Prognosis of cryptogenic fibrosing alveolitis

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ABSTRACT We have analysed retrospectively 100 consecutive patients with cryptogenic fibrosing alveolitis, who were treated with corticosteroids and followed for at least three years. At the time of diagnosis biopsy specimens were available in 64 cases. The clinical, radiographic, physiological, and histological features and the response to steroid treatment have been correlated with the prognosis. An early objective functional improvement was observed in 30%. Analysis of the survival data (life table and log rank test) showed a longer survival in younger patients and in patients with a shorter duration of symptoms before presentation, less radiographic abnormality, and less impairment of diffusing capacity, but not clearly in patients with more cellular histological appearances. The most favourable prognostic sign seemed to be an early response to steroid treatment.

Fibrosing alveolitis is a clinical syndrome with a notably variable course. Although the first patients described by Hamman and Rich¹ died within 12 months of the onset of symptoms, a more chronic course is usual.^{2,3}

Despite the variability of diagnostic criteria and histological features in the different published studies, there is agreement that factors affecting prognosis include the short-term response to corticosteroid drugs and the cellularity of lung biopsy specimens.^{2,4-7} We have further evaluated the influence of clinical features, histological findings, and treatment on prognosis in 100 patients with cryptogenic fibrosing alveolitis diagnosed and treated from 1967 to 1979.

Methods

The patients

From a total of 113 consecutive patients 13 are excluded from this report as they did not receive corticosteroids. The mean age of the remaining 100 patients at the onset of symptoms was 53 years (range 16-77 years); 51 were women and 49 men. All patients were followed for at least three years from the time of diagnosis or to death (mean follow-up 6.8 years). Assessment of the last 88

patients has been prospective. Patients with associated rheumatoid arthritis, systemic sclerosis, and other connective tissue diseases were included. The criteria for the selection of patients were: exclusion of other causes of diffuse lung disease (especially sarcoidosis, pneumoconiosis, allergic alveolitis, and nitrofurantoin hypersensitivity reactions); diffuse, persisting lung opacities; lowered pulmonary carbon monoxide diffusing capacity (TLCO) or restrictive ventilatory impairment. In the 70 cases in which histological specimens of lung tissue were available the appearances were compatible with fibrosing alveolitis—that is, alveolar walls were thickened by active fibrosis or chronic inflammation or both. If lung histological specimens were not available (30 cases) or if they showed only widespread interstitial fibrosis without evidence of alveolitis (six cases), the following supporting diagnostic criteria were required: crepitant rales with at least one of: (a) finger clubbing, (b) a positive result from the latex test (titre $\geq 1/16$), and (c) antinuclear antibodies in a titre of at least 1/80. Our hospital is a secondary referral centre, and we estimate the population of patients studied to represent about two-thirds of all cases diagnosed in an area with one million inhabitants.

Respiratory measurements and chest radiographs

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) were recorded with either a Bernstein spirometer or a CPI rolling-seal spirometer (model 220). The values obtained were expressed as percentages of the reference values of

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Berglund *et al.*⁸ TLCO was measured by the single-breath method for carbon monoxide⁹ and the results were related to the reference values of Cotes.¹⁰

All chest radiographs were assessed and coded by two radiologists (OK and MV) in conformity with the standard films of the ILO U/C International Classification.¹¹

Histological examination

Histological specimens of lung tissue were available in 70 cases. An adequate biopsy specimen was obtained before treatment from the right lower lobe with a TruCut needle in 50 patients; a transbronchial biopsy was performed in one case; and a surgical biopsy specimen from the middle lobe or lingula was obtained in 13 cases. Postmortem material alone was subsequently available in six cases. The thickness of the alveolar walls was assessed by comparison with the diameter of the alveolar lumen and was estimated to be mild, moderate, or considerable.¹² The overall activity of the disease was evaluated from the thickness of the alveolar walls, the extent of inflammation and fibrosis, and in some borderline cases the degree of fibroblastic activity. The changes were classified as mainly inflammatory if (a) inflammatory cell infiltration was virtually the only finding (fig 1); or (b) specimens contained both inflammatory cell infiltration and slight-to-moderate fibroblastic proliferation, the former being predominant (fig 2).

Twenty-two of the 64 biopsy specimens satisfied

one or other of these criteria and in the remaining 42 specimens the changes were predominantly fibrotic (fig 3).

Steroid treatment and follow-up

Patients were treated with prednisolone in an initial dose of 40 mg/day in most cases. The dose was lowered stepwise to 10 mg/day over a period of three months. On the basis of the results of six months' treatment, treatment was either terminated or continued in low dosage (5–10 mg/day). The mean duration of treatment was 2.9 years, being less than one year in 18 cases and more than three years in 45 cases. The patients' progress was followed with serial determinations of TLCO and FVC and with chest radiographs.

Because consecutive values of TLCO and FVC showed fluctuations in some patients the significance of a possible improvement in borderline cases was assessed after several measurements. If the FVC or TLCO rose by more than 15% above the initial value the improvement was considered significant.

Survival curves were constructed according to the life table method and differences between groups were tested by the log rank test.¹³ Chi-squared test statistics with Yates's correction were used in the tables. The significance limit was taken as $p = 0.05$. Survival and prognosis were calculated from the time of diagnosis. The numbers of patients still at risk at specific times are recorded on the graphs of survival. The numbers do not include all the patients

Fig 1 Mainly inflammatory pulmonary changes in fibrosing alveolitis: inflammatory lymphoid cell infiltration and slight thickening of the alveolar septa. (Haematoxylin and eosin, $\times 230$.)

Fig 2 Intermediate case showing both inflammatory and fibrotic pulmonary changes in fibrosing alveolitis, alveolar septa having slight-to-moderate thickening; the finding has been interpreted as mainly inflammatory change. (Haematoxylin and eosin, $\times 230$.)

Fig 3 Mainly fibrotic pulmonary changes in fibrosing alveolitis, septa showing fibroblastic proliferation and moderate thickening. (Haematoxylin and eosin, $\times 230$.)

followed for this length of time, but only patients who are still alive and thus "at risk."¹³ Patients who have been followed for a shorter time and patients who died before each point are not included in the numbers.

Results

Causes of death

During the follow-up period 44 patients died. Twenty-two of the deaths were due to respiratory

insufficiency. Ten patients died of cardiovascular disease and three of pulmonary embolism. Two patients died of bronchial carcinoma and one each of rectal carcinoma, breast carcinoma, and gastric carcinoma. (A bronchial carcinoma was diagnosed in one additional patient and a gastric carcinoma in another; both of these patients were still alive at the time of collection of this material.) Of the 13 excluded from the patients reported here because no treatment was given, three died of bronchial carcinoma.

The mean age of the patients at the onset of symptoms or the appearance of the first radiographic opacities (or both) was 53 years (range 16–77 years). The mean age at presentation at the Helsinki University Central Hospital was 55 years (range 18–80 years). Age had a significant influence on survival. The life table probability of survival at 90 months was 62% in those under 50 years and 56% in the age group 50–65 years but only 31% among those over 65 years of age. The difference in survival between these age groups was significant ($p = 0.006$, log rank test). There was no significant difference in survival between the sexes ($p = 0.924$, log rank test).

Patients with symptoms or known radiographic changes of less than two years' duration when first seen survived longer than those with a longer history ($p = 0.04$, log rank test).

Crepitant rales were heard in 94 cases (94%) and clubbing was noted in 46 (46%). Neither of these features had any influence on survival.

Cryptogenic fibrosing alveolitis was associated with a systemic disease in 33 cases (rheumatoid arthritis, 19; systemic sclerosis, 8; dermatomyositis, 2; and systemic lupus erythematosus, Sjögren's syndrome, primary biliary cirrhosis, and chronic active hepatitis one each). Twenty-four other patients had systemic manifestations (transient arthritis, Raynaud's phenomenon, etc). The presence of associated diseases or systemic manifestations had no overall effect on survival (log rank test). It was, however, noteworthy that none of the patients with systemic sclerosis showed any objective improvement during steroid treatment, and after five years only two of eight patients were alive.

A positive result in the latex or antinuclear antibody test, or both, was found in 56% of the cases. These immunological features did not influence survival.

Restrictive ventilatory impairment (FVC less than 80% of the predicted value) was observed in 70 patients on admission and developed in 10 additional cases. At the time of diagnosis the percentage (mean $\pm$ SD) of the predicted FVC was 64.1 ± 18.9 (range 30–111) and of the predicted FEV₁ $65.1 \pm$

Fig 4 Survival curves of 97 patients with fibrosing alveolitis showing better survival in those with diffusing capacity (TLCO) $\geq 45\%$ of predicted (curve A) at the time of diagnosis than in those with TLCO $< 45\%$ (curve B) ($p = 0.002$, log rank test). The numbers of patients at risk are recorded on the graphs of survival. (TLCO was not measurable in three patients.)

Fig 5 Survival curves of 100 patients with fibrosing alveolitis showing better survival in those with lesser profusion scores at the time of diagnosis ($p = 0.01$, log rank test). The numbers of patients at risk are recorded on the graphs of survival.

19.7 (range 36–92). There was no relationship between these volumes and the prognosis (FVC; $p = 0.44$, log rank test).

The mean percentage of the predicted diffusing capacity was 43.2 ± 12.0 (range 11–75). Survival was significantly longer in patients with a TLCO 45% or more of the predicted value than in patients with lower TLCO values (fig 4). TLCO was not measured in three cases with far advanced disease (FVC 32–43% of predicted).

The lower radiographic scores according to the ILO classification correlated with longer survival (fig 5).

Table 1 Response to prednisolone treatment related to histological appearance of lung biopsy specimen

Response after 6 months' treatment	Histological appearance		Total
	Mainly inflammatory changes	Mainly fibrotic changes	
Responders	13	8	21
Non-responders	9	34	43
Total	22	42	64

Significance of difference in steroid response between those with inflammatory and those with fibrotic changes: $p = 0.003$ (χ^2 test).

Fig 6 Survival curves of 64 patients with fibrosing alveolitis according to histological type—mainly inflammatory and mainly fibrotic. The difference between the groups was not statistically significant ($p = 0.17$, log rank test). The numbers of patients at risk are recorded on the graphs of survival.

Table 2 Histological appearance of lung biopsy specimen related to outcome at four years in 60 patients followed for at least four years from diagnosis.

Histological appearance	Outcome at 4 years			Dead	Total
	Alive				
	Improved	Unchanged	Progressed		
Mainly inflammatory changes	8	7	2	3	20
Mainly fibrotic changes	5	7	15	13	40
Total	13	14	17	16	60

Significance of difference in prognosis between those with inflammatory and those with fibrotic changes: $p = 0.009$ (χ^2 test).

Histology

Improvement after steroid treatment for six months was more common in patients with mainly inflammatory changes (table 1). Inflammatory changes in lung biopsy specimens were also associated with longer survival (fig 6) but this was not statistically significant. If clinical progress of the dis-

Fig 7 Survival curves of 100 patients with fibrosing alveolitis showing better survival in those with objective improvement during an initial six months of steroid treatment ($p = 0.002$, log rank test). The numbers of patients at risk are recorded on the graphs of survival.

Table 3 Response to prednisolone treatment related to outcome at four years in 89 patients followed for at least four years from diagnosis.

Response after 6 months' treatment	Outcome at 4 years				
	Alive			Dead	
	Improved	Unchanged	Progressed		Total
Responders	21	2*	1*	3	27
Non-responders		12	22	28	62
Total	21	14	23	31	89

*Initially improved but later progressed to the previous or worse functional level.

Significance of difference in prognosis between responders and non-responders: $p = 0.001$ (χ^2 test).

ease is included, however, the patients with an inflammatory histological appearance had a better prognosis over four years compared with those with a fibrotic appearance (table 2).

Corticosteroid response

An early favourable response to corticosteroid treatment indicates a better prognosis for survival (fig 7). There was no difference between the ages of the corticosteroid responders (mean 52.4 years) and of the non-responders (mean 53.4 years) but within the group of non-responders age had a significant effect on survival. The relative four-year survival (adjusted for normal life expectancy) was only 24% in patients over 65 but 75% in patients under 50. In relation to the overall clinical course (table 3), the prognostic value of an early response to steroids was even more significant.

Discussion

Comparison of our series of patients with fibrosing alveolitis with those of other published reports shows no major differences in clinical, functional, and radiographic features.^{2,3,14,15} In some series rheumatoid arthritis, systemic sclerosis, and similar conditions have been excluded,^{2,14} but since the pulmonary features do not differ significantly³ patients with these disorders were included in the present study. Some series^{3,14} have shown a higher proportion of men than women but in our series the sex incidence was equal, as reported in some of the other studies.^{2,15}

Half of the patients died of respiratory failure; respiratory infections and pulmonary embolism were also causes of death possibly associated with fibrotic lung disease. Among other causes of death, cardiovascular disease was common. The series of Turner-Warwick *et al*³ had four times as many

deaths from cardiovascular disease as expected but the reason is not clear.

The occurrence of bronchial carcinoma in five of 113 patients followed for over three years is rather lower than the proportions (7% and 10%) reported by Stack *et al*² and by Turner-Warwick *et al*.¹⁶ No particular histological variety of carcinoma was found either in our cases or in the other series reported. It is, however, of interest that patients have occasionally developed alveolar-cell carcinoma—one of our five patients and two of the 15 described by Turner-Warwick *et al*.¹⁶ All four patients who died of bronchial carcinoma and one additional patient with bronchial carcinoma who is still alive had digital clubbing, which was also noted in 19 of 20 cases of bronchial carcinoma and cryptogenic fibrosing alveolitis in the series of Turner-Warwick *et al*.¹⁶

There is close agreement on survival in the various reported series. The five-year survival was about 50% in the series of Turner-Warwick *et al*³ and Wright *et al*¹⁴ and slightly higher (60%) in the present series. We excluded, however, 13 patients who were not given steroids and, if these cases are included, the five-year survival was close to 50%. The better survival of young patients and the longer survival associated with lesser radiographic abnormalities have also been noted in other series.^{3,14} In addition, we have shown that a more favourable prognosis is related to higher diffusing capacity at presentation.

The correlations between histological appearance, response to steroids, and survival are difficult to compare in different series because of different criteria and methods used in analysis. The presence of more intra-alveolar large mononuclear cells, less fibrosis, and no more than slight alveolar wall thickening has been related to a better steroid response.^{4,5,14} Other workers have found that patients with a more cellular picture respond to steroid treatment.^{2,17} Our histological analysis divided the patients into a mainly inflammatory and a mainly fibrotic group. Patients with a cellular histological picture would correspond to our inflammatory group and these patients showed a better short-term response to steroids and a more favourable long-term outcome. Our findings were, however, not as clearcut as those of Wright *et al*.¹⁴

The value of needle biopsy in the diagnosis of diffuse lung disease is closely related to the size of the biopsy specimen.¹² Open lung biopsy is the most reliable diagnostic procedure, but in clinical practice the TruCut needle biopsy method can be used successfully. In our material the biopsy was diagnostically helpful in 45 of 54 patients (85%) and open lung biopsy in 12 of 13.

The main factor influencing the long-term prognosis was the short-term response to steroid treatment, which is in agreement with the findings of other studies.^{2,7} An objective functional improvement was observed in 30 of 100 cases and, in contrast to the results of Turner-Warwick *et al*,⁷ the response to steroids was independent of age and sex. The prognostic value of the initial steroid response seems to be better than that of the lung biopsy appearance. In our patients with fibrosing alveolitis a trial of steroid treatment of six months' duration is started irrespective of the nature of the lung biopsy finding. After six months a decision whether or not to continue this treatment is based on the steroid response. Lung biopsy findings do not influence our treatment regimen in most cases. We therefore suggest that lung biopsy is primarily of value in the differential diagnosis of diffuse lung disease rather than for prognostic purposes alone.

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