Acute Fibrinous and Organizing Pneumonia

A Histologic Pattern of Lung Injury and Possible Variant of Diffuse Alveolar Damage

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• ***Context.*—The histologic patterns of diffuse alveolar damage (DAD), bronchiolitis obliterans with organizing pneumonia (BOOP), and eosinophilic pneumonia (EP) are well-recognized histologic patterns of lung injury associated with an acute or subacute clinical presentation. We have recognized acute fibrinous and organizing pneumonia (AFOP) as a histologic pattern, which also occurs in this clinical setting but does not meet the classic histologic criteria for DAD, BOOP, or EP and may represent an underreported variant.**

***Objectives.*—To investigate the clinical significance of the AFOP histologic pattern and to explore its possible relationship to other disorders, including DAD and BOOP.**

***Design.*—Open lung biopsy specimens and autopsy specimens were selected from the consultation files of the Armed Forces Institute of Pathology, which showed a dominant histologic pattern of intra-alveolar fibrin and organizing pneumonia. Varying amounts of organizing pneumonia, type 2 pneumocyte hyperplasia, edema, acute and chronic inflammation, and interstitial widening were seen. Cases with histologic patterns of classic DAD, BOOP, abscess formation, or eosinophilic pneumonia were excluded. To determine the clinical behavior of patients with this histologic finding, clinical and radiographic information and follow-up information were obtained. Statistical analysis was performed using Kaplan-Meier and χ^2 analysis.**

***Results.*—Seventeen patients (10 men, 7 women) with a mean age of 62 years (range, 33–78 years) had acute-onset symptoms of dyspnea (11), fever (6), cough (3), and hemoptysis (2). Associations believed to be clinically related to the lung disease included definitive or probable collagen vascular disease (3), amiodarone (1), sputum culture positive for *Haemophilus influenza* (1), lung culture positive for *Acinetobacter* sp. (1), lymphoma (1), hairspray (1), construction work (1), coal mining (1), and zoological work (1). Six patients had no identifiable origin or association. Follow-up revealed 2 clinical patterns of disease progression: a fulminate illness with rapid progression to death (n = 9; mean survival, 0.1 year) and a more subacute illness, with recovery (n = 8). Histologic analysis and initial symptoms did not correlate with eventual outcome, but 5 of the 5 patients who required mechanical ventilation died (P = .007).**

***Conclusions.*—Acute fibrinous and organizing pneumonia is a histologic pattern associated with a clinical picture of acute lung injury that differs from the classic histologic patterns of DAD, BOOP, or EP. Similar to these patterns of acute lung injury, the AFOP pattern can occur in an idiopathic setting or with a spectrum of clinical associations. The overall mortality rate is similar to DAD and therefore may represent a histologic variant; however, AFOP appears to have 2 distinct patterns of disease progression and outcome. The need for mechanical ventilation was the only parameter that correlated with prognosis. None of the patients with a subacute clinical course required mechanical ventilation.**

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Classification of biopsy specimens from patients with a clinical picture of acute lung injury often presents a difficult diagnostic challenge. Diffuse alveolar damage (DAD) and bronchiolitis obliterans with organizing pneumonia (BOOP) are well-recognized histologic patterns associated with an acute or subacute clinical presentation, respectively. Both the DAD and BOOP patterns may be associated with known causes, such as collagen vascular diseases, or they may be idiopathic.[1] In a recently proposed multidisciplinary consensus classification sponsored jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), idiopathic DAD may be referred to as acute interstitial pneumonia and idiopathic BOOP may be referred to as cryptogenic organizing pneumonia (COP).[2] This ATS/ERS statement also recommended using the term *organizing pneumonia* (OP) for the histologic pattern, rather than BOOP.[2] Eosinophilic pneumonia (EP) may also present clinically as an acute or subacute illness in the form of acute EP and chronic EP, respectively.[1,3]

We have encountered a histologic pattern associated with an acute or subacute clinical presentation, which does not meet the criteria for the patterns of DAD, OP, or EP, but instead is composed of predominantly intra-alve-

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olar fibrin and OP. This pattern appears to represent an unusual pattern of acute lung injury, which can prove problematic on biopsy specimens. The goal of our study is to better define this histologic pattern and the associated clinical features and outcome.

METHODS

Cases that had been originally diagnosed as DAD, OP, or descriptively as ''acute pneumonia with prominent fibrin'' or ''acute fibrinous pneumonia with organizing pneumonia'' (AFOP) were retrieved from the consultation files of the Armed Forces Institute of Pathology (AFIP). Cases were selected for the study if they demonstrated a dominant histologic pattern of intra-alveolar fibrin with organization. Cases were excluded if they demonstrated classic histologic features of DAD, OP, EP, acute pneumonia with abscess formation, or features suggestive of a primary vasculitic process. Cases with only transbronchial biopsy material were also excluded. One hundred fourteen cases were reviewed and a total of 17 cases were included in the study, which included 15 open lung biopsy specimens and 2 autopsy specimens. Clinical and follow-up information was obtained from patient records and the referring pathologists and clinicians.

Histologic features were evaluated on paraffin-embedded hematoxylin-eosin–stained sections. Grocott methenamine silver and Ziehl-Neelsen stains were also performed on all cases. Brown-Brenn and/or Brown-Hopps bacterial stains were evaluated in 9 cases.

Statistical analysis was performed using SPSS 9.0 statistical software for Windows (SPSS Inc, Chicago, Ill). Cross tables with χ^2 and Fisher exact tests and Kaplan-Meier analysis with the log-rank test were used, regarding a P value of .05 or less as significant. Only death related directly to the disease was regarded as a censored event.

RESULTS

Clinical Features

The presenting and associated clinical features, treatment modalities, and outcomes are summarized in Table 1. Ten cases occurred in men and 7 in women. Race distribution consisted of 10 whites, 4 Hispanics, and 1 black. Race was unknown in 2 cases. The average patient age was 62 years, with a range of 33 to 78 years.

Presenting Symptoms

Presenting symptoms were acute or subacute in nature, and none of the patients were symptomatic for more than 2 months before biopsy. The average time from symptom onset to biopsy was 19 days (range, 2–60 days). The symptoms were often multiple. Six patients reported fever, which was typically described as ''spiking.'' Four patients reported cough, 12 shortness of breath, and 2 hemoptysis. Five patients reported constitutional symptoms such as weakness or malaise, including 1 with an antecedent flu-like illness. Five patients reported chest, pleural, or abdominal pain. One reported arthralgias with an associated rash.

Associated Conditions

Two patients reported a definitive history of underlying collagen vascular disease (polymyositis and ankylosing spondylitis). One additional patient was regarded as having fibromyalgia. Possible exposure histories that were regarded by the treating physicians as being clinically related to the disease onset were reported in 4 patients (a zoologist with exposure to multiple exotic animals, a coal miner, a construction worker with exposure to wood dusts, and a patient who reported using multiple [4–5] cans of hairspray every day). One patient was discovered to have an underlying high-grade lymphoma. Six patients were considered to have an altered immune status: 4 patients taking long-term steroids (2 patients with collagen vascular disease, 1 with possible fibromyalgia, and 1 with unspecified chronic renal failure), 1 patient with poorly controlled diabetes who was also an alcoholic, and the patient with the underlying lymphoma. Possible contributing drug history included 1 patient taking amiodarone and 1 patient who reported that his symptoms began after taking 4 Lorcet, an unspecified amount of Valium, and several alcoholic beverages. Information regarding tissue and sputum cultures was available for 11 of the cases, with 1 patient having a sputum culture positive for *Haemophilus influenza* and one having a lung tissue culture positive for *Acinetobacter baumanii*. Three patients had multiple associations (1 environmental exposure and collagen vascular disease and long-term steroid use; 1 environmental exposure and positive sputum culture; 1 collagen vascular disease and long-term steroid use), and 6 patients had no identifiable underlying origin or association.

Radiographic Findings

Chest radiographic information, which was obtained primarily from submitted radiology reports, was available for 15 of the cases. The films on 2 of the cases were reviewed by the Department of Radiological Pathology at the AFIP. The most common radiographic pattern was that of bilateral basilar infiltrates, which was seen in 4 cases. The chest radiographs were described as bilateral diffuse infiltrates greater in the lower lobes in 1 case, as bilateral airspace disease in 2 cases, as bilateral reticulonodular infiltrates in 1 case, as diffuse patchy infiltrates in 1 case, simply as ''infiltrates'' in 2 cases, as ''consistent with atypical pneumonia'' in 1 case, as ''consistent with pulmonary edema'' in 1 case, as ''consistent with interstitial pneumonia'' in 1 case, and as a diffuse infiltrate in the right lung only in 1 case.

Therapy

Treatment modalities used included antibiotics only in 7 patients, steroids only in 2, steroids after no improvement with antibiotics in 3, both antibiotics and steroids simultaneously in 2, diuretics in 1, and mechanical ventilation only in 1. Treatment in 1 patient was unknown. A total of 5 patients required mechanical ventilation.

Clinical Outcome

Nine patients were dead of disease, 7 patients were alive and well, and 1 patient was dead of other causes at the time of follow-up. Overall, follow-up time ranged from 6 days to 5 years, with a mean follow-up of 1.1 years. There appeared to be 2 distinct patterns of disease progression: those with a fulminate illness with rapid progression to death and those with a subacute, less fulminate course who recovered. Among patients who died, the time from presentation of symptoms to death ranged from 6 to 36 days, with an average of 29 days.

HISTOLOGIC FEATURES

Specimen type consisted of 15 open lung biopsy specimens and 2 autopsy specimens. All of the specimens had similar histologic findings as observed on hematoxylin-eosin–stained sections. The dominant finding in all specimens was the presence of intra-alveolar fibrin in the form

Table 1. Summary of Clinical Features, Treatment, and Outcome*

Case No.	Sex	Age, y	Presenting Features		Associated Findings	
			Symptoms	Radiology	Lung or Sputum Culture	Exposure History
1	M	77	Dyspnea, pain	Bilateral, basilar infiltrates	*Haemophilus influenza*	NA
2	M	33	Pneumothorax	Consistent with interstitial pneumonia	*Acinetobacter baumanii*	Construction worker
3	M	55	Cough, dyspnea, hemoptysis	Bilateral perihilar airspace	Negative	Zoologist
4	F	76	Dyspnea	Bilateral, diffuse, greater in lower lobes	Negative	Excessive hairspray
5	M	74	Cough, dyspnea, pain	"Consistent with edema"	NA	Coalminer
6	F	78	Dyspnea	Bilateral reticulonodular	Negative	No
7	F	58	Fever, arthralgia	"Consistent with atypical pneumonia"	NA	No
8	M	47	Fever, pain, dyspnea, hemoptysis	Bilateral, basilar infiltrates	NA	NA
9	M	39	Dyspnea, pain	Patchy, bilateral basalar infiltrates	Negative	NA
10	F	59	Cough	Bilateral airspace disease	Negative	NA
11	M	70	Fever, dyspnea	Diffuse, patchy	Negative	No
12	F	72	Dyspnea	NA	NA	NA
13	M	36	Fever, cough, dyspnea, arthralgia	"Infiltrates"	Negative	NA
14	M	76	NA	NA	NA	NA
15	F	65	Fever, dyspnea, pain	Diffuse right lung infiltrates	Negative	No
16	F	68	NA	"Infiltrates"	NA	NA
17	M	66	Fever, dyspnea	Bilateral basilar infiltrates	NA	NA

* NA indicates not available.

of fibrin "balls" within the alveolar spaces (Figure 1). The fibrin was found in a primarily patchy distribution within the lung parenchyma, involving 25% to 90% of the alveolar spaces within a specimen, with an average of 50% airspace involvement (Figure 2). In one specimen nearly 100% of the airspaces were filled with fibrin (Figure 3). The distribution was typically patchy, but not exclusively peribronchiolar. Classic hyaline membranes as seen in DAD were not observed. Organizing pneumonia consisting of intraluminal loose connective tissue was observed within the alveolar ducts and bronchioles associated with the fibrin. A variety of histologic findings were observed within the lung parenchyma associated with the areas of intra-alveolar fibrin accumulation. These findings were located primarily in the alveolar walls and were essentially restricted to the portions of lung containing intra-alveolar fibrin. The intervening lung parenchyma showed minimal changes in most cases and typically consisted of a sparse inflammatory infiltrate and/or minimal interstitial widening.

Within the lung parenchyma associated with areas of intra-alveolar fibrin accumulation, an interstitial lymphoplasmacytic infiltrate was present in all cases, which was typically mild to moderate, but was quite marked in 3 cases. Rare eosinophils were noted in 6 cases, but an EP pattern was not seen. Cases with an EP pattern were excluded from the study. Neutrophils were observed in all cases, but were generally sparse. Like the lymphocytic infiltrate described herein, the neutrophils were located primarily within the alveolar walls and the pattern did not simulate the airspace involvement of typical acute pneumonia. Cases with features typical of acute pneumonia were excluded from the study. Although the neutrophils were predominantly located in the alveolar walls or interstitium, capillaritis was not observed and none of the cases contained features to suggest chronic hemorrhage. Cases with features of a primary vasculitic process were excluded from the study. Organizing pneumonia in the form of completely fibroblastic Masson bodies or in the form of fibroblasts surrounding cores of intra-alveolar fibrin (Figure 4) were seen in all cases and were prominent in 3 cases, although intra-alveolar fibrin remained the dominant finding. Type 2 pneumocyte hyperplasia was also observed in all cases, as was edematous interstitial widening. Myxoid fibroblastic tissue in the alveolar walls, like that typically seen in DAD, was noted in the interstices of all cases; however, it was typically minimal or focal. Prominent myxoid fibroblastic proliferation was observed in 4 cases. Dense collagen deposition was not observed. Vascular thrombi were observed in 5 cases and were prominent in 2 cases. Alveolar edema was noted in 10 cases and was prominent in 1. No micro-organisms were identified on any of the sections stained with Grocott methenamine silver, Ziehl-Neelsen, Brown-Brenn, or Brown-Hopps. Nei-

Table 1. Extended

Associated Findings			Treatment		
Collagen Vascular Disease	Drug History	Other Medical History	Treatment	Mechanical Ventilation	Outcome
NA	NA	NA	Antibiotics	No	Dead
NA	NA	None	Antibiotics	No	Alive
Ankylosing spondylitis	Steroids, amiodarone	Cardiomyopathy	Antibiotics	NA	Alive
No	No	NA	Antibiotics followed by steroids	No	Alive
NA	NA	NA	Lasix, dopamine	Yes	Dead
Polymyositis	Low-dose steroids	NA	Steroids	NA	Dead of unrelated cause
Possible fibromyalgia	None	NA	Antibiotics	NA	Alive
NA	Lorcet, Valium	Alcoholism	Antibiotics	NA	Alive
No	None	Ki-1 lymphoma	Steroids	Yes	Dead
No	Prednisone	Renal failure	Antibiotics and steroids	Yes	Dead
No	No	Diabetes, alcoholism	Antibiotics	NA	Alive
NA	NA	NA	Antibiotics followed by steroids	NA	Alive
NA	NA	NA	Ventilator only	Yes	Dead
NA	NA	NA	Antibiotics and steroids	NA	Dead
NA	NA	NA	Antibiotics	NA	Dead
NA	NA	None	NA	NA	Dead
NA	NA	NA	Antibiotics followed by steroids	Yes	Dead

ther viral cytopathic effects nor granulomatous inflammation was observed in any of the cases.

STATISTICAL ANALYSIS

Clinical symptoms, histologic features, and treatment were evaluated with regard to patient outcome. None of the presenting clinical symptoms correlated with ultimate patient outcome. Treatment modality used similarly did not correlate with final outcome. The presence of a relatively more pronounced inflammatory cell infiltrate, prominent OP, more extensive fibrin accumulation, prominent pneumocyte hyperplasia or prominent interstitial widening, or myxoid connective tissue deposition did not correlate with patient outcome. The need for mechanical ventilation emerged as the only significant parameter ($P = .007$), with all patients who required mechanical ventilation dying.

COMMENT

The histologic pattern of AFOP appears to be a histologic pattern associated with an acute or subacute clinical presentation that differs histologically from the classically described acute lung injury patterns of DAD or OP and also differs from EP. Patients with the AFOP pattern have a similar clinical outcome to those with DAD, and AFOP may in fact represent a fibrinous variant of DAD, which has not been well described in the literature and therefore has proven problematic on biopsy specimens.

The histologic pattern of AFOP differs from the classic patterns of DAD and OP in that organizing intra-alveolar fibrin constitutes the dominant histologic finding and differs from the pattern of EP by the lack of prominent eosinophils. Although fibrin deposits have been described in both the DAD and OP patterns, they do not comprise a major component of the process.[4–7] The AFOP pattern further differs from that of DAD in that the fibrin is organized into balls within the alveolar spaces and classic hyaline membranes are not seen. The fibrin present in the AFOP pattern is typically patchy, with an average of 50% airspace involvement, as opposed to the diffuse changes typically present in the pattern of DAD. The alveolar walls adjacent to areas of fibrin deposition demonstrate a variety of associated changes, such as acute or chronic inflammatory cell infiltrate and interstitial widening and type 2 pneumocyte hyperplasia, but the intervening lung shows only minimal histologic changes. The key histologic features of the AFOP pattern are summarized in Table 2.

Based on our review, the AFOP pattern appears to have an array of possible underlying associations, and a certain number of cases appear to be idiopathic in nature, similar to other histologic patterns of acute lung injury. Presumed infectious causes were identified in 2 of the cases by positive cultures. Consideration was given as to whether these cases represented typical acute pneumonia and had undergone biopsy before the influx of neutrophils; however,

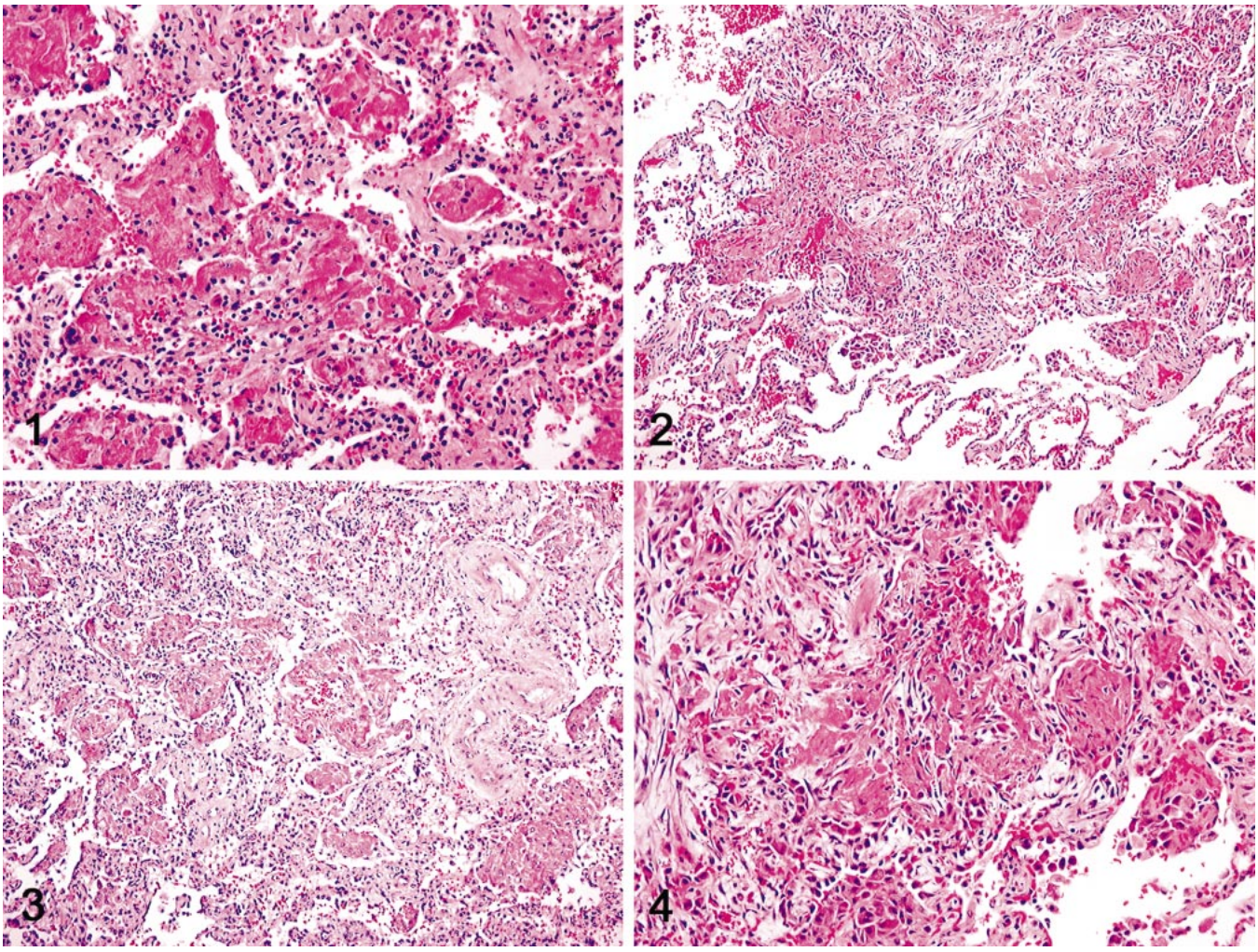

Figure 1. *Intra-alveolar fibrin in the form of "fibrin balls" without formation of hyaline membranes (hematoxylin-eosin, original magnification ×160).*

Figure 2. *Intra-alveolar fibrin and organizing pneumonia with patchy involvement (hematoxylin-eosin, original magnification ×320).*

Figure 3. *Acute fibrinous and organizing pneumonia with more diffuse involvement (hematoxylin-eosin, original magnification ×80).*

Figure 4. *Organizing pneumonia with fibroblastic tissue surrounding alveolar fibrin (hematoxylin-eosin, original magnification ×160).*

both of these biopsy specimens were obtained a minimum of 2 weeks after the onset of symptoms, so we do not believe that this is the case. Other associated findings included the presence of collagen vascular diseases, occupational exposures, and drug exposures, again similar to the spectrum of associations encountered in other forms of acute lung injury. One of the patients was also reported to have a history of chronic renal failure, and although this was not indicated to be clinically related to the patient's lung disease, a relationship to uremia might be considered. The renal function status of the remaining patients was not reported. Of interest, we identified numerous *Histoplasma* organisms in one case with an AFOP pattern that was not included in the study due to lack of follow-up. The AFOP pattern has also been observed in a case of busulfan pneumonitis.[8]

Treatment modalities included primarily antibiotics or steroids, either alone or in various combinations. Although half of the patients recovered, the same number did not, including one patient in whom an underlying infectious agent was identified. Treatment modality used did not correlate with eventual patient outcome, and therefore, a clear-cut optimal treatment was not identified. Although the mortality rate associated with the AFOP pattern was slightly more than 50%, similar to DAD, the clinical course is not always as catastrophic, with only 30% of patients requiring mechanical ventilation. The primary histologic patterns in the differential diagnosis of the AFOP pattern are the other histologic patterns of acute lung injury: DAD, OP, and EP.

Briefly, the histologic pattern of DAD is classically described as having an early exudative phase consisting of capillary congestion, interstitial and alveolar edema, and distinctive eosinophilic hyaline membranes composed of condensed plasma proteins that line alveolar walls. The exudative phase is followed by proliferative and fibrotic phases in which there is organization of the intra-alveolar exudate and proliferation of type 2 pneumocytes followed by progressive interstitial fibrosis.[1,5] Although the term *diffuse* in DAD refers specifically to damage to all elements of the alveolus, the histologic changes of DAD are usually present throughout the lung parenchyma. Cases of local-

Table 2. Histologic Features of Acute Fibrinous and Organizing Pneumonia

Major features
Dominant finding of organizing intra-alveolar fibrin
Organizing pneumonia
Patchy distribution
Minor features
Associated interstitial changes
Acute and/or chronic inflammation
Type 2 pneumocyte hyperplasia
Alveolar septal expansion with myxoid connective tissue
Interstitial inflammation and expansion typically mild to moderate
Interstitial changes primarily confined to areas adjacent to intra-alveolar fibrin with the intervening lung showing only minimal changes
Pertinent negatives
Hyaline membranes NOT observed
Eosinophils inconspicuous or absent
Extensive bronchopneumonia and/or abscess formation absent
Granulomatous inflammation absent

ized lung involvement have been reported as ''regional alveolar damage.''[9] Intra-alveolar fibrin is mentioned in some descriptions of DAD; however, these cases were also described as containing classic hyaline membranes, and the feature of prominent intra-alveolar balls of organizing fibrin as seen in the AFOP pattern is not emphasized.[5–7] The patchy distribution seen in AFOP is also not a typical feature of DAD. The clinical manifestation of DAD is that of acute respiratory distress syndrome, which presents as acute respiratory failure usually requiring mechanical ventilation. The mortality rate is between 50% and 60%.[1,5,7] Although histologically less diffuse than DAD, patients with lung biopsy specimens showing the AFOP pattern have a similar mortality rate (50%), and we believe that the AFOP pattern may represent a fibrinous variant of DAD that is not well documented. Of interest, we observed the AFOP pattern focally in otherwise classic cases of DAD; however, these cases were excluded from the study. It is possible that some of the cases included in the study could represent inadequately sampled DAD; however, classic diagnostic features of DAD were lacking in these specimens, which included open biopsy specimens and 2 generously sampled autopsy specimens. Although a sampling problem cannot be entirely excluded in all cases, we believe that the AFOP pattern may represent the sole histologic finding in some patients. An important clinical difference is that almost all patients with a classic histologic pattern of DAD require ventilatory support, whereas this was needed in only 30% of the patients in this study.

The histologic pattern of OP is characterized by patchy plugs of granulation tissue within the bronchioles, alveolar ducts, and alveoli. Extensive fibrosis is not typically present. Clinically, the OP pattern is associated with a 4- to 6-week onset of shortness of breath and cough.[4] The respiratory symptoms generally improve with steroid therapy, and the mortality is less than 10%.[4] In differentiating the AFOP pattern from the OP pattern, both processes may be patchy from low power; however, organized fibrin balls are the dominant histologic finding in AFOP, whereas fibroblastic Masson bodies within alveolar spaces, ducts, and bronchioles are the dominant finding in OP. Further, the AFOP pattern has a different clinical manifestation than that seen with the OP pattern in that the mortality rate associated with the AFOP pattern is much higher, and several patients required mechanical ventilation. The relationship of cases of fatal OP and AFOP patterns needs to be determined. Of note, in 1995, Yoshinouchi et al[10] described a variant of COP, a term often used synonymously with BOOP, which differed from conventional COP by the presence of fibrin within Masson bodies. They proposed the name ''type 2 COP'' for this entity and found that this subgroup responded poorly to steroids compared with patients with a conventional histologic picture of COP. Although the ultimate clinical outcome of these patients was not addressed and the study was performed using material from transbronchial biopsy specimens, these cases of type 2 COP may represent the same entity as our collection of AFOP cases.

Another consideration in the diagnosis of the AFOP pattern is the pattern of EP. The histologic pattern of EP may present clinically as chronic EP, which presents as a subacute illness typically of several weeks' duration, or as acute EP, in which patients develop respiratory failure rapidly throughout several days. The histologic features seen in association with both acute and chronic EP are essentially identical, although hyaline membranes and other features of DAD may be encountered in the histologic findings seen in acute EP.[11] Histologically, EP may have prominent intra-alveolar fibrin like that seen in AFOP. However, the major histologic finding in EP is the intra-alveolar accumulation of eosinophils and macrophages. The macrophages may vary in number, but the eosinophils predominate. The interstitium associated with these areas is typically expanded by a lymphoplasmacytic infiltrate, which also contains eosinophils, and eosinophil abscesses may also be present.[12,13] Although 6 of our cases of AFOP had small numbers of eosinophils, large numbers were not observed and neither eosinophilic abscesses nor intra-alveolar collections of histiocytes and eosinophils were observed. We considered whether these cases may have represented partially treated EP, since the prominent fibrin seen in the AFOP pattern greatly resembles that seen in many cases of EP, and steroid therapy can reduce the number of eosinophils present within a biopsy specimen rather rapidly. However, review of the clinical information on the 6 cases with eosinophils revealed that only 3 patients had received steroid therapy and that the therapy was instituted only after lung biopsy was performed in these cases. Information on peripheral blood eosinophil counts was only available for 3 patients, none of whom had peripheral eosinophilia. Therefore, we do not believe that these cases represent partially treated EP.

Like the OP pattern, it is difficult to be certain of the diagnosis of the AFOP pattern on a bronchoscopic biopsy specimen, and it is best made on larger biopsy specimens with appropriate clinical information. Similar to the OP pattern, an AFOP pattern can also appear as a nonspecific reaction, which can be associated with other entities. Although cases that showed only a pure histologic pattern of AFOP were included in this study for analysis, review of our archival material showed that a focal pattern of AFOP could be seen as a component of other processes. We observed focal patterns that resembled AFOP at the periphery of abscess cavities and necrotizing granulomas, as well as in cases of Wegener granulomatosis with extensive capillaritis. Intra-alveolar fibrin was also observed ad-

jacent to lung carcinomas. The possibility of such a secondary reaction should be taken into account on smaller biopsy specimens. Clinical and radiographic correlation may be useful in these situations.

In summary, the histologic pattern of AFOP appears to be a distinctive pattern of lung injury, which is histologically different from the classic patterns of DAD, OP, or EP. The mortality rate associated with the AFOP pattern mirrors that associated with DAD, and this pattern may represent a fibrinous variant. However, the clinical course was not always as catastrophic as typical DAD. As such, AFOP may not be a clearly distinct clinical entity from DAD, but a histologic pattern of DAD that is not well appreciated. Patients who have milder symptoms and more localized infiltrates radiographically may correspond closer to the clinical and radiographic picture of COP or BOOP. The importance of the AFOP pattern is that it represents a pattern of lung injury that does not meet the classic criteria for DAD, OP, or EP and has proven to be problematic on biopsy. Recognition of this pattern is important given the potentially adverse clinical outcome, although some cases do not appear to be as fulminate as is typically seen with the pattern of DAD. Similar to the patterns of DAD and OP, the AFOP pattern also appears to be associated with a variety of possible underlying origins; however, no treatment was identified as optimal, even when the underlying agent was known. Similar to the pattern of OP, the AFOP pattern may be a secondary reaction to other processes such as abscesses or infarcts, which should be taken into account in smaller specimens. Radiographically, the AFOP pattern appears to manifest most often with a diffuse, patchy appearance that is often more prominent in the bases or may be restricted to the bases. With the exception of the need for mechanical ventilation in all patients who died, there were no identifiable clinical or histologic parameters that were predictive of patient outcome and an optimal therapy was not clearly identified.

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