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REVIEW

Cryptogenic fibrosing alveolitis/idiopathic pulmonary fibrosis

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Cryptogenic fibrosing alveolitis/idiopathic pulmonary fibrosis. R.M. du Bois, A.U. Wells. ©ERS Journals Ltd 2001.

ABSTRACT: Cryptogenic fibrosing alveolitis (CFA), synonymous with idiopathic pulmonary fibrosis (IPF), remains a life-threatening disease: 50% of patients die within 5 yrs. Historically, many diseases that are now considered to be quite distinct have been "labelled" as CFA. More recently, high-resolution computed tomography and new appreciation of the histopathological patterns of idiopathic interstitial pneumonias have enabled disease variants to be defined according to their different responses to therapy and survival.

CFA is believed to be induced by an external agent, although it is not clear whether CFA represents the final common outcome of numerous pathogenetic mechanisms or has a single cause. In addition, there are currently no prospective double-blind, placebo-controlled trials of treatment showing superiority of one drug regimen over another.

This review attempts to dissect the different patterns of cryptogenic fibrosing alveolitis, illustrate the major features of each, and refine the clinico-radiological-pathological descriptors that together define cryptogenic fibrosing alveolitis as it is understood today.

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The fibrosing alveolitides, as first defined by SCADDING [1], are characterized by variable proportions of inflammation and fibrosis of the pulmonary interstitium and air spaces. These disorders are the most common category of nongranulomatous, non-neoplastic chronic diffuse lung disease found at open lung biopsy. Pulmonary fibrosis, which is usually the predominant finding, can be viewed as the final outcome of inflammation and repair. Often, an aetiological insult (environmental organic or inorganic dust exposure, autoimmune-mediated damage) can be identified. However, when no underlying cause is apparent, the combination of inflammatory cell infiltration in the gas-exchanging parts of the lung and progressive interstitial fibrosis is known as cryptogenic fibrosing alveolitis (CFA), synonymous with idiopathic pulmonary fibrosis (IPF).

Pathology

In 1944, HAMMAN and RICH [2] described four patients with progressive interstitial inflammation and fibrosis, which was fulminant and rapidly fatal. Subsequently, SCADDING and HINSON [3] described a more indolent progression. It is likely that these represent different diseases. Since these studies, other diseases that clinically resemble CFA have been shown to have quite distinct histopathological appearances. Therefore, what has historically been called CFA is undoubtedly a mixture of different entities. Clarification of this confusing situation is beginning, and it must be stressed that diagnostic "labels" of diffuse lung diseases require a comprehensive clinico-radiological-pathological approach. Organization of histopathological classification dates back to LIEBOW's [4] descriptions in 1975 (table 1).

In 1975, LIEBOW [4] sub-classified the "chronic interstitial pneumonias" into five groups. Two of these make up the traditional histological spectrum seen in CFA: usual interstitial pneumonia (UIP) and desquamative interstitial pneumonia (DIP). UIP is characterized by coexisting fibrosis and interstitial/airway inflammation; there is progressive derangement of distal lung architecture and the formation of large cystic air spaces lined by bronchiolar epithelium (honeycomb lung). Most CFA patients have the histological appearances of UIP. In DIP there are prominent aggregates of intra-alveolar macrophages and interstitial infiltration by lymphocytes and monocytes, with little or no fibrosis.

Of the other histopathological variants, all have been shown to be either of known cause (giant cell interstitial pneumonia (GIP)), associated with lymphoproliferation or acquired immune deficiency

Table 1. – Classification of the chronic interstitial pneumonias by LIEBOW [4]

Usual interstitial pneumonia
Desquamative interstitial pneumonia
Bronchiolitis obliterans with usual interstitial pneumonia
Lymphoid interstitial pneumonia
Giant cell interstitial pneumonia

syndrome (AIDS) (lymphoid interstitial pneumonitis (LIP)) or to have been redefined as comprising predominant intra-alveolar disease (bronchiolitis obliterans with interstitial pneumonia (BIP)). One thing they have in common is that they have been mistaken for CFA.

More recently, KATZENSTEIN and MYERS [5] have updated the classification (table 2). Of the additions to LIEBOW's [4] classification, acute interstitial pneumonia (AIP) is perhaps now best understood as HAMMAN and RICH [2] described it: it has a subacute or acute presentation, is an acute respiratory distress syndrome (ARDS) of unknown cause, and has a diffuse alveolar damage pattern of histopathology. Nonspecific interstitial pneumonia (NSIP) is a more difficult new variant to define and understand. This is arguably the least satisfactory histopathological entity and diagnostic "label". Despite its name, there are specific features that define this histopathological pattern. There are varying degrees of interstitial inflammation and fibrosis within the interstitium but, unlike UIP, with which it is most likely to be confused, the appearances are uniform with none of the temporal heterogeneity of UIP and significantly less fibroblastic foci, which are hallmarks of UIP.

Although all of the interstitial pneumonias, especially those of idiopathic origin, have been mistakenly called CFA, the most important variants today are UIP, DIP and NSIP. CFA has recently been defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement as requiring a UIP pathology to carry that diagnosis [6]. However, the classification of histopathological appearances as predominantly interstitial (mural) as opposed to air space (luminal) and as UIP as opposed to DIP is not always clear-cut. DIP is probably a separate disease. In several large series, DIP was associated with a prolonged survival and a high likelihood of a response to therapy, whereas UIP was irreversible and associated with a high mortality. The histopathlogical entity of NSIP can be the result of a number of pathogenetic processes. When idiopathic, however, there is a distinct subgroup of individuals that have all of the clinical, radiological and bronchoalveolar lavage (BAL) features of CFA, but that are found to have the NSIP pattern of histopathology. Several series have now shown a better outcome in terms of response to treatment and survival with this variant [7–10]. At present it would be best to define these patients as having the nonspecific interstitial variant of CFA.

Table 2. – Pathological classification of the interstitial pneumonias by KATZENSTEIN and MYERS [5]

Interstitial pneumonias of unknown cause (idiopathic interstitial pneumonias; IIP)
Usual interstitial pneumonia
Desquamative interstitial pneumonia (DIP)
Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD; possibly a subset of DIP)
Acute interstitial pneumonia
Nonspecific interstitial pneumonia
Interstitial pneumonias of known cause
Lymphoid interstitial pneumonia
Bronchiolitis obliterans with usual interstitial pneumonia
Giant cell interstitial pneumonia

Pathogenesis

The responses of the lung to injury are limited and thus, the histological appearances of advanced disease, "honeycomb" or "end-stage" lung, may be identical in a number of diffuse lung diseases. However, earlier in disease, individual processes may be distinctive for the nature of the initiating factors and the pathological response (whether immunological, inflammatory or fibrogenetic).

Ultrastructural observations in human and animal models of lung fibrosis have indicated that lung injury is likely to be the first event in fibrosing alveolitis, although the cause of lung injury is unknown [11]. An initial insult leads to an influx of acute and chronic inflammatory cells that maintain immunological and inflammatory responses and thus produce progressive disease [12–16]. It is generally accepted that immune mechanisms are likely to make a contribution to pathogenesis; circumstantial support for an immunopathogenetic hypothesis includes the abundance of activated antigen-primed memory T-cells within the lung interstitium [17], the presence of lymphoid follicles with germinal centres [18] and increased levels of serum and bronchoalveolar immunoglobulins.

Other inflammatory cells are involved. Macrophages produce a number of cytokines: "early" cytokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6; chemokines known to enhance the traffic of other inflammatory cells to disease sites such as IL-8, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, MIP-1β, MIP-2; fibrogenetic factors such as transforming growth factor (TGF)-β, insulin-like growth factor (IGF)-1, platelet derived growth factor (PDGF) [19–21]. Neutrophils are likely to contribute to tissue damage by the generation of oxygen radicals and proteolytic enzymes [22]. The pathogenetic role of eosinophils and mast cells remains uncertain, but both are present in increased numbers in the lung interstitium in CFA and may contribute to lung injury through release of secretory products (eosinophilic cationic protein, vasoactive amines) [23, 24].

The end result of inflammatory and immunological events in CFA is the presence of excess collagen within the lungs. The number and activation levels of fibroblasts are increased in CFA, compared to normal individuals, and as disease progresses, the interstitial deposition of collagen and other connective tissue matrix proteins interferes with lung function. The control mechanisms for fibroblast proliferation and collagen deposition are not fully understood and may become autonomous [25]. Indeed, in the most classical form of UIP, there is relatively little inflammation but marked fibroblastic foci. In the overexpression animal models of fibrosis described by SIME *et al.* [26], the transient expression of active TGF-β in the airway epithelium of the adenoviral construct results in progressive fibrosis in the lung, long after the expression of the TGF-β transfectant has ceased [26].

It is also well recognized that collagen deposition is not an end-stage process, with 10% of lung collagen being turned over every day: metalloproteinase expression and particularly its balance with connective tissue deposition is likely to be important in the overall picture. Future treatment strategies will need to introduce antifibrogenesis drugs into the therapeutic armamentarium.

Epidemiology and aetiology

Epidemiological investigations of CFA have been severely hampered by diagnostic imprecision. Death certificate diagnoses of CFA have proven to be even more inaccurate than in most other chronic diseases [27, 28]. Questionnaire-based diagnoses have their own limitations: as discussed later, the clinical diagnosis of CFA is not always straightforward. Thus, the apparent increase in the annual mortality from CFA over the last decade may be spurious, resulting from a reduced diagnostic threshold amongst clinicians, especially in elderly patients. Currently, the annual mortality from CFA is likely to exceed three per 100,000 in the UK [29], and a recent international survey indicates that mortality from CFA is comparable in many other Western countries [30]. CFA occurs more frequently in current or former smokers [31]; in nonsmokers the male:female ratio approximates 1:1. In populations drawn from tertiary institutions, the median age at presentation generally lies within the sixth decade; by contrast, in secondary populations, the peak prevalence occurs in individuals at or over the age of 70, indicating over-representation of younger patients at tertiary centres [32].

It is not clear whether CFA has a single cause or represents the final common outcome of numerous pathogenetic mechanisms. A genetic predisposition has not been identified (other than rare familial cases that follow a pattern of autosomal dominant inheritance with variable penetrance). Support for an inhaled antigen hypothesis is circumstantial; associations have been observed between fibrosing alveolitis and heavy exposure to metal dusts, hydrogen peroxide and smoke from wood fires [33–35]. Striking similarities in the distribution and pattern of disease on high-resolution computed tomography (HRCT) between asbestosis and CFA have stimulated a close scrutiny of other occupational exposures, but the findings are inconclusive. An increase in the prevalence of Epstein-Barr virus carriage within the type II pneumocytes of the respiratory epithelium has been reported in CFA, but this finding was not confirmed in a further study and its aetiological significance therefore remains uncertain [36, 37]. Studies of inhaled ^{99m}Tc-diethylenetriamine penta-acetic acid (DTPA) have given rise to the suggestion that increased epithelial permeability [38] may be the cardinal pathogenetic factor, allowing an increased penetration of a variety of inhaled antigens to the lung interstitium. For the epidemiologist, the distinction between exposures responsible for the onset of CFA and those that induce progression of established disease is particularly difficult; this problem is exacerbated by the late clinical presentation of CFA, years after the initiating events.

In collagen vascular disease, the prevalence of fibrosing alveolitis varies greatly between individual systemic diseases. Patients tend to be younger and more often female than in CFA, especially in systemic sclerosis [39]. Fibrosing alveolitis is found at autopsy in >80% of patients with systemic sclerosis [40], but is less prevalent in other connective tissue disorders, judging from autopsy studies and cross-sectional lung function and radiological surveys. Pulmonary fibrosis may be moderately common in polymyositis/dermatomyositis (*i.e.* in excess of 20%), although no precise prevalence data exist. By contrast, in rheumatoid arthritis and systemic lupus erythematosus, <5% of patients have interstitial fibrosis on plain chest radiography (although the prevalence is higher if HRCT is used). In primary Sjögren's syndrome, classical fibrosing alveolitis is rare.

A genetic predisposition to pulmonary fibrosis has been identified in systemic sclerosis patients with more extensive lung disease [41, 42]. A number of occupational exposures are known to induce systemic sclerosis, but it is not clear whether lung disease is produced chemically or develops during subsequent systemic disease progression. Pulmonary fibrosis in rheumatoid arthritis is more prevalent in heavy smokers. Autoantibody associations with an increased risk of pulmonary fibrosis include anti-deoxyribonucleic acid (DNA) topoisomerase in systemic sclerosis and anti-Jo1 antibodies in polymyositis/dermatomyositis.

Prognosis

In large clinical series, ~50% of CFA patients die within 5 yrs of the onset of dyspnoea [32, 39, 43–46]. Some have argued that patients referred to tertiary centres might have unusually rapidly progressive CFA, which is not representative of non-tertiary populations. A recent large series drawn from secondary centres in the UK documented a 2-yr survival in CFA of only 55% [32]. However, a note of caution has to be struck. All studies of outcome in CFA have probably included populations of patients with the NSIP variant of the disease. In systemic sclerosis, the NSIP pattern of lung involvement is probably more frequent than the UIP pattern [47]. This means that the median survival is likely to be an overestimation and that the true survival for CFA with a UIP pattern only is closer to 3 yrs.

Historically, the most reliable determinant of prognosis in CFA has been the distinction between predominantly inflammatory and predominantly fibrotic disease made at open lung biopsy evaluation [43]. The majority of patients with a fibrotic picture do not respond to therapy, whereas a minority with marked inflammatory change (DIP) respond well to treatment and have a low mortality [48, 49]. With the exception of HRCT (discussed later), noninvasive indices (including chest radiography, lung function tests, BAL and gallium scanning) have failed to make this distinction.

In fibrotic nonresponsive CFA, the severity of impairment of lung function indices at presentation, including lung volumes, arterial blood gases and carbon monoxide diffusing capacity, provides a strong indication of the likely outcome. It is clear that lung function tests are a more reliable indicator of underlying disease severity than symptoms or findings at chest radiography. Whether nonsmokers have a better prognosis than smokers is unclear, with conflicting findings reported in different series. For practical purposes, the clinician can expect to have an approximate idea of the probable outcome from lung function indices, once reversible disease has been identified and treated.

In fibrosing alveolitis associated with collagen vascular disease, the prognosis is much better than in CFA [39]. To some extent, this reflects the earlier diagnosis of fibrosing alveolitis in patients with collagen vascular disease, due to a heightened awareness of the possibility of pulmonary involvement. In asymptomatic patients, routine investigations may disclose the presence of pulmonary fibrosis. However, the better survival in collagen vascular disease is not wholly ascribable to diagnostic lead-time. When disease severity is matched with that of CFA, as in a large series of patients with the fibrosing alveolitis of systemic sclerosis, mortality in CFA is substantially higher [39]; most respiratory deaths in systemic sclerosis were ascribable to pulmonary vascular disease rather than pulmonary fibrosis. The outcome in rheumatoid arthritis and polymyositis/dermatomyositis has not been definitively documented; there are strong anecdotal impressions that survival is better than in CFA, but in both diseases a minority of patients may follow an explosive or inexorably progressive course.

Clinical features

History

The typical patient with CFA presents with progressive breathlessness on exertion. In some cases, the onset of dyspnoea is recent, never <3 months, but there is often a lengthy delay before the diagnosis is made; many patients with CFA attribute the development of dyspnoea to smoking-related pulmonary damage and do not seek medical advice until symptoms become disabling. Cough is well recognized and may be productive of mucoid sputum, especially in advanced disease. Haemoptysis is not a feature and should alert the clinician to the possibility of concurrent lung malignancy (seen with an up to 14-fold increased frequency in CFA, compared to a general population with matched smoking histories [50, 51]). Chest pain is rare and is most likely to be cardiac, especially in advanced disease; cardiac events are the most common cause of death in CFA and are likely to be triggered by increasing hypoxia. Systemic symptoms, including weight loss and malaise, may occur in CFA. Occasionally, the diagnosis is made incidentally on chest radiography.

Fibrosing alveolitis associated with collagen vascular disease differs from CFA in that the presence and severity of respiratory symptoms are highly variable and often bear no relationship to the severity of lung disease (as judged by pulmonary function tests and radiographic appearances). Lung disease is often advanced before it is recognized, sometimes because of exercise limitation due to musculoskeletal disease. In other cases, the presence of systemic disease may give rise to a heightened awareness by patients or medical practitioners of the possibility of lung involvement, leading to the detection of fibrosing alveolitis at an early or asymptomatic stage, often on routine radiographic staging.

In suspected CFA, a full history of possible occupational or environmental exposures is paramount. Asbestosis and hard metal exposure may both produce a clinical picture identical to CFA. The chronic fibrosing form of extrinsic allergic alveolitis, resulting from prolonged exposure to inhaled avian or fungal antigens, may also mimic CFA clinically. Lung involvement may be the most prominent feature of collagen vascular disease and thus, a careful history of Raynaud's phenomenon, arthritis, myositis, sicca symptoms and gastro-oesophageal regurgitation should be taken. A full drug history should be elicited to exclude diffuse lung disease due to drug therapy (especially cytotoxic agents, nitrofurantoin and amiodarone). Previous or current malignant disease is particularly important, as lymphangitis may present in a similar manner to CFA.

Physical examination

The characteristic clinical sign of fibrosing alveolitis is the presence of fine crackles on auscultation, most prominent at the lung bases and generally heard best in mid to late inspiration. In advanced disease, crackles may be obvious throughout the lungs and throughout inspiration. In less extensive disease, crackles may disappear at the bases when the patient leans forward, but generally persist in the mid-axillary line. Except in limited diffuse lung disease, the absence of inspiratory crackles should cause the clinician to question the diagnosis of fibrosing alveolitis.

Digital clubbing is seen in ~70% of patients with CFA, is common in lung disease in rheumatoid arthritis and in many patients with asbestosis, but is not a feature of other nonmalignant diffuse lung diseases (such as sarcoidosis, extrinsic allergic alveolitis, Langerhans' cell histiocytosis and lymphangioleiomyomatosis). Thus, the presence of unequivocal clubbing increases the likelihood that a diffuse pulmonary process represents CFA, but the absence of clubbing is not especially helpful diagnostically. Digital clubbing appears to be less common in the NSIP variant of CFA.

As disease advances, central cyanosis develops and is often associated with severe tachypnoea; patients with CFA hyperventilate in order to compensate for hypoxia, and have a breathing pattern and body habitus similar to the "pink puffer" subgroup seen in chronic obstructive pulmonary disease (COPD). The

poor nutrition exhibited by patients with end-stage CFA is likely to result from the caloric cost of the increased work of breathing, but may also reflect reduced gastrointestinal absorption due to venous congestion, the well recognized phenomenon of "cardiac cachexia" due to right ventricular failure. With increasing obliteration of the pulmonary circulation by lung fibrosis, pulmonary hypertension may supervene. In preterminal disease, severe hypoxia may result in cardiac decompensation, triggering clinical evidence of left ventricular failure or cardiac arrhythmias.

Occasionally, there may be clinical evidence indicating that a provisional diagnosis of CFA is incorrect. Prominent inspiratory squeaks may be an important clue that the patient has extrinsic allergic alveolitis. The presence of lupus pernio or erythema nodosum point to a diagnosis of sarcoidosis. Physical examination may also disclose evidence of rheumatological disease. Sclerodactyly is an especially important sign as the combination of lung fibrosis and sclerodactyly fulfils diagnostic criteria for systemic sclerosis, but the clinician should also look for proximal scleroderma, telangiectasiae, calcinosis, and clinical evidence of arthropathy or myopathy.

Technical investigations

Chest radiography

On chest radiography, fibrosing alveolitis is characterized by irregular nodular or reticulonodular shadows, which are usually most extensive in the lower zones (a key diagnostic feature). Although the chest radiograph is often normal in patients with rheumatological disorders and limited lung disease, bilateral abnormalities that may be asymmetrical are usually evident in CFA. In advanced disease, the characteristic lower zone distribution is often lost and all lung zones may be equally involved. However, overt honeycombing is rare, except in end-stage disease.

Mediastinal lymphadenopathy is not seen on chest radiography in fibrosing alveolitis and, if present, should alert the clinician to the possibility of concurrent lung cancer. Pleural involvement is not a feature of CFA but is common in rheumatological disease, especially rheumatoid arthritis and systemic lupus erythematosus, and is virtually always present in asbestosis. Cardiomegaly may reflect left ventricular decompensation, especially in the CFA patient with severe hypoxia, or right ventricular enlargement secondary to pulmonary vascular disease; prominence of the pulmonary arteries is an important ancillary sign of pulmonary hypertension.

High-resolution computed tomography

HRCT scanning now has a central role in the clinical evaluation of diffuse lung diseases, including fibrosing alveolitis. HRCT has enhanced the detection of diffuse lung disease. Before the HRCT era, the combination of unexplained respiratory symptoms and lung function abnormalities, in the absence of chest radiographic abnormalities, posed the clinician a difficult dilemma: the choice between continued observation and open lung biopsy. In large series, ~10% of patients with biopsy-proven diffuse lung disease have normal appearances on chest radiography [52, 53]. The ability of HRCT to reveal disease before the chest radiograph becomes abnormal is especially useful in limited fibrosing alveolitis associated with collagen vascular disease [54].

As well as improving the detection of disease, HRCT has enhanced the ability of radiologists and clinicians to achieve accurate diagnoses; in a number of series containing a wide variety of diffuse lung disorders, HRCT has been more accurate than chest radiography in predicting the correct histological diagnosis [55–61]. The advantage of HRCT over chest radiography extends to the confidence with which diagnoses are made [56, 60], an issue of great practical importance. The HRCT features of fibrosing alveolitis have a high specificity [62]; false-positive diagnoses of CFA are rare when HRCT appearances are typical.

In early fibrosing alveolitis, a posterior lower zone subpleural rim of increased attenuation is typical. It is often useful to acquire sections in the prone position (in addition to the usual supine sections), as the normal gravitational distribution of blood and water in the dependent position may mimic fibrosing alveolitis. As disease becomes more extensive, it spreads to the anterior subpleural aspects of the right middle lobe and lingula; in end-stage disease, all lung zones are involved, peripheral and central.

The most prevalent HRCT abnormality, a reticular pattern, consists of a network of dense lines, enclosing microcystic spaces (which evolve into overt honeycombing in advanced disease). This HRCT pattern is always indicative of irreversible fibrotic disease [63–65]. By contrast, a ground-glass pattern denotes an increased likelihood of reversible inflammatory cell infiltration [66], especially when ground-glass attenuation is the most extensive abnormality [67–69].

In rheumatological disease, pulmonary fibrosis is, on average, less extensive on HRCT than in CFA, but the distribution of disease is similar [68–70]. It is not yet clear whether the subset of patients with NSIP can be consistently distinguished from those with usual UIP; early anecdotal experience suggests that NSIP may be characterized by a finer reticular pattern [8]. Pleural thickening is a frequent incidental finding in rheumatoid arthritis and systemic lupus erythematosus, but is not a feature of uncomplicated CFA. Mediastinal lymphadenopathy (usually 1.5–2 cm in diameter) may be seen on HRCT (but not on chest radiography) in all forms of fibrosing alveolitis, increasing in prevalence as the disease becomes more extensive [71], and, thus, more prominent in CFA [72].

Other imaging techniques

Ventilation/perfusion scans are of no clinical value in fibrosing alveolitis. As the cystic air spaces of

end-stage disease continue to ventilate but are not perfused, ventilation/perfusion scans typically show mismatched defects in perfusion, which mimic thromboembolism [73]. This limitation is potentially important because pulmonary embolism is increased in prevalence in CFA. Fortunately, the recent application of spiral (helical) computed tomography scanning has facilitated the diagnosis of pulmonary embolism in fibrosing alveolitis [74].

Although widely used in the 1980s, gallium scanning adds nothing to the evaluation of established fibrosing alveolitis. The ingestion of gallium by activated macrophages in diffuse lung disease led to attempts to use the technique to assess disease activity. However, clinical application was frustrated by marked imprecision in the quantification of abnormal signals. Before the advent of HRCT, gallium scanning was of some value in identifying subtle diffuse lung disease when the chest radiograph was normal.

Abnormally rapid clearance of inhaled ^{99m}Tc-DTPA, denoting increased lung epithelial permeability, has been used to identify patients with early fibrosing alveolitis, especially in systemic sclerosis [75]. However, as with gallium scanning, DTPA scanning adds little to HRCT in this regard. The greater utility of DTPA scanning lies in the identification of the subgroup of patients with normal DTPA clearance, who have a greatly reduced risk of subsequent functional deterioration. Based upon normal DTPA clearance, it is sometimes possible to justify a policy of observation rather than immediate therapeutic intervention [76]. This application of DTPA scanning is more useful in fibrosing alveolitis associated with rheumatological disease (in which progression of disease is not the rule) than in CFA.

Lung function tests

The characteristic functional defect is restrictive, with reductions in spirometric volumes, total lung capacity, residual volume and pulmonary compliance. The carbon monoxide transfer factor (diffusing capacity, $T_{L,CO}$) is often more impaired than other functional indices due to damage to the pulmonary vascular bed, as well as reduction in alveolar volume. Arterial gas measurements generally reveal hypoxia in CFA, often associated with a reduced arterial carbon dioxide tension (P_{a,CO_2}) as a result of increased ventilatory drive; increased P_{a,CO_2} is seldom seen except in preterminal disease. The widened alveolar-arterial oxygen gradient is largely attributable to a ventilation/perfusion mismatch, with impaired diffusion contributing only an average of 10% to the impairment of gas exchange at rest. Increased hypoxia and widening of the alveolar-arterial oxygen gradient are seen on exercise, in association with an exaggerated sensation of dyspnoea (typical of patients with reduced lung compliance); reduced oxygen diffusion contributes increasingly to the impairment of gas exchange during exercise, and accounts for ~40% of the widened alveolar-arterial oxygen gradient at maximal exercise [77].

Pulmonary processes coexisting with fibrosing alveolitis may have a major confounding effect on lung function indices. Concurrent emphysema counters the restrictive effect of lung fibrosis, resulting in relative preservation of lung volumes, but marked depression of the $T_{L,CO}$ (as emphysema and fibrosing alveolitis both reduce diffusing capacity) [78–80]. Isolated fibrosing alveolitis in rheumatological disease is functionally identical to lone CFA, with one striking exception: hypoxia at rest and on exercise is much more severe for a given disease extent in lone CFA [78, 81].

Lung function indices provide a more accurate impression of the severity of the underlying disease process than symptoms or chest radiography. However, there has been no overall consensus on which of the many lung function tests routinely available to the clinician should be used as the primary measure of disease severity. Attempts to resolve this problem by examining correlations between structure and function, based on the evaluation of open lung biopsy material, have been largely disappointing; the conflicting results of different studies are likely to reflect small numbers of patients and the fact that biopsies taken from a small part of the lung periphery will not necessarily be representative of global lung morphologic abnormalities [82–84]. Recently, correlations between lung function indices and HRCT have shown that the $T_{L,CO}$ and oxygen desaturation (adjusted for respiratory work) best reflect the global extent of disease on HRCT; lung volumes correlate poorly with disease extent [78, 85]. On this basis, it can be argued that measurement of gas transfer and exercise testing should both be performed in fibrosing alveolitis.

Functional indices are routinely used at follow-up to identify progression or regression of disease. Change is often marginal and it may be helpful to plot repeated measurements graphically, in order to demonstrate unequivocal change over the course of multiple testing. Generally, forced vital capacity and $T_{L,CO}$ are used to monitor disease serially.

Blood tests

Routine haematological and biochemical tests are seldom abnormal in CFA. Occasionally, secondary polycythaemia in advanced disease may give rise to an increased haematocrit, and the erythrocyte sedimentation rate (ESR) is often modestly elevated. Hypergammaglobulinaemia is common. A neutrophilia is seen with intercurrent infection, but may also be ascribable to steroid therapy. Marked elevation of the ESR should alert the clinician to infection, malignancy or underlying rheumatological disease.

Serological markers of rheumatological disease may be positive in CFA without clinical evidence of a systemic autoimmune disorder; a positive rheumatoid factor and elevated titres of antinuclear antibodies are present in ~30% of patients with CFA, but titres are low and rarely approach levels seen in acute rheumatological diseases and give no indication of outcome [86]. Anti-DNA topoisomerase antibodies (anti-Scl70 antibodies) in systemic sclerosis and anti-transfer

ribonucleic acid (tRNA) synthetase antibodies (*e.g.* anti-Jo1 antibodies) in polymyositis/dermatomyositis denote an increased likelihood of pulmonary fibrosis and are thus likely to be present in those diseases, in established fibrosing alveolitis [87]. Furthermore, lung disease is often the first manifestation of a rheumatological disease and it is therefore recommended that rheumatoid factor and antinuclear antibody (ANA) (with subsequent extractable nuclear antigen if positive) are tested in all patients with CFA; the diffuse lung diseases in rheumatological disease carry a better prognosis than CFA.

It is often helpful to measure levels of precipitins against fungal antigens known to produce hypersensitivity pneumonitis (extrinsic allergic alveolitis), such as farmer′s lung (thermophilic actinomycetes, micropolysporium faeni precipitins) or bird fancier′s lung (avian precipitins). Although not definitive in isolation, the presence or absence of precipitin levels has a major influence on diagnostic probability when the history is suggestive of hypersensitivity pneumonitis, or there is doubt about relevant exposures; it is sometimes difficult to clinically distinguish between CFA and chronic fibrotic hypersensitivity pneumonitis.

Bronchoalveolar lavage

BAL has been used for nearly 20 yrs to sample cells and noncellular material from the lower respiratory tract [88, 89]. Initial hopes that BAL might serve as a substitute for open lung biopsy in fibrosing alveolitis, diagnostically and in terms of staging disease activity, have not been fulfilled [89, 90]. Typically, patients with fibrosing alveolitis have elevations of BAL neutrophils and eosinophils [91]. However, these findings are seen in a wide variety of fibrosing lung conditions other than fibrosing alveolitis, limiting the utility of BAL in diagnosis. The subset of patients responding to corticosteroid therapy has higher numbers of BAL lymphocytes than other patients with fibrosing alveolitis [92, 93]. It is possible that they represent the NSIP subset, in which an excess of lymphocytes appears to be a more frequent finding [9]. However, these relationships are too inconsistent in individual patients for BAL to be used as a reliable prognostic guide. BAL findings are seldom clinically definitive.

Provided its limitations are kept in mind, there is still a place for BAL in the evaluation of diffuse lung disease. The presence of a BAL neutrophilia increases the likelihood of an underlying fibrosing process, as in CFA; the fibrosing alveolitis of rheumatological disease, asbestosis, or fibrotic sarcoidosis [94, 95]. A BAL lymphocytosis is more suggestive of NSIP, a drug-induced lung disease or a granulomatous disorder. By indicating the likely nature of the underlying disease process, BAL can be useful when the diagnosis is unclear. Despite its inconsistency, the relationship between BAL findings and outcome with treatment may become influential when therapeutic decisions are a close call; for example, an unusually high lymphocyte count may prompt the clinician to prolong aggressive therapy as well as inducing a review of the underlying diagnosis.

Lung biopsy

Fibrescopic transbronchial lung biopsies have no diagnostic value in CFA, except for excluding other pathologies. The only biopsy procedure that can provide a sufficiently large sample to assess the pattern of idiopathic interstitial pneumonia is an open or thoracoscopic lung biopsy. It should, however, be kept in mind that the UIP pattern is not specific for CFA. For instance, UIP may be found in other conditions, such as drug-induced diffuse lung disease, fibrosing alveolitis associated with collagen vascular disease and asbestosis.

In the majority of patients with CFA, the diagnosis is still made without surgical lung biopsy. In a recent International Consensus Statement [6] criteria for diagnosis of CFA/IPF in the absence of a surgical biopsy have been proposed (table 3).

Treatment

Treatment options and their pros and cons must be discussed in detail with the patient. Even those that

Table 3. – Criteria for diagnosis of cryptogenic fibrosing alveolitis/idiopathic pulmonary fibrosis (IPF) in the absence of a surgical lung biopsy [6]

Major criteria
Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and connective tissue disease
Abnormal pulmonary function studies that include evidence of restriction (reduced vital capacity often with an increased forced expiratory volume in one second/forced vital capacity ratio) and/or impaired gas exchange (increased alveolar-arterial oxygen tension difference at rest or on exercise or decreased transfer factor of the lung for carbon monoxide
Bibasilar reticular abnormalities with minimal ground-glass opacities on high-resolution computed tomography
Transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternate diagnosis
Minor criteria
Age >50 yrs
Insidious onset of otherwise unexplained dyspnoea on exertion
Duration of illness $\geqslant$3 months
Bibasilar, inspiratory crackles (dry or "velcro"-type in quality)

In the immunocompetent adult, the presence of all of the above major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

are well informed often have not grasped the concept that there is no "magic bullet" cure and that destroyed scarred lung cannot regenerate. The rationale for lifelong treatment in the hope of achieving stability (rather than improvement in symptoms and objective measures) needs to be explained carefully. The doctor must not make the patient feel responsible for making decisions, but the patient should be an active participant in discussions of management strategies, especially the decision on whether to observe or start treatment.

Three treatment regimens have been widely used in CFA: corticosteroids alone or in combination with either cyclophosphamide or azathioprine. There are no prospective double-blind placebo-controlled trials of treatment. It must also be recognized that most, if not all reports of treatment efficacy in CFA have included a mixed population, especially a proportion of patients with NSIP.

Corticosteroids

Corticosteroids produce an objective response (in chest radiography or lung function tests) in ~25% of patients [6]. A subjective response is reported in >50%, but this may represent the boosting effect of corticosteroids on patient mood in some cases. A higher chance of response to steroids is seen with less dyspnoea, less extensive disease on chest radiography, higher P_{a,O_2} at presentation, a BAL lymphocytosis, a more cellular open lung biopsy, and predominance of ground-glass attenuation on HRCT. These latter features are quite unlike the picture seen in most patients with UIP, endorsing the likelihood of NSIP "contamination" of the study population.

It is now unusual to start with high dose corticosteroid therapy for CFA with a UIP pattern. High dose regimens should be reserved for DIP. In this situation, therapy for 6–8 weeks with prednisolone 0.75–1 $mg \cdot kg^{-1}$ daily (maximum 60 mg daily), followed by a phased reduction to 20 mg on alternate days over the next 4–6 months, produces a good response. The balance of good to bad effects of treatment is favourable in this situation, but not in UIP. Initial treatment with pulsed methylprednisolone has been used occasionally, but the efficacy of this approach has not been studied formally.

Combination therapy

This is the preferred treatment for CFA with a UIP pattern and also, until the results of prospective studies become available, for NSIP. Two treatment regimens have been evaluated in CFA in double-blind studies [96–98]. Cyclophosphamide (up to 125 mg daily, depending on body weight) in combination with prednisolone (20 mg on alternate days) was compared with prednisolone alone, using the standard high dose regimen previously described [96]. The objective response rate of ~20% and 5-yr mortality of 50% was similar in the two treatment arms, but a few patients responded to the combination regimen, having failed to improve with prednisolone alone. A similar study compared high dose prednisolone alone and a combination of azathioprine (3 $mg \cdot kg^{-1} \cdot day^{-1}$, up to 200 mg daily) and prednisolone 20 mg daily [97]; there was a nonsignificant trend towards a higher response rate and survival, in favour of the combination regimen. Low numbers and difficulties in controlling definitively for baseline disease severity limited both studies. However, the findings and anecdotal reports of patients responding to combination therapy lend circumstantial support to the early use of combination therapy, especially in patients who have deteriorated on prednisolone alone, as well as those at higher risk of corticosteroid side-effects (*e.g.* diabetics and patients with hypertension or osteoporosis). This is supported by small studies of patients with systemic sclerosis. Maximal improvement with combination regimens may require >6 months of treatment; pulsed cyclophosphamide has not engendered better survival than with oral therapy, although lung function improvement was seen in those who survived >6 months from institution of therapy [99].

Immunosuppressive therapy should be monitored by weekly full blood counts for the first month, and 2- to 4-weekly full blood counts thereafter. Dipstick urine testing for haematuria should be performed weekly in patients on cyclophosphamide. Abnormal liver function tests, sometimes associated with dyspepsia, develop in a minority of patients treated with cyclophosphamide and azathioprine, but these abnormalities resolve when treatment is discontinued. The high rate of bladder malignancy in patients on long-term oral cyclophosphamide makes azathioprine the immunosuppressant of choice [100].

Other treatment regimens

Penicillamine [101], cyclosporin [102, 103], pirfenidone [104], pentoxyfylline, interferon (IFN)-γ [105, 106] and colchicine [107] have all been tried in CFA. Of these, there is little evidence of efficacy for penicillamine or cyclosporin. Colchicine (at 0.6 mg twice a day) was as efficacious as corticosteroids, but with fewer side-effects.

Pirfenidone appeared to stabilize a small subset of patients but is no longer available. The more novel treatments, such as pentoxifylline, a powerful blocker of inflammation, and specific anticytokine strategies (currently undergoing pilot study) require further study. A recent report of IFN-γ use appeared to demonstrate striking improvement in lung function, but it seems unlikely that the group studied had clear-cut UIP [106]. The most attractive options for potential future therapy for IPF are IFN-γ, anti-TNF-α, anti-TGF-β1 and antioxidants [108].

Duration of pharmacological treatment

It is not known what the optimal duration of treatment is, but it is likely to be highly individual,

given the range of clinical courses. One approach is to try to achieve stability, continue treatment at an acceptable dose for at least a year in the hope of maintaining stability, and then attempt to discontinue treatment. In CFA, stability amounts to success, and the authors believe that the early withdrawal of treatment is usually an unrealistic aim. One compromise is to attempt to withdraw immunosuppressive treatment after a year of stability and to continue alternate day prednisolone in the long term. It is reassuring that patients compelled to stop immunosuppressive therapy due to side-effects seldom relapse immediately, provided corticosteroid therapy is maintained.

The effect of treatment on long-term outcome

Therapeutic regimens in fibrosing alveolitis usually consist of corticosteroid and/or immunosuppressive therapy. Perhaps surprisingly, the efficacy of treatment in slowing progression of disease and prolonging survival in irreversible disease has never been definitively studied. In an inexorably progressive disease, treatment may be regarded as successful if it slows the rate of decline, irrespective of a lack of initial improvement. Recent therapeutic trials have been confined to comparisons between corticosteroid regimens and combinations of corticosteroid and immunosuppressive agents. Any differences in outcome would have provided strong, indirect evidence that treatment can modulate the natural history of CFA. However, the studies were inconclusive, largely due to small numbers of patients and difficulties in the precise matching of initial disease severity. Thus, many clinicians remain ambivalent about the role of therapy in apparently stable, predominantly fibrotic disease, pending a definitive placebo-controlled trial of therapy.

In the absence of definitive evidence, most authorities argue for empirical therapy in progressive disease, in the hope of slowing disease progression. The alternative strategy is to await the development of symptoms before instituting therapy. However, this approach takes little account of the considerable reserve of the lungs; by the time normal day-to-day activities are compromised by dyspnoea, major structural damage that might have been prevented by earlier treatment has generally occurred. Moreover, if inflammation precedes and leads to fibrosis, the opportunity to treat reversible disease may be lost. Fortunately, the use of HRCT to identify potentially reversible disease alerts the physician to the need for immediate treatment. The greatest dilemma lies in asymptomatic patients who present with limited or moderately extensive fibrotic abnormalities on HRCT and mild-to-moderate impairment of lung function indices.

It is now the authors' policy to start treatment in patients who are symptomatic, in those with a 30–40% reduction in lung function indices, and in patients with evidence of disease progression on serial lung function testing. This approach applies equally to CFA and the fibrosing alveolitis of rheumatological disease; a major decline is seen less frequently in rheumatological disease, but may be equally catastrophic to the patient when it occurs (although, in general, progression of disease is slower, especially in systemic sclerosis). Thus, meticulous observation in untreated patients is an essential part of routine management. Eventually, it may be possible to use noninvasive indices to predict patients at greatest risk of deterioration and thus, to prompt earlier therapy: ^{99m}Tc-DTPA clearance shows promise in this regard. Greater impairment of lung function reduces the threshold for treatment, irrespective of symptomatic status, for two reasons. Firstly, patients with severe functional impairment have a "track-record" of previous disease progression and may be more likely to progress in future. Equally importantly, a given fall in lung function indices is likely to result in much greater morbidity in patients with functionally severe disease and, therefore, if progression of disease can be blunted, there is more to lose by delay in this context.

Transplantation

Considerable experience of single lung transplantation for end-stage fibrosing alveolitis has now been obtained. Survival rates at 3 yrs (~60%) are encouraging. Unfortunately, two factors reduce the applicability of transplantation to CFA. Most patients present over the age of 50, reducing the proportion that will be accepted for transplantation in view of the present shortage of organs. Equally importantly, referral for transplantation may be difficult to time; CFA sometimes progresses explosively after a period of apparent stability, and it is easy to miss a brief window of opportunity.

Treatment of complications

In end-stage disease, supportive therapy is crucial to minimizing morbidity. Supplemental oxygen, provided through oxygen concentrators in the home and also through portable liquid oxygen outside the house, may help to alleviate the dyspnoea of respiratory failure and improve the function of other organs. Cardiac complications are the most common cause of death in CFA; heart failure should always be suspected and cautious empirical diuretic therapy is often helpful. Vasodilator therapy is risky in CFA, particularly if there is evidence of right ventricular failure. There is an increased incidence of both pulmonary embolism and lower respiratory tract infection in advanced CFA; these complications should be actively treated to improve patient comfort, but the efficacy of prophylactic therapy is uncertain for both disorders.

In preterminal disease, small doses of opiates may suppress the very distressing dyspnoea seen with increasingly noncompliant lungs. Counselling and other support is usually required for the patient and family and is best initiated and coordinated with the community as part of hospital-based team management.

In conclusion, cryptogenic fibrosing alveolitis, synonymous with idiopathic pulmonary fibrosis, remains a life-threatening disease. Historically, many diseases that are now considered to be quite distinct have been "labelled" as cryptogenic fibrosing alveolitis. More recently, high-resolution computed tomography and new appreciation of histopathological patterns of the idiopathic interstitial pneumonias have defined disease variants with different responses to therapy and survival. This review has attempted to dissect these different patterns, to illustrate the major features of each and to refine the clinico-radiological-pathological descriptors that together define cryptogenic fibrosing alveolitis as it is understood today.

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