

The management of cryptogenic fibrosing alveolitis in three regions of the United Kingdom

I.D.A. Johnston*, S.A. Gomm**, S. Kalra**,
A.A. Woodcock**, C.C. Evans***, C.R.K. Hind***

The management of cryptogenic fibrosing alveolitis in three regions of the United Kingdom. I.D.A. Johnston, S.A. Gomm, S. Kalra, A.A. Woodcock, C.C. Evans, C.R.K. Hind. ©ERS Journals Ltd 1993.

ABSTRACT: The case notes of 200 patients with cryptogenic fibrosing alveolitis, from three regions in the United Kingdom, were reviewed, in order to determine how physicians manage this uncommon condition. In the majority of cases (119), the diagnosis was based solely on clinical grounds, with no attempt at histological confirmation of the diagnosis. Transbronchial biopsy was attempted in 66 patients, but was unhelpful in confirming a diagnosis of pulmonary fibrosis in 30% of these patients. Thirty five patients underwent bronchoalveolar lavage, and 15 had an open lung biopsy. Of the 132 patients treated, 110 received prednisolone alone, and the rest a combination of other immunosuppressive agents. The doses and duration of therapy varied considerably.

These results suggest that, in the late 1980s, there were wide variations of practice in the management of cryptogenic fibrosing alveolitis in the United Kingdom. This is likely to reflect a paucity of information on the optimum management of this uncommon condition.

Eur Respir J., 1993, 6, 891-893.

* University Hospital, Queens Medical Centre, Nottingham, UK. ** North West Lung Centre, Wythenshawe Hospital, Manchester, UK. *** The Cardiothoracic Centre, Liverpool, UK.

Correspondence: C.R.K. Hind
The Cardiothoracic Centre
Liverpool L14 3PE, UK

Keywords: Bronchoalveolar lavage
cryptogenic fibrosing alveolitis
transbronchial biopsy

Received: May 13 1992
Accepted after revision December 28 1992

This study was supported by the British Lung Foundation

Cryptogenic fibrosing alveolitis (CFA) is a relatively rare condition, with a reported prevalence of about 5 per 100,000 [1, 2]. Mortality due to the disease appears to be increasing, with over 700 recorded deaths due to this condition in England and Wales in 1988 [3]. Nevertheless, most general or respiratory physicians will see only a few new cases each year.

As part of a multicentre study in three regions (Merseyside, North West and Trent) on the epidemiology of CFA in the United Kingdom (UK), clinical data on patients with CFA have been entered onto a computerized register. Since January 1988, over 200 such patients have been entered. The case notes of all of the first 200 patients have now been analysed, with two main aims in mind. Firstly, to determine whether the diagnosis was based on clinical grounds alone, or also on biopsy. Secondly, to determine how many patients were treated, and the mode of that therapy.

Methods and Patients

Criteria for inclusion

Patients were included in the study if they fulfilled all of the following criteria: bilateral basal crackles on auscultation of the chest; basal interstitial shadowing present on the chest X-ray; demonstration of a restrictive

ventilatory defect on pulmonary function testing; the absence of any documented exposure to fibrogenic dusts (e.g. asbestos) or drugs, or any history of exposure to birds, or work on a farm; the absence of any clinical evidence to suggest a systemic connective tissue disease; and a diagnosis of CFA by the consultant in charge of the case [4].

Study population

Current cases of CFA were identified from Hospital Activity Analysis data, lung function laboratory records, and personal enquiry to respiratory physicians in hospitals in Nottingham, Manchester and the Merseyside Region. All case notes for patients with a diagnosis of CFA were available for review. The case notes of the first 200 patients who fulfilled the criteria for inclusion into the study were assessed separately, by one author from each region, using a standard questionnaire. The following details were noted: patient age at the time of diagnosis; sex; whether any attempt had been made to obtain histological proof of the diagnosis (e.g. transbronchial or open lung biopsy), or whether bronchoalveolar lavage (BAL) had been performed; the doses and duration of any immunosuppressive treatments used; whether a respiratory or non-respiratory physician was managing the patient; and whether in a Regional Cardiothoracic Unit, or District General/Teaching Hospital setting. In cases in which

transbronchial lung biopsy had been performed, the pathology reports were categorized as to whether the pathologist considered that: 1) a firm diagnosis of CFA had been made; 2) the appearances were suggestive of CFA; or that 3) the appearances were nonspecific.

Statistical methods

Chi-squared tests were used to analyse any differences in the proportions of patients in the various settings (as detailed above) who had histological confirmation of diagnosis, and in the proportions of those patients who were given immunosuppressive treatment.

Results

Of the 200 patients, 130 were male and 70 female, and the median age at the time of diagnosis of CFA was 62 yrs (range 21–87 yrs).

Distribution of patients

Twenty five patients (13%) were being managed by 16 non-respiratory physicians in District General/Teaching Hospitals. The remainder were looked after by respiratory physicians in a tertiary referral Regional Cardiothoracic Unit (69 patients (35%); 7 physicians), or in a District General/Teaching Hospital (106 patients (53%); 12 physicians) (table 1).

diagnosis was confirmed, and the remainder showed pulmonary fibrosis consistent with CFA. The mean age of the patients who underwent an open lung biopsy was 47 yrs (range 22–58 yrs), and of those who did not was 64 yrs (range 40–87 yrs).

A total of 35 patients (18%) had BAL performed (of whom 30 had TBB taken at the same time), although whether this was for clinical or research purposes was not indicated in the case notes.

Patients managed in a Regional Cardiothoracic Centre were significantly more likely to have undergone an attempt to obtain histology (table 1) than those seen elsewhere ($p < 0.001$). Older patients were less likely to have undergone invasive procedures, although this trend was not statistically significant.

Immunosuppressive treatment

Sixty eight patients (34%) received no specific therapy with any form of immunosuppressive drugs (*e.g.* steroids). One hundred and ten patients received prednisolone only (starting dose range 2.5–60 mg; median duration of treatment 12 months, range 1 week to 20 yrs), with a tendency for the lower doses to be used by non-respiratory physicians. Twelve patients (6%) had cyclophosphamide and steroids (dose of cyclophosphamide 50–100 mg daily; duration 1–48 months). Eight patients (4%) had received azathioprine and steroids (dose of azathioprine 50–150 mg daily; duration 1–36 months); and two patients had penicillamine and steroids (375 mg penicillamine daily, in both patients).

Table 1. – Management of patients with cryptogenic fibrosing alveolitis

Patient under care of:	Patients n	Attempt to obtain histology n			Treatment n		
		TBB	BAL	OLB	None	Steroids	Steroids + other
Respiratory physicians in a Regional Thoracic Unit	69	38	20	10	17	41	11
Respiratory physicians in a Teaching/District Hospital	106	20	15	5	32	64	10
Non-Respiratory physicians in a Teaching/District Hospital	25	8	0	0	19	5	1

TBB: transbronchial biopsy; BAL: bronchoalveolar lavage; OLB: open lung biopsy.

Histological proof of diagnosis

In 119 patients no attempt to obtain lung histology had been made. Sixty six patients (33%) had had a transbronchial biopsy (TBB), performed before starting any form of immunosuppressive therapy in all but six. Of these 66, 26 (40%) were reported as diagnostic of CFA, 20 (30%) were "suggestive" of CFA, and in 20 (30%) no diagnosis was confirmed. The number of pathologists involved in the diagnosis was 18.

Fifteen patients (8%) had an open lung biopsy, in all cases while receiving steroid therapy. In 11, the

Patients managed by respiratory physicians were significantly more likely to have been treated for their CFA with immunosuppressive therapy (table 1) ($p < 0.001$). There was no statistically significant relationship between either age or attempt to obtain histology and the use of immunosuppressive therapy.

Discussion

Cryptogenic fibrosing alveolitis (CFA) is an uncommon disease [1, 2], which carries a serious prognosis, with a

reported median survival of only 4 or 5 yrs from diagnosis [1, 5]. In the light of current rising mortality due to the disease [3] and changes in available investigative techniques and treatments [6–14], we felt that it was important to ascertain the spectrum of current management in a variety of specialist and non-specialist settings.

The first conclusion from this study is that in the majority of patients the diagnosis of CFA is made clinically, with no attempt at histological confirmation. Attempts at TBB were made in only one third of cases, with a diagnostic yield of 40%. The low use of this technique is perhaps not surprising, since it is known to have a low value in both diagnosing and staging the disease [1, 6]. In the present study, no attempt was made to review the actual TBB histology. We merely categorized the available pathology reports. However, it is possible that had the histological sections been subject to expert scrutiny, the yield would have been even lower than 40%. In contrast, current practice in the USA (as assessed by postal questionnaire) suggests that 75% of patients with suspected CFA do undergo TBB [15]. The role of TBB would appear to be not in the confirmation of diagnosis or staging of CFA, but in the exclusion of other diagnoses, such as sarcoidosis or carcinoma. The use of BAL is also greater in the USA (28% of cases), than in this UK study [15].

The most direct method to evaluate lung inflammation is by open lung biopsy, a procedure used in 25% of USA cryptogenic fibrosing alveolitis patients [15], and in 8% of the UK patients reported here. Thus, although lung histology obtained at open lung biopsy is regarded as important in diagnosis and staging by some authors [1, 7], it is clear that this view is not shared by most practising physicians, either in the UK or, indeed, in the USA. Why should this be? It is possible that in a case with characteristic symptoms and signs, physicians doubt whether an alternative diagnosis will be found, and, indeed, it is not known in what percentage of patients with clinical CFA an alternative diagnosis would be revealed by open lung biopsy. Finally, the low use of an invasive procedure may reflect the fact that many patients will not go on to receive specific treatment for their CFA. The impression gained in this study was that open lung biopsy was reserved mainly for younger patients, who had not responded to prednisolone, and in whom additional immunosuppressive treatment was being considered or used.

In those who did receive treatment, almost always steroids with or without other immunosuppressive therapy, there was a wide variation in both the starting and maintenance doses of the drugs used, and the total duration of therapy. Such variability in therapeutic regimens was also found in the USA [15].

These results highlight the difficulties clinicians face in managing this uncommon disease, and the differences in management when compared with previous studies from

specialist centres. Amongst the many important questions about this serious disease, this study underscores the pressing need for information about the value of histology in unselected populations, and for the development of markers of disease activity to guide the initiation, type, and duration of therapy.

References

1. Crystal RG, Bitterman PB, Rennard SI, Hance AJ, Keogh BA. – Interstitial lung disease of unknown cause. *N Engl J Med* 1984; 310: 154–163.
2. Grant IWB. – Cryptogenic fibrosing alveolitis. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*. Oxford, Oxford University Press, 1987; pp. 123–125.
3. Johnston IDA, Britton JR, Kinnear WJK, Logun RFA. – Rising mortality from cryptogenic fibrosing alveolitis. *Br Med J* 1990; 301: 1017–1021.
4. Turner Warwick M, Burrows B, Johnson A. – Cryptogenic fibrosing alveolitis: clinical features and their outcome on survival. *Thorax* 1980; 35: 171–180.
5. Tukiainen P, Taskinen E, Holsti P, Korhola O, Valle M. – Prognosis of cryptogenic fibrosing alveolitis. *Thorax* 1983; 38: 349–355.
6. Wall CP, Gaensler EA, Carrington CB, Hayes JA. – Comparison of transbronchial and open lung biopsies in chronic infiltrative lung diseases. *Am Rev Respir Dis* 1981; 123: 280–285.
7. Raghu G. – Idiopathic pulmonary fibrosis: a rational clinical approach. *Chest* 1987; 92: 148–154.
8. Danielle RP, Elias JA, Epstein PE, Rossman MD. – Bronchoalveolar lavage: role in the pathogenesis, diagnosis and management of interstitial lung disease. *Ann Intern Med* 1985; 102: 93–108.
9. Klech H, Hutter C. – Side-effects and safety of BAL. *Eur Respir J* 1990; 8: 961–969.
10. Gulsvik A, Kjelsberg F, Bergmann A, et al. – High dose intravenous methylprednisolone pulse therapy as initial treatment in cryptogenic fibrosing alveolitis: a pilot study. *Respiration* 1986; 50: 252–257.
11. Winterbauer RH, Hammar SP, Hallman KO, et al. – Diffuse interstitial pneumonitis: clinicopathological correlations in 20 patients treated with prednisolone/azathioprine. *Am J Med* 1978; 65: 661–672.
12. O'Donnell K, Keogh B, Cantin A, Crystal RG. – Pharmacologic suppression of the neutrophil component of the alveolitis in idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1987; 136: 288–292.
13. Johnson MA, Kwan S, Snell NJC, et al. – Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. *Thorax* 1989; 44: 280–288.
14. Raghu G, Depaso WJ, Cain K, et al. – Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomised, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991; 144: 291–296.
15. Smith CM, Moser KM. – Management of interstitial lung disease: state of the art. *Chest* 1989; 95: 676–678.