75 months later.

lator or death. All patients initially received ventilation in the pressure assist-control mode, with a PEEP of 11 cm H$_2$O (range, 8 to 16 cm H$_2$O) and tidal volume of 6.97 mL per measured body weight (range, 6.05 to 8.86 mL).

Surgical lung biopsy by minithoracotomy performed under general anesthesia was undertaken on day 3.5 (range, day 2 to 9). High-dose steroid pulse therapy was initiated on day 3.5 (range, day 1 to 10). This antiinflammatory therapy consisted of 1 g/d IV methylprednisolone for 3 consecutive days followed by 1 mg/kg/d IV methylprednisolone or oral prednisolone for 4 weeks with subsequent gradual tapering. The total duration of corticosteroid therapy in the survivors was 81 days (range, 28 to 126 days).

Treatment Outcome

Despite aggressive management, two patients (patients 1 and 8) died of worsening respiratory failure on day 18 and day 32, respectively. The conditions of eight patients (80%) improved, and they were successfully weaned from the ventilator. The median duration of mechanical ventilation in the survivors was 9.5 days (range, 4 to 98 days). Age, respiration rate, APACHE II score, time to hospital admission from the onset of symptoms, time to surgical lung biopsy from the onset of symptoms, and time to the initiation of corticosteroid therapy from the onset of symptoms were not different between the survivors and the nonsurvivors (p > 0.05).

Eight survivors were followed up for a median duration of 59.5 months (range, 12 to 78 months). One patient (patient 2), who needed mechanical ventilation for 98 days but was successfully weaned from the ventilator, developed slowly progressive lung fibrosis and eventually died of pneumonia 75 months later. The remaining seven patients were asymptomatic without showing a recurrence of disease or significant residual lung fibrosis on follow-up posteroanterior chest radiograph or HRCT scan.

Radiologic Findings

Diffuse bilateral lung haziness was noted on initial plain chest radiographs in all patients. The main abnormalities seen on the initial HRCT scan (median, day 1; range, day 1 to 3) were ground-glass opacity (10 of 10 patients) and airspace consolidation (9 of 10 patients). Bilateral pleural effusions (4 of 10 patients), reticulation (1 of 10 patients), and nodules (1 of 10 patients) were also seen. Honeycombing was absent. The total extent of lung involvement was calculated to be 80% (range, 45 to 95%). Ground-glass opacities comprised of 52.5% (range, 25 to 85%) and consolidation comprised 20% (range, 10 to 30%) [Table 2]. There was no difference in the total extent of lung involvement or in the extent of each specific lung lesion between the survivors and the nonsurvivors (p > 0.05). Although the pattern of multifocal patchy consolidation was seen in the nonsurvivors and in patient 2 (Fig 1, *bottom left*, E; *bottom right*, F), it was also noted in two of the survivors (patients 6 and 10). On the contrary, the pattern of diffuse bilateral white lung or ground-glass opacity on chest HRCT scan was seen in the rest of the surviving patients (Fig 1, *top left*, A: *top right*, B, *middle left*, C).

Pathologic Findings

On the surgical lung biopsy specimens, a DAD pattern in the exudative phase (n = 3) [Fig 2, *middle*

Table 2—*Initial Chest HRCT Scan Findings and Pathology of Patients With AIP**

Patient	Total Extent, %	GGO, %	Consolidation, %	Reticulation, %	Nodule, %	Pathology
1	80	50	30	–	–	Early proliferative phase with architectural distortion
2	60	40	20	–	–	Early proliferative phase with architectural distortion
3	90	80	10	–	–	Mixed exudative and proliferative phase with patchy distribution
4	80	55	25	–	–	Exudative phase with uniform distribution
5	95	65	30	–	–	Exudative phase with uniform distribution
6	90	65	20	–	5	Exudative phase with uniform distribution
7	70	50	20	–	–	Mixed exudative and proliferative phase with airway organization
8	50	30	20	–	–	Early proliferative phase with architectural distortion
9	95	85	–	10	–	Mixed exudative and proliferative phase with airway organization
10	45	25	20	–	–	Mixed exudative and proliferative phase with airway organization

*GGO = ground-glass opacity. See Table 1 for abbreviation not used in the text.

right, *D*], in a mixed exudative and proliferative phase (n = 4) [Fig 2, *top left*, *A*], and in the early proliferative phase (n = 3) [Fig 2, *bottom left*, *E*; *bottom right*, *F*] were noted. Two nonsurvivors and one patient (patient 2) who eventually died showed markedly increased volumes of interstitium due to myofibroblastic proliferation, with severe architectural distortion and enlarged alveolar spaces. Also found was prominent hyaline membrane formation and active fibrinous exudates in the alveoli, suggesting that active lung injury was ongoing with severe fibrosis. In comparison, seven patients who survived were in the exudative phase of DAD with uniform distribution (n = 3), the mixed exudative and proliferative phase of DAD with somewhat patchy distribution (n = 1), and the mixed exudative and proliferative phase of DAD with airway organization (n = 3). None of these survivors showed architectural distortion. No case of the chronic fibrotic phase of DAD was found in this study.

Discussion

This retrospective study suggests that rapid confirmatory diagnosis and early therapeutic intervention may increase survival in patients with AIP. As outlined above, our diagnostic and therapeutic approach was quite decisive. Appropriate cultures and serology for microbial agents were performed on median day 1 with the institution of empirical antibiotics as recommended by American Thoracic Society. All patients eventually warranted mechanical ventilation with a lung-protective strategy. BAL was performed on median day 2. Once infection was deemed unlikely, high-dose steroid pulse therapy was started on median day 3. To confirm the diagnosis of AIP, surgical lung biopsy was performed on median day 4. With this aggressive diagnostic and therapeutic approach, 80% of our patients with AIP

survived to hospital discharge although they had presented with acute lung injury/ARDS, as indicated by a rapid respiration rate, low PaO_2/FIO_2 ratio, and the need for mechanical ventilation in all patients. The high survival rate of our patients is sharply contrasted with the rate in early reports on AIP patients and is more similar to the rates in more recent reports (Table 3). In the reports from before 2000, the mortality rate of patients with AIP was very high, ranging from 59 to 100%.[4–9] Even in the study by Vourlekis et al[10] in 2000, which had reported an overall mortality rate of 33%, the mortality rate is 50% if patients who were referred from other hospitals are excluded. The only series showing a similar mortality rate was the one by Quefatieh et al[12] in 2003, which reported a 12.5% hospital mortality rate in eight patients with AIP.

The main reason for the observed difference in mortality rate may be that our patients underwent surgical lung biopsy and received corticosteroid therapy quite early in the course of disease (on median hospital day 4 and day 3, respectively), which may have abrogated the severe fibroproliferative response before irreversible architectural distortion occurred. The pathologic features of our patients support this finding because nonsurvivors and one patient with residual fibrosis showed markedly increased fibroproliferative reactions with severe architectural distortion (Fig 2, *bottom left*, *E*, and *bottom right*, *F*) compared to other survivors without residual fibrosis (Fig 2, *top left*, *A*, *top right*, *B*, *middle left*, *C*, and *middle right*, *D*). Interestingly, the patients in the only other AIP series[12] with similar prognoses to those of our patients also underwent surgical lung biopsy earlier than the time reported in other studies (day 8) [Table 3].

The role of corticosteroids in the treatment of AIP is controversial. Corticosteroids can inhibit the production of a number of proinflammatory mediators,
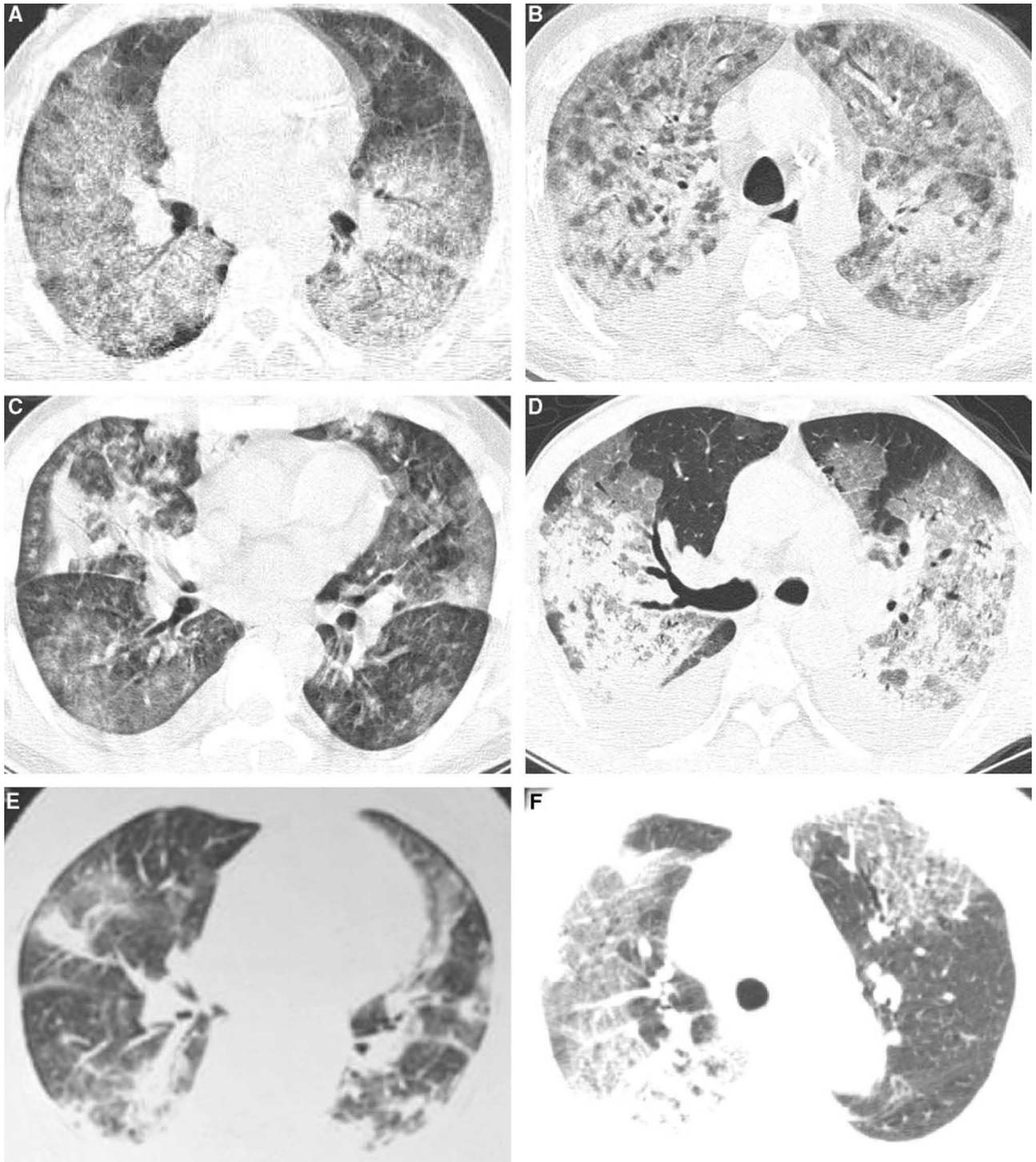
FIGURE 1. HRCT scan findings of AIP patients 3 (*top left*, *A*), 5 (*top right*, *B*), 6 (*middle left*, *C*), and 7 (*middle right*, *D*), who survived, are shown. There are variable amounts of diffuse ground-glass opacity covering both lungs. Patient 6 has some areas of multifocal patchy consolidations. HRCT scans of patient 1 (*bottom left*, *E*) and 8 (*bottom right*, *F*), who died, are shown. Multifocal patchy consolidation is seen along with areas of ground-glass opacity and with some areas of relatively normal looking lung.

such as cytokines, chemokines, oxygen radicals, eicosanoids, and complement products, which are thought to be involved in the pathogenesis of AIP. Therapy with corticosteroids also can inhibit the fibrotic response, which may be beneficial in AIP patients.[18] Olson et al[8] analyzed the impact of corticosteroid therapy on patient survival in their series of AIP patients and found no association. But a dra-
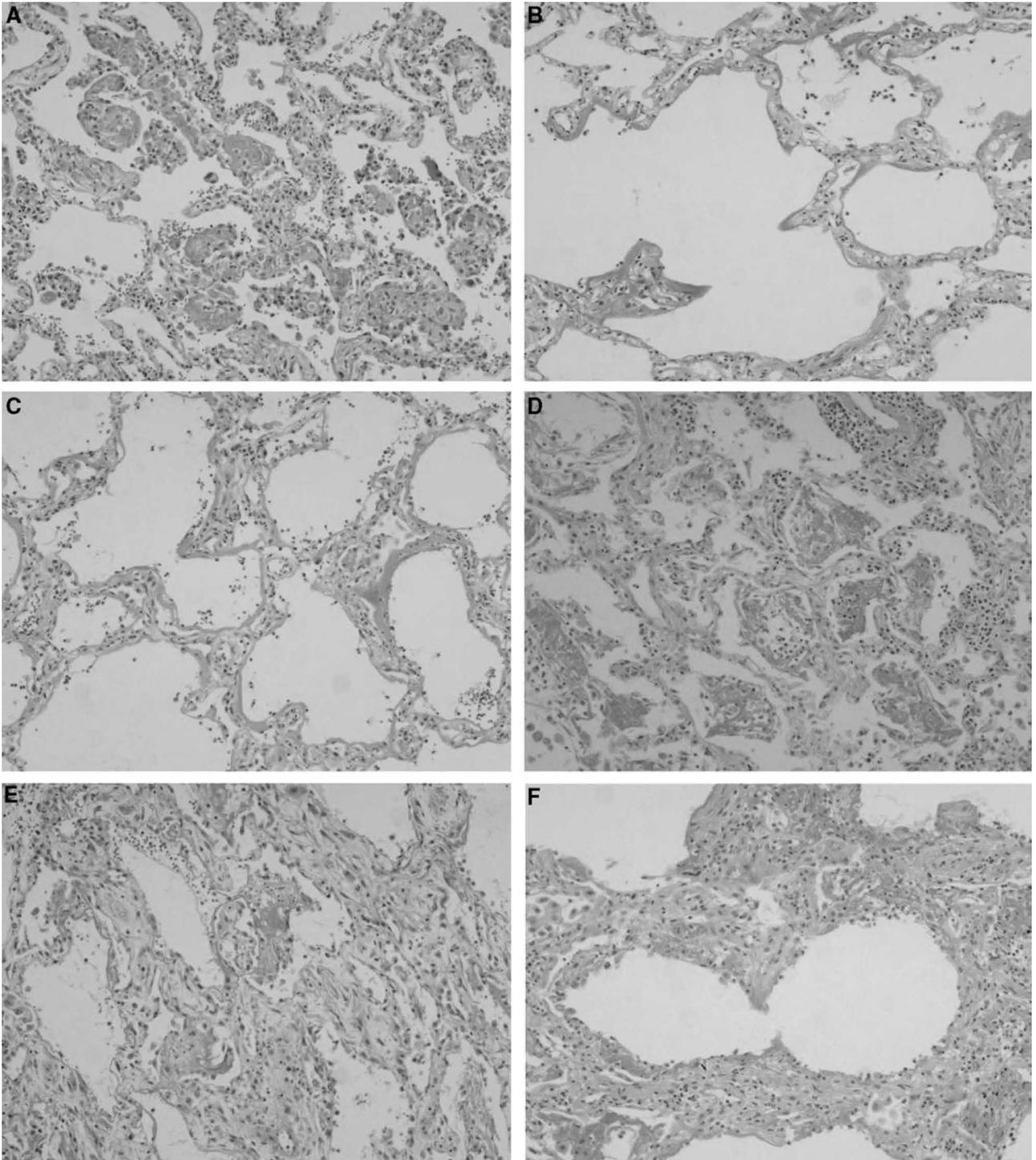
FIGURE 2. Pathology of AIP. Pathologic findings of patient 3 (*top left*, A), 5 (*top right*, B), 6 (*middle left*, C), and 7 (*middle right*, D), who survived, are shown. *Top right*, B, and *middle left*, C: early exudative phase of DAD. Microscopic examination reveals diffuse interstitial edema, inflammatory infiltrates, and congestion with hyaline membrane. *Top left*, A, and *middle right*, D: mixed exudative and proliferative phase of DAD. Microscopic examination shows edema and inflammatory cell infiltration in the alveolar interstitium with organizing fibrosis. Pathologic findings of patient 1 (*bottom left*, E) and 8 (*bottom right*, F), who died, are shown. Diffuse interstitial thickening due to fibroblastic proliferation with structural distortion of alveoli is noted. A small amount of intraalveolar fibrin is also seen (hematoxylin-eosin, original ×100).

Study/Year	Patients, No.	Age, yr	Biopsy Type		Adm-LBx, d	Steroid Tx, %	Adm-Steroid	Mortality Rate, %
			SLBx	Autopsy				
Hamman and Rich[4]/1944	4	43	0	4	NA	NA	NA	100
Katzenstein et al[7]/1986	8	28	8	0	13	NA	NA	88
Olson et al[8]/1990	29	50	23	6	10	69	NA	59
Primack et al[9]/1993	9	65	5	4	NA	NA	NA	89
Ichikado et al[5]/1997	14	53	3	11	NA	NA	NA	100
Johkoh et al[6]/1999	36	61	11	25	NA	NA	NA	89
Vourelkis et al[10]/2000	13	54	13	0	13	90†	15	33‡
Ichikado et al[21]/2002	31	60	10	17	NA	100	NA	68
Quefatieh et al[12]/2003	8	48	8	0	8	100	NA	13
This study	10	68	10	0	4	100	3	20

* SLBx = surgical lung biopsy; Adm-LBx = time interval from admission to lung biopsy; Tx = treatment; NA = not available. See Table 1 for abbreviation not used in the text.
†Therapy is not known for three patients.
‡Outcome is not known for one patient.

matic response to corticosteroids in AIP patients has been reported in isolated cases.[11,13] All patients in the series by Quefatieh et al[12] received corticosteroids, prompting the authors to suggest that the earlier and more frequent use of corticosteroids may have favorably influenced the outcome of their patients with AIP.

We chose to use pulse steroid therapy followed by the prolonged administration of corticosteroids. To our knowledge, this report is the first one that has used a standard corticosteroid regimen in AIP patients. Pulse steroid therapy has been reported to be effective in patients with fulminant lupus pneumonitis. Domingo-Pedrol and coworkers[19] reported the successful treatment of patients with lupus pneumonitis with the administration of 1,000 mg/d methylprednisolone for 5 days followed by 60 mg of prednisolone. Also, Freter and coworkers[20] used 750 mg/d methylprednisolone for 3 days followed by 60 mg of prednisolone in their patient. Since the lung injury seen in AIP patients is also immune-mediated and is similar in severity to that seen in patients with fulminant lupus pneumonitis, we used comparable doses of these drugs in our patients. Ichikado et al[21] used a similar steroid regimen to treat their AIP patients. Pulse steroid therapy is also reported to be more effective than lower dosages of steroids in patients with severe acute respiratory syndrome.[22]

In treating patients who are suspected of having AIP, it is our practice to investigate extensively to rule out respiratory infection as an etiology of respiratory failure. Blood and sputum cultures, and serologic tests for *Legionella pneumophila*, *Mycoplasma pneumonia*, and *Chlamydia pneumoniae* are performed. BAL is done with stains and cultures of BAL fluid for bacterial organisms, acid-fast bacilli, *Pneumocystis carinii*, and viruses such as respiratory syncytial virus, adenovirus, influenza virus, parainfluenza virus, herpes simplex virus, herpes zoster virus, and cytomegalovirus. Also, lung tissue obtained during surgical lung biopsy is processed for tissue culture and immunostaining for cytomegalovirus, herpes simplex virus, and adenovirus. The results of these microbiological studies were extensively reviewed in our patients to rule out infection. In some of the patients, the severity of their conditions necessitated the initiation of steroid therapy before all of the results of microbiological studies had been reported, and in two patients steroid therapy was initiated before BAL was performed. But in every patient, BAL was performed within 24 h of the initiation of steroid therapy.

Using our approach, there is a possibility that patients with atypical pneumonia might be exposed to steroids due to the difficulties in diagnosing atypical pneumonia, including viral pneumonia. Viral cultures are tricky and are slow to grow, special studies on lung specimens take time, and the serologic diagnosis could take weeks to confirm. In fact, of our original 42 patients with DAD, 4 of 13 patients with DAD of infectious origin received steroid pulse therapy due to unexplained rapid progressive lung infiltration in a previously healthy individual after confirming the presence of DAD in a biopsy specimen with negative culture findings. Legionella pneumonia was later diagnosed in one patient because of a fourfold increase in the antibody titer, and three patients were later found to be positive for adenovirus on immunostaining of their lung specimen. Two patients who were positive for adenovirus on immunostaining died. This reflects the real clinical situation in which the clinician is faced with a difficult decision of whether or not to institute potentially harmful therapy before the occurrence of irrevers-

ible damage to vital organs, in this case the lung. But, we think that the early institution of treatment may be important in improving the prognosis of AIP patients and that our overall management approach was beneficial to these patients as a whole (survival rate, 72%). Besides, therapy with corticosteroids, including pulse therapy, has been used to treat different viral pneumonias especially when they are life-threatening.[23]

Mechanical ventilation can cause lung injury, if alveolar overdistension or cyclic collapse and reopening of alveolar units occur during tidal breathing.[24,25] To minimize ventilator-associated lung injury, lung-protective strategies have been proposed for patients with ARDS, emphasizing the need to "open the lung and keep the lung open" while avoiding alveolar overdistension.[26] It is widely accepted that the use of low tidal volume to limit airway pressure and alveolar overdistension can improve survival in patients with acute lung injury,[27] although the clinical usefulness of therapy with high PEEP in patients already receiving ventilation with low tidal volume has been questioned.[28] The improvement in the survival of ARDS patients over the last few years is thought to reflect changes in the ventilatory approach in these patients.[29] In our institution, from as early as 1996 our standard approach to ventilating acute lung injury patients was low tidal volume (ie, 6 to 8 mL/kg) with a moderate level of PEEP. Thus, most of our patients received mechanical ventilation in this manner, which may have contributed to the favorable outcome seen in our series. The tidal volume data in Table 1 were calculated from measured body weight, which is known to be about 20% higher than the predicted body weight (used by the Acute Respiratory Distress Syndrome Network[27]) in Western countries. So, the tidal volumes used in our patients may have been slightly higher than those used in the lower tidal volume group of the Acute Respiratory Distress Syndrome Network study[27] but were still lower than those used in the higher tidal volume group. Also, all of our patients had peak airway pressures (a good surrogate for plateau pressure since patients were ventilated with pressure-limited ventilation) of < 30 cm H_2O, at least until the time surgical lung biopsies were performed, suggesting that the overstretching of the alveoli should have been minimal. But it is not possible to evaluate the contribution, if any, that our ventilatory approach had on mortality in our patients based on our data alone.

There are other possible explanations for the difference in mortality rate observed in our series compared to those in other series. One explanation may be a sampling error due to the relatively small size of the sample and the possibility that patients whose lungs were less severely injured might have been preferentially included in the study. But with a rare disease such as AIP, it is very difficult to have a large number of patients, and other studies of AIP also had numbers of patients that were comparable to those in our study. Also our patients were severely ill, as evidenced by low the PaO_2/FIO_2 ratio and the high respiration rate. Thus, it is unlikely that the differences in mortality that were seen in our patients were due entirely to this factor. Also, it is impossible to rule out that patients with more severe AIP might have died before reaching our hospital or could not undergo open-lung biopsy due to the severity of their condition. This is a limitation of the retrospective design of this study and previous studies of AIP as well, and it will not be adequately addressed until a prospective study is performed.

In summary, we have reported on the favorable management outcome of AIP patients, which included the prompt investigation for respiratory infection as a potential etiology for ARDS, the application of mechanical ventilation with a lung-protective strategy, a rapid confirmatory diagnosis of DAD by surgical lung biopsy, and the early initiation of high-dose steroid pulse therapy. These results suggest that early intervention may improve the clinical outcomes of patients with AIP.

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