Terminal Diffuse Alveolar Damage in Relation to Interstitial Pneumonias

An Autopsy Study

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Abstract

Acute exacerbations of idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis (IPF/CFA) are rare and typically terminal events, but their relationship to underlying patterns of idiopathic interstitial pneumonias is unknown. We reviewed autopsy material from patients who died of diffuse alveolar damage in the clinical setting of pulmonary fibrosis, both idiopathic and with background fibrosing alveolitis with connective tissue disorders (FA-CTDs), and compared them with cases of acute interstitial pneumonia. Of 15 patients with acute exacerbations of IPF/CFA (n = 12) or FA-CTD (n = 3), 12 had a background pattern of usual interstitial pneumonia and 3 had fibrotic nonspecific interstitial pneumonia. All cases of fibrotic nonspecific interstitial pneumonia were seen in association with FA-CTD. The cause of acute exacerbations is unknown, but our data suggest that toxic effects of oxygen and triggering infection are unlikely causes. In patients with CTDs, it remains uncertain whether the acute exacerbation is related to the fibrosis, the associated CTD, or a combination of these factors. Acute exacerbations of IPF/CFA may be a more common terminal event than previously thought.

Since the original classification of idiopathic interstitial pneumonias by Liebow and Carrington,[1] there have been several proposed changes,[2-5] with new entities such as nonspecific interstitial pneumonia[6] and respiratory bronchiolitis–associated interstitial lung disease[7,8] being included and others such as giant cell interstitial pneumonia[9] being removed. To unify terminology, a consensus classification system has been proposed, which includes 7 histologic patterns of idiopathic interstitial pneumonia, each corresponding to an associated clinicopathologic entity **Table 1**.[10] Six of these patterns relate to chronic disease, with diffuse alveolar damage being the sole pattern recognized in association with acute clinical disease. Diffuse alveolar damage is the histologic pattern most commonly seen in the acute respiratory distress syndrome, but the clinical disease in an idiopathic setting is termed acute interstitial pneumonia, and the few published series of acute interstitial pneumonia describe a relatively consistent pattern of clinical manifestations.[11-13]

However, patients with idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis (IPF/CFA) also may have acute and typically terminal exacerbations, in which a histologic pattern of diffuse alveolar damage is superimposed on chronic changes,[14-17] although data on the histologic features are limited.[14,15] Also, both the cause and relationship of the acute exacerbations to more recently described histologic patterns, such as nonspecific interstitial pneumonia, and patients with connective tissue disorders (CTDs) are unknown. Finally it is not clear whether there are any differences in the pattern of disease between patients with acute interstitial pneumonia and patients with CTD in whom diffuse alveolar damage develops.

Table 1
Histologic Patterns of Interstitial Pneumonias and Clinicopathologic Counterparts in an Idiopathic Setting[10]

Histologic Pattern	Clinicopathologic Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/ cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Organizing pneumonia	Cryptogenic organizing pneumonia
Diffuse alveolar damage	Acute interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis–associated interstitial lung disease
Lymphocytic interstitial pneumonia	Lymphocytic interstitial pneumonia

The purpose of the present study was to review autopsy material from patients who died of diffuse alveolar damage in the clinical setting of pulmonary fibrosis, CTDs, and idiopathic disease (acute interstitial pneumonia) for better delineation of the histologic findings in these groups.

Materials and Methods

Between 1989 and 2001, 57 patients who died with a histologic pattern of diffuse alveolar damage, IPF/CFA, and/or fibrosing alveolitis associated with CTDs (FA-CTDs) were identified from the thoracic autopsy database of the Royal Brompton Hospital, London, England (n = 40), and from the referral files of a pathologist (A.G.N.) (n = 17). These cases were subdivided into 2 groups.

Twenty-five had IPF/CFA, as defined by American Thoracic Society (ATS) and European Respiratory Society (ERS) consensus criteria,[18] or FA-CTD, of which 15 had superimposed diffuse alveolar damage considered to be the cause of death. Ten patients were excluded from the study because they had died of other causes (infection, 3; carcinomatosis, 4; pulmonary embolism, 2; cardiovascular disease, 1).

Thirty-two patients died of diffuse alveolar damage without underlying lung fibrosis; of these, 6 fulfilled the criteria for acute interstitial pneumonia[10] and another 5 had an associated CTD. The remaining 21 patients were excluded because clinical associations other than CTDs were identified that were considered to have caused the diffuse alveolar damage. During the study period, 4 additional patients with IPF/CFA died as inpatients, but an autopsy was not performed.

The clinical, imaging, microbiologic, and histologic findings for these patients were reviewed, and the terminal episode was subcategorized as an acute exacerbation of IPF/CFA (n = 12), acute exacerbation of FA-CTD (n = 3), acute interstitial pneumonia (n = 6), or diffuse alveolar damage associated with a CTD (n = 5).

In patients with FA, the background histologic patterns were classified according to the recently published ATS/ERS criteria for interstitial pneumonias.[10]

Results

Acute Exacerbations of IPF/CFA and FA-CTD

Fifteen cases were identified in which acute exacerbation of FA was given as the cause of death. In 12 patients, the ATS/ERS clinical criteria for IPF/CFA were fulfilled before their terminal episode. One of these cases was positive for rheumatoid factor titer (1:60), but no clinical manifestations of CTD were noted before death. Three additional patients had FA-CTD (scleroderma, 2; systemic lupus erythematosus [SLE], 1). The clinical features of these groups are summarized in **Table 2**. In addition, data on oxygen therapy were available for 12 patients. One patient died without oxygen therapy and 8 were given oxygen (35%-80%) via a face mask only. Two patients received 100% oxygen delivered by

Table 2
Acute Exacerbations of Fibrosing Alveolitis

Variable	IPF (n = 12)	FA With CTD (n = 3)
Median age, y (range)	66 (46-88)	53.5 (38-72)
Sex (M/F)	10:2	0:3
Mean duration of preexisting disease, mo (range)	29 (4-94)	116 (24-264)
Mean duration of symptoms before admission, d (range)	24 (3-60)	29 (2-60)
Mean WBC count, /μL (range)*	9,200 (2,500-13,900)	15,200 (7,700-25,300)
Mean C-reactive protein level, mg/L (range)*	115.1 (48-187)	76.7 (19-142)
Mean time from admission to death, d (range)	19 (4-36)	17 (3-42)
No. of patients with CTD	0	3

CTD, connective tissue disorder; FA, fibrosing alveolitis; IPF, idiopathic pulmonary fibrosis.
* To convert the WBC values to Système International units ($\times 10^9$/L), multiply by 0.001; the reference range is 3,500-10,000/μL (3.5-10 $\times 10^9$/L). The reference range for C-reactive protein is 0-10 mg/L.

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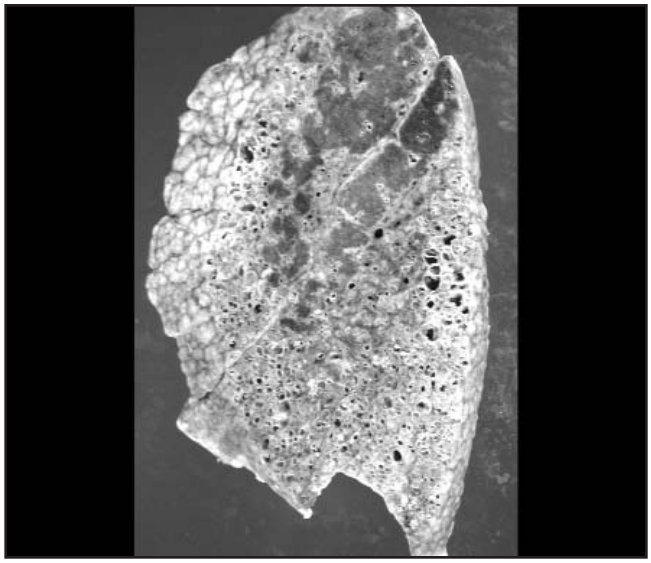

Image 1 A section of lung shows an acute exacerbation of fibrosing alveolitis, with advanced chronic changes of subpleural fibrosis and honeycombing most marked in the lower lobe and consolidation and hemorrhage consistent with diffuse alveolar damage in less involved, more central parenchyma.

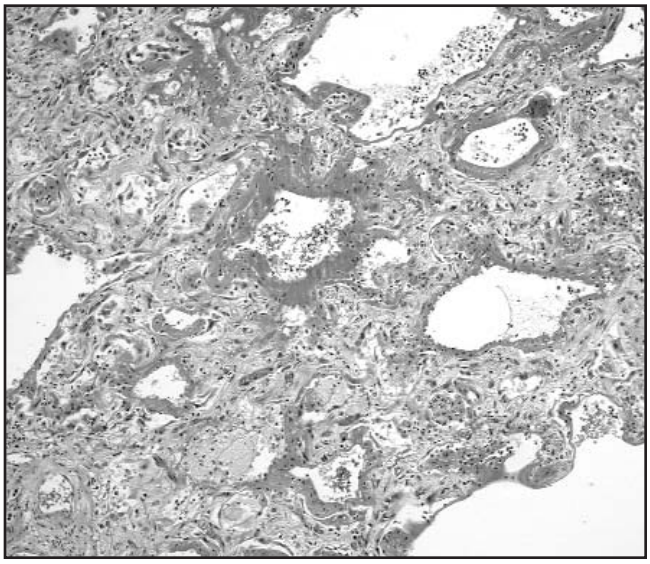

Image 2 Diffuse alveolar damage with hyaline membranes superimposed on background fibrotic lung (H&E, ×100).

continuous positive airway pressure mask, and 1 patient was mechanically ventilated, but these interventions were made late in the acute exacerbation and, thus, could not be implicated etiologically. Eight patients were treated with corticosteroids, 4 received immunosuppressive therapy (cyclophosphamide and/or azathioprine), and 7 received antibiotics.

Premortem microbiologic study results were available for 11 of 15 patients. In 8 of 9 cases, viral culture and antibody test results were negative. One case had antibodies to herpes simplex virus (HSV) and cytomegalovirus (CMV), although there was no histologic evidence of infection at autopsy. In 8 of 9 patients, the results of blood and sputum cultures were negative. In 1 patient, bronchoalveolar lavage fluid and sputum grew *Stenotrophomonas maltophilia* and *Proteus* organisms on several occasions after the initial deterioration in lung function; the patient was treated with appropriate antibiotics. In 4 of 5 patients, culture of lung tissue taken at autopsy was negative. One case grew *Staphylococcus aureus.*

At autopsy, the lungs were heavy (mean weight, 818 g) and macroscopically showed the surface nodularity associated with FA, as well as relative shrinkage of the lower lobes. In the lung parenchyma relatively unaffected by fibrosis, the cut surface was typically hemorrhagic or consolidated, reflecting superimposed diffuse alveolar damage **Image 1**. In 12 of 15 patients, histologic examination revealed a background pattern of usual interstitial pneumonia (UIP) on autopsy (n = 11) or on premortem biopsy and autopsy (n = 1). All had a premortem diagnosis of IPF/CFA. Three additional cases showed a background pattern of fibrotic nonspecific interstitial pneumonia, all of which were associated with CTDs. All 15 cases showed superimposed changes of diffuse alveolar damage **Image 2**. Increased numbers of lymphoid aggregates were noted in 5 cases, although these were seen in patients with idiopathic disease and in those with CTDs. In the cases with background UIP, there was a wide distribution in the extent of fibroblastic foci, while they were not seen in fibrotic nonspecific interstitial pneumonia. Fibroblastic foci were distinguished from buds of intra-alveolar organization seen in the organizing phase of diffuse alveolar damage by their immediate adjacency to areas of established fibrosis and their presence away from areas of established diffuse alveolar damage. Areas showing honeycomb changes contained aggregates of abundant neutrophils within the air spaces; however, staining for organisms was uniformly negative in these areas and the results for tissue taken for culture at autopsy also were negative. In contrast, there were 2 cases with focal bronchopneumonia superimposed on the other pathologies, 1 of which grew *S aureus* from tissue taken at autopsy. Given the absence of any evidence of infection before autopsy and the type of organism identified, these were interpreted as nosocomial secondary events rather than the primary cause of acute deterioration in lung function. In 2 cases, histologic examination at autopsy showed very occasional CMV inclusions, again thought to be a secondary phenomenon on the basis of their

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scarcity, the absence of an associated increase in serum antibodies to CMV, and treatment with high-dose corticosteroids during the terminal episode.

Computed tomography (CT) scans taken before the acute exacerbations were available for 8 patients. Of 5 cases with UIP, 3 had a concordant histologic and radiologic diagnosis, while in 2 cases, the CT appearances were more in keeping with fibrotic nonspecific interstitial pneumonia.[10,19,20] In contrast, all 3 patients with a CTD showed concordant radiologic and histologic patterns of nonspecific interstitial pneumonia.

Acute Interstitial Pneumonia and Diffuse Alveolar Damage Associated With CTD

Six patients fulfilled the clinicopathologic criteria for acute interstitial pneumonia, and 5 patients were identified with a histologic pattern of diffuse alveolar damage at autopsy and a history of an underlying CTD (dermatomyositis, 1; rheumatoid arthritis, 2; Still disease, 1; and SLE, 1). There was no clinical evidence of lung disease before admission. The clinical features of this group are summarized in **Table 3**.

There was no clinical evidence of infection at the time of admission in all 11 patients, although microbiologic studies later in the disease showed positive bacterial cultures in 4 patients, 3 with nosocomial organisms (*S maltophilia,* 1; *Klebsiella* species, 2) and 1 with *Streptococcus pneumoniae*. Viral antibody titers for adenovirus, CMV, HSV, influenza, and parainfluenza were negative in 5 of 6 patients. In 1 patient who previously tested negative, antibodies to CMV and HSV developed immediately before death, and occasional CMV inclusions were seen during histologic examination at autopsy; these were interpreted as secondary events rather than the primary cause of the acute deterioration in lung function.

At autopsy, the lungs were heavy (mean weight, 1,084 g) with hemorrhagic or consolidated cut surfaces, the features characteristic of the exudative and organizing phases of diffuse alveolar damage. All 11 cases showed the histologic features of diffuse alveolar damage, with 1 case showing occasional CMV inclusions. In the cases with an associated CTD, there was no evidence of a background interstitial pneumonia, in particular fibrotic nonspecific interstitial pneumonia, or lymphoid hyperplasia.

Discussion

IPF/CFA is a chronic progressive interstitial lung disease of unknown cause that results in respiratory failure and death with an average survival of 2 to 3 years.[2,4,5,10,18] Most cases show a histologic pattern of UIP, although a substantial minority have fibrotic nonspecific interstitial pneumonia.[5,10,21] Death typically is due to respiratory failure, associated cardiac disease, supervening infection, or development of a neoplasm, but acute terminal events also have been reported, although little is known about their relationship to the background fibrosis and background clinical associations such as CTDs, upon which FA may develop.[14-16]

A review of the literature shows few cases in which the histologic features were analyzed. Kondoh et al[14] described 3 patients in whom surgical lung biopsies during the acute exacerbation showed alveolar wall edema with a mild to moderate mononuclear cell infiltrate and intra-alveolar organization, but without hyaline membrane formation. Away from these areas of acute lung damage, the lung showed typical changes of UIP. Interestingly, all 3 patients survived following treatment with corticosteroids and antibiotics.[14] A series by Akira et al[16] concentrated predominantly on imaging features and the prognostic significance of these findings in an acute exacerbation. In patients who survived, biopsies from 2 patients showed "fibroblastic foci" only (these would now be termed *foci of intra-alveolar organization*), while in those who died and underwent autopsy, all showed the exudative phase of diffuse alveolar damage with the presence of hyaline membranes. However, there was no histologic analysis of the background fibrosis in relation to patterns of interstitial pneumonia.[16]

Table 3
AIP and DAD With CTD

Variable	AIP (n = 6)	DAD With CTD (n = 5)
Median age, y (range)	60.5 (37-84)	46 (43-76)
Sex (M/F)	4:2	2:3
Mean duration of symptoms before admission, d (range)	25 (3-90)	42 (18-90)
Mean WBC count, /μL (range)*	18,400 (7,300-41,600)	18,000 (8,000-26,000)
Mean C-reactive protein level, mg/L (range)*	153.5 (150-157)	181 (112-287)
Mean time from admission to death, d (range)	27 (15-45)	22 (12-41)

AIP, acute interstitial pneumonia, CTD, connective tissue disease; DAD, diffuse alveolar damage.
* To convert the WBC values to Système International units ($\times 10^9$/L), multiply by 0.001; the reference range is 3,500-10,000/μL (3.5-10 $\times 10^9$/L). The reference range for C-reactive protein is 0-10 mg/L.

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As expected, the histologic findings in our series are similar to those found at autopsy by Akira et al.[16] In addition, our study shows that acute exacerbations can occur in the clinical setting of IPF/CFA and FA-CTD and on a histologic background of both UIP and fibrotic nonspecific interstitial pneumonia. Indeed, it also is interesting that in these previous publications,[14,16] the patients who survived had intra-alveolar organization but no hyaline membranes. Whether the organization seen in these survivors relates to the organizing phase of diffuse alveolar damage or a separate, less aggressive or localized process is unknown. Independent of these data, the incidence of terminal acute exacerbations of IPF/CFA and FA-CTD may be higher than previously thought, given that 60% (15/25) of patients showed these features in the present study. However, this finding should be viewed in the light of likely bias reflecting not only referral of patients with sudden unexplained deterioration of chronic disease to a tertiary center but also requesting of autopsy in patients in whom the cause of death, in particular relating to the differential diagnosis of infection and diffuse alveolar damage, is uncertain.

Patients with FA-CTD have a better prognosis than those with IPF/CFA,[22] but the present study shows that these patients also may have acute terminal exacerbations. Interestingly, all 3 patients had a histologic pattern of fibrotic nonspecific interstitial pneumonia, in keeping with the findings of recent studies that show a high frequency of nonspecific interstitial pneumonia in association with various CTDs.[23-25] It is possible that diffuse alveolar damage may progress to a pattern of fibrotic nonspecific interstitial pneumonia if patients survive beyond the organizing phase,[6] but a pattern of fibrotic nonspecific interstitial pneumonia was confirmed by review of CT scans taken before the acute exacerbation in all 3 patients, using recently defined criteria.[10,19,20]

Our results also document that honeycomb lung also may develop eventually on a background of fibrotic nonspecific interstitial pneumonia. Indeed, it is interesting to note that areas of honeycombing all contained intraluminal neutrophils, but no organisms were identified, while 1 case with focal bronchopneumonia showed *S aureus* on culture. Thus, the presence of neutrophils in bronchoalveolar lavage fluid from patients with UIP or nonspecific interstitial pneumonia does not necessarily indicate the presence of a complicating infection and may simply represent stasis and accumulation of neutrophils in severely damaged lung tissue.

With regard to acute histologic changes, there were no differences in any of the groups in relation to UIP or fibrotic nonspecific interstitial pneumonia or in relation to acute interstitial pneumonia and diffuse alveolar damage associated with CTDs occurring de novo. CTDs are known to be associated with the development of diffuse alveolar damage,[26-29] in particular, SLE.[30-33] Our data confirm these findings, with no evident subclinical chronic features identified at autopsy. However, it remains uncertain whether the acute exacerbation in patients with FA/CTD is related to the underlying fibrosis, the associated CTD, or a combination of these factors. In particular, our data have not established whether fibrotic nonspecific interstitial pneumonia can induce an acute exacerbation in its own right. In addition, although the term *secondary acute interstitial pneumonia* has been suggested for cases associated with a CTD,[34] there is no evidence to suggest a distinct clinicopathologic group, and acute respiratory distress syndrome associated with CTD is an equally appropriate term. Patients with acute interstitial pneumonia in our series had demographics similar to those with CTDs and to those in other series.[11-13]

The pathogenesis of sudden deterioration and development of diffuse alveolar damage in patients from all subgroups is unknown. Because our study was retrospective, our data are not complete for all parameters for all patients, but certain associations can be excluded. For example, only 1 patient underwent mechanical ventilation, and with regard to toxic effects of oxygen, although no threshold for the concentration of fraction of inspired oxygen (F_{IO_2}) has been identified above which diffuse alveolar damage is known to occur, only 3 patients received high F_{IO_2} (>60%), and all were already in preterminal phases. With regard to infections, impaired lung function is a predisposing factor, and superimposed infection without evidence of diffuse alveolar damage was a recognized cause of death in our general database. However, these cases showed clinical and radiologic evidence of infection, with significant bronchopneumonia at autopsy, and were distinct from those in whom nosocomial infections developed after acute deterioration in lung function. It is difficult to exclude entirely a viral infection as a trigger for these changes, but no case showed strong supportive evidence, with only 3 cases showing incidental secondary CMV infection at autopsy. Indeed, treatment with high-dose corticosteroids during the terminal episode may well have been a contributing factor in a proportion of these patients.

Acute exacerbations of IPF/CFA may be more common than previously thought and should be considered along with other causes in any patient with IPF/CFA who has a sudden deterioration in lung function. Acute exacerbations may occur on a background of both UIP and nonspecific interstitial pneumonia and in patients with FA/CTDs. In the latter group, it is uncertain whether the fibrosis, the associated CTD, or both are the trigger. The histologic features in the acute phase are the same in relation to background fibrosis and de novo disease, but the cause for such acute exacerbations remains unknown.

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References

1. Liebow AA, Carrington CB. The interstitial pneumonias. In: Simon M, Potchen EJ, Lemay E, eds. *Frontiers in Pulmonary Radiology*. New York, NY: Grune and Stratton; 1969.
2. Bjoracker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathological subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1998;157:199-203.
3. Katzenstein ALA, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med*. 1998;157:1301-1315.
4. Travis WD, Matsui K, Moss J, et al. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. *Am J Surg Pathol*. 2000;24:19-33.
5. Nicholson AG, Colby TV, du Bois RM, et al. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med*. 2000;162:2213-2217.
6. Katzenstein AA, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis: histologic features and clinical significance. *Am J Surg Pathol*. 1994;18:136-147.
7. Myers JL, Veal CF Jr, Shin MS, et al. Respiratory bronchiolitis causing interstitial lung disease: a clinicopathologic study of six cases. *Am Rev Respir Dis*. 1987;135:880-884.
8. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis–associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. *Mayo Clin Proc*. 1989;64:1373-1380.
9. Anttila S, Sutinen S, Paananen M, et al. Hard metal lung disease: a clinical, histological, ultrastructural and X-ray microanalytical study. *Eur J Respir Dis*. 1986;69:83-94.
10. Travis WD, King TE. Consensus classification of idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2002;165:277-304.
11. Hamman L, Rich A. Acute diffuse interstitial fibrosis of the lung. *Bull Johns Hopkins Hosp*. 1944;74:177.
12. Katzenstein A-L, Myers JL, Mazur MT. Acute interstitial pneumonia: a clinicopathologic, ultrastructural, and cell kinetic study. *Am J Surg Pathol*. 1986;10:256-267.
13. Olson J, Colby TV, Elliott CG. Hamman-Rich syndrome revisited. *Mayo Clin Proc*. 1990;65:1538-1548.
14. Kondoh Y, Taniguchi H, Kawabata Y, et al. Acute exacerbation in idiopathic pulmonary fibrosis: analysis of clinical and pathologic findings in three cases. *Chest*. 1993;103:1808-1812.
15. Akira M. Computed tomography and pathologic findings in fulminant forms of idiopathic interstitial pneumonia. *J Thorac Imaging*. 1999;14:76-84.
16. Akira M, Hamada H, Sakatani M, et al. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. *AJR Am J Roentgenol*. 1997;168:79-83.
17. Kitaichi M. Pathologic features and the classification of interstitial pneumonia of unknown etiology. *Bull Chest Dis Res Inst Kyoto Univ*. 1990;23:1-18.
18. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International Consensus Statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). *Am J Respir Crit Care Med*. 2000;161:646-664.
19. MacDonald SL, Rubens MB, Hansell DM, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. *Radiology*. 2001;221:600-605.
20. Hartman TE, Swensen SJ, Hansell DM, et al. Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. *Radiology*. 2000;217:701-705.
21. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med*. 2001;164:1722-1727.
22. Wells AU. Lung disease in association with connective tissue disorders. In: Olivieri D, du Bois RM, eds. *Interstitial Lung Diseases*. Sheffield, England: ERS Journals; 2001.
23. Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. *Am J Respir Crit Care Med*. 2001;164:1182-1185.
24. Bouros D, Nicholson AG, Colby TV, et al. Histopathological subsets of fibrosing alveolitis in patients with scleroderma and their relationship to natural history and treated course. *Am J Respir Crit Care Med*. 2002;165:1581-1586.
25. Kim DS, Yoo B, Lee JS, et al. The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis*. 2002;19:121-127.
26. Lakhanpal S, Lie JT, Conn DL, et al. Pulmonary disease in polymyositis/dermatomyositis: a clinicopathological analysis of 65 autopsy cases. *Ann Rheum Dis*. 1987;46:23-29.
27. Tazelaar HD, Viggiano RW, Pickersgill J, et al. Interstitial lung disease in polymyositis and dermatomyositis: clinical features and prognosis as correlated with histologic findings. *Am Rev Respir Dis*. 1990;141:727-733.
28. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. *Am Rev Respir Dis*. 1985;131:770-777.
29. Muir TE, Tazelaar HD, Colby TV, et al. Organizing diffuse alveolar damage associated with progressive systemic sclerosis. *Mayo Clin Proc*. 1997;72:639-642.
30. Cheema GS, Quismorio FP. Interstitial lung disease in systemic lupus erythematosus. *Curr Opin Pulm Med*. 2000;6:424-429.
31. Kim JS, Lee KS, Koh EM, et al. Thoracic involvement of systemic lupus erythematosus: clinical, pathologic, and radiologic findings. *J Comput Assist Tomogr*. 2000;24:9-18.
32. Nadorra RL, Landing BH. Pulmonary lesions in childhood onset systemic lupus erythematosus: analysis of 26 cases, and summary of literature. *Pediatr Pathol*. 1987;7:1-18.
33. Orens JB, Martinez FJ, Lynch JP. Pleuropulmonary manifestations of systemic lupus erythematosus. *Rheum Dis Clin North Am*. 1994;20:159-193.
34. Bouros D, Nicholson AG, Polychronopoulos V, et al. Acute interstitial pneumonia. *Eur Respir J*. 2000;15:412-418.

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