James Ward
Christine McDonald

Interstitial lung disease

An approach to diagnosis and management

Background
Interstitial lung disease (ILD) is a term that describes a diverse range of lung conditions, which are an important cause of morbidity and mortality in all age groups. Idiopathic pulmonary fibrosis is the most common ILD in older adults and generally has a poor prognosis. Sarcoidosis is more common in younger adults and generally has a more benign prognosis.

Objective
This article aims to increase the reader's understanding of the aetiology of ILD and to provide a general approach to diagnosis along with the basic principles of management of these conditions.

Discussion
As ILDs can progress to pulmonary fibrosis, early detection is important. The clinical course of ILD varies considerably, largely determined by the underlying cause. While some forms of ILD remain essentially untreatable, many forms respond well to treatment. It is therefore imperative that a prompt and accurate diagnosis of the underlying cause is made so that appropriate management can be instituted.

Keywords: lung diseases, interstitial; pulmonary fibrosis

CPD

What diagnosis would you think of?

- Mrs MP is 35 years of age with a 10 week history of progressive breathlessness associated with a dry cough, night sweats and malaise (*Case study 1*)
- Mr DB is 61 years of age, an exsmoker with a 4 month history of progressive breathlessness associated with a dry cough, who recently started an angiotension converting enzyme inhibitor (*Case study 2*)
- Mr PL is 81 years of age with 3 months of progressive breathlessness, with other active problems of ischaemic heart disease and atrial fibrillation (*Case study 3*).

The interstitial lung diseases (ILDs) are a group of over 200 disease entities which affect the lung interstitium and share similar clinical and radiological manifestations.[1] The interstitium refers to the tissue of the alveolar wall between the capillary endothelium and the alveolar epithelium and it is here that the primary site of injury occurs. The term 'interstitial' can be misleading, as most of the disorders can also involve the airspaces, peripheral airways and vessels. In general, these disorders can progress to irreversible pulmonary fibrosis.

There are no formal statistics on the incidence or prevalence of ILDs in Australia. Extrapolating from population based registries in other countries suggests an incidence of around 30 in 100 000 per year.[1]

Aetiology

Conceptually, the ILDs can be thought of as those with a known aetiology (most commonly due to occupational and environmental exposures) and those with an unknown aetiology, including idiopathic pulmonary fibrosis (IPF), sarcoidosis and ILD associated with connective tissues diseases.[2] A brief description of some of these diseases follows.

Idiopathic pulmonary fibrosis is the most common ILD in older adults. Its peak age of onset is in the 50–60 years age group and it has a poor prognosis with a median survival of only 3–5 years.[3]

Sarcoidosis is a multisystem granulomatous disease which often involves the lungs. It occurs in a younger age group (peak incidence 20–50 years) and generally has a good prognosis.

Connective tissue diseases of all types can cause ILD, with an overall incidence across the range of diseases of 15%. Prognosis and treatment will vary depending upon histopathologic/radiologic findings as well as the course of the underlying connective tissue disease.

Pneumoconioses (due to inhaled inorganic dusts, eg. asbestos, coal, silica) still account for a significant proportion of all ILD but their incidence is decreasing in Australia due to improved work place practices.

Hypersensitivity pneumonitis (secondary to inhaled organic dusts/allergens, eg. bird dander, domestic fungal spores) is important to recognise and generally has a favourable prognosis if the allergen is avoided.

Idiopathic interstitial pneumonias (IIP) that are not IPF account for a small proportion of cases and in general have a significantly better prognosis than IPF.[4]

Drug induced ILDs are rare but important due to the preventable and potentially reversible nature of the exposure. Many different classes of drugs can cause ILD. A useful website describing potential drug induced lung diseases is available at www.pneumotox.com.

Classification of disease

A new classification released in 2002 by the European Respiratory Society and the American Thoracic Society has now been accepted internationally (*Table 1*).[5] Interstitial lung disease has largely replaced the term diffuse parenchymal lung disease, and idiopathic pulmonary fibrosis has now replaced the term cryptogenic fibrosing alveolitis. The other area of clarification has been over the classification of the 'idiopathic interstitial pneumonias', which include idiopathic pulmonary fibrosis. This is now based on the histopathological pattern seen on lung biopsy.

Diagnostic features

Patients with ILD typically develop shortness of breath and a dry cough that are indolent in nature and progressive. These symptoms are often attributed to aging or deconditioning, resulting in a delay to diagnosis. The rate of progression of these symptoms is generally slow (months to years) but varies with the type of disease and can occasionally mimic pneumonia in its acuity. Other symptoms, such as wheezing, haemoptysis and chest pain are rare. Common presentation(s) of ILD are presented in *Table 2*.

If ILD is suspected, a detailed medical history is essential, in particular focusing on any symptoms to suggest connective tissue disorders, smoking and medication history and any other medical problems. It is important to carefully document all possible occupational and environmental exposures.

The physical examination can suggest the presence of ILD. Inspiratory crackles and digital clubbing are common in some ILDs (IPF, asbestosis) but rare in others (sarcoidosis, hypersensitivity pneumonitis).[6] Exercise induced hypoxaemia (measured via pulse oximetry during a simple walk test) may be present. Examination looking for potential underlying causes, such as connective tissue diseases and sarcoidosis, is also useful.

Table 1. Classification of interstitial lung diseases

ILD of known cause or association

- Environmental (eg. bird, other allergen exposure)
- Occupational (eg. asbestos, silica)
- Drugs (eg. cyclophosphamide, methotrexate, amiodarone)

ILD of unknown cause

- Idiopathic interstitial pneumonias (IIP)
  - idiopathic pulmonary fibrosis (IPF)
  - IIP other than IPF
    - nonspecific interstitial pneumonia
    - cryptogenic organising pneumonia
    - desquamative interstitial pneumonia
    - respiratory bronchiolitis ILD
    - acute interstitial pneumonia
    - lymphocytic interstitial pneumonia
- ILD associated with connective tissue diseases (eg. rheumatoid arthritis, scleroderma)
- Granulomatous ILD (eg. sarcoidosis)
- Other forms
  - lymphangioleiomyomatosis
  - pulmonary Langerhans cell histiocytosis/ histiocytosis X
  - eosinophilic pneumonias

Table 2. How ILD comes to clinical attention

Symptoms

- Progressive breathlessness with exercise
- Persistent nonproductive cough
- Pulmonary symptoms related to another disease (eg. connective tissue disease)

Abnormal investigations

- Chest X-ray
- Lung function abnormalities – particularly a restrictive ventilatory pattern

Investigations

Lung function tests

All patients with suspected ILD should undergo full lung function testing, including measurement of spirometry, lung volumes and diffusing capacity for carbon monoxide (DLCO). Most have a restrictive lung defect with a reduction in lung volumes, and a decrease in the DLCO. Other spirometric patterns can be seen, with

obstructive or mixed lung function defects seen in some ILDs such as sarcoidosis.

Chest X-ray

Chest X-ray is usually the first radiological investigation ordered but it has limited diagnostic sensitivity and specificity in ILD. Many diseases remain occult or are not correctly diagnosed on chest X-ray, appearing as a nonspecific 'reticulodnodular pattern'. Further imaging may guide diagnosis.

High resolution computed tomography

High resolution computed tomography (HRCT) has a greater diagnostic accuracy than chest X-ray and is the imaging modality of choice in anyone with suspected ILD.[6] Some patterns and distributions are suggestive, or even diagnostic, of an underlying cause and may avoid the need for further investigations. However, its overall accuracy in determining a specific aetiology of ILD is poor. Common HRCT findings in ILD are shown in *Figure 1* and *2*.

Bronchoscopy

Fibreoptic bronchoscopy may be useful to exclude infections (which can masquerade as ILD). Although the diagnostic yield is much lower than that of the more invasive surgical lung biopsies, transbronchial biopsies are often performed. In the appropriate clinical setting, they can be used to diagnose some of the ILDs, in particular sarcoidosis and hypersensitivity pneumonitis, thereby avoiding surgical lung biopsy. In a stable patient, bronchoscopy can be done as a day procedure and requires only mild sedation.

Surgical lung biopsy

Surgical lung biopsy is required to diagnose most types of ILD. Surgical lung biopsy is most commonly performed with minimally invasive techniques (video assisted thoracic surgery) but requires general anaesthesia and mechanical ventilation during the procedure. In some cases, notably IPF (*Table 3*) with the classic radiologic features of basal and peripheral reticular abnormalities, honeycombing and traction bronchiectasis, lung biopsy is not needed for a diagnosis.[7]

Management

Once ILD is suspected based on clinical features, HRCT scan and lung function tests, prompt referral to a respiratory specialist is warranted. The management of ILD is complex and varies depending on the underlying diagnosis. A detailed discussion of management of each form of ILD is beyond the scope of this article, however there are general measures that apply across most forms of ILD. A brief summary of some specific management options is also presented.

General measures

Pulmonary rehabilitation has been shown to be of benefit in ILD and should be available to all patients, preferably in a centre with expertise in ILD.[8,9] Early referral to a respiratory specialist is recommended.

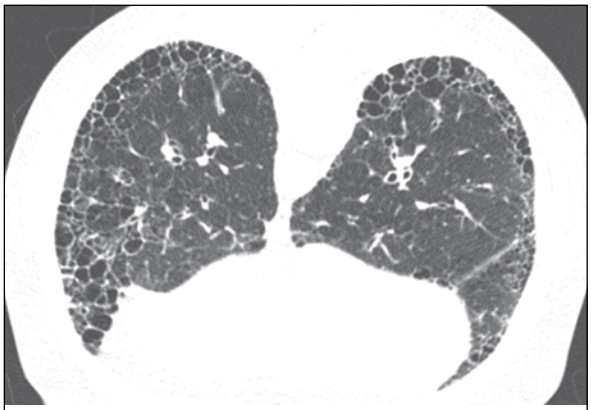

Figure 1. HRCT of idiopathic fibrosis with 'honeycombing'

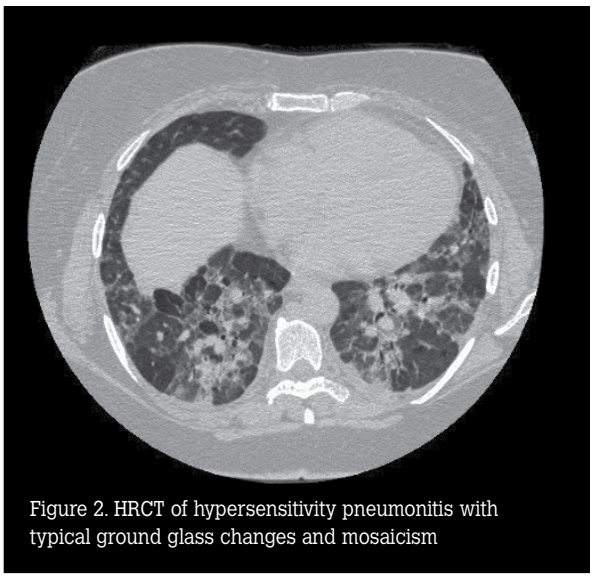

Figure 2. HRCT of hypersensitivity pneumonitis with typical ground glass changes and mosaicism

Smoking cessation is of paramount importance and current smokers should be offered specialist support and nicotine replacement therapy or other pharmacotherapy as needed.

Oxygen therapy may be considered if there is significant hypoxia at rest or on exercise.

Identify and treat other commonly associated diseases – several diseases that commonly exist in patients with ILD are believed to contribute to worsening of symptoms:

- gastroesophageal reflux disease – if present it should be treated with behavioural modification and medications
- pulmonary hypertension – as well as worsening symptoms, patients with ILD and pulmonary hypertension have a shortened survival. Unfortunately, at present there are no effective medications for pulmonary hypertension associated with ILD
- depression and anxiety – these are very common in patients with ILD and significantly impact on their quality of life. Involvement in support groups can be helpful and selected patients may benefit from pharmacological therapy.

Table 3. Criteria for diagnosis of IPF in absence of surgical biopsy[5]

Major criteria

- Exclusion of known causes of ILD
- Abnormal lung function (restriction and impaired gas exchange)
- Hypoxia (rest or exercise)
- Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT
- Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis

Minor criteria

- Age >50 years
- Insidious onset of otherwise unexplained dyspnoea on exertion
- Duration of illness >3 months
- Bibasal inspiratory crackles

Best supportive care should include patient education,[10] an explanation of the poor prognosis associated with many of these diseases (notably IPF) and planned discussion of end of life care. Management of intractable dyspnoea may include low dose opioids, which are of documented efficacy.

Specific measures

There is ongoing controversy over the role of specific treatments in subgroups of ILD due to a lack of good quality evidence for many of the specific treatments proposed. At times, no specific treatment may be an appropriate option after discussion between the patient and the specialist.[11]

Idiopathic pulmonary fibrosis

No therapy has been proven to improve the survival or otherwise significantly alter the clinical course of IPF. There is no evidence to support the widespread use of high dose prednisolone alone, and its use is associated with significant morbidity. A trial of prednisolone, azathioprine and N-acetyl cysteine may be warranted but strong evidence for benefit is lacking. If the patient is a suitable candidate a referral for consideration of lung transplantation is essential. Enrolment in a high quality clinical trial should also be considered.[12]

Sarcoidosis

Treatment for pulmonary sarcoidosis is only indicated if there is progressive disease on radiology and lung function, or if there are significant symptoms or extrapulmonary disease. Prednisolone (0.5 mg/kg/day) is usually first line treatment for 1 month, weaning to a maintenance dose that controls symptoms and then continuing for up to 6–24 months.

Connective tissue diseases

Treatment of connective tissue disease associated ILD is based on disease severity (ie. symptoms, HRCT extent and lung function) and longitudinal disease behaviour. Treatment will frequently involve prednisolone (0.5 mg/kg/day), tapering to a maintenance dose of 10 mg/day. This is often combined with immunosuppressive agents (usually oral or intravenous cyclophosphamide). The exception to this is systemic sclerosis where higher doses of prednisolone should be avoided, due to the risk of precipitating a renal crisis.

Hypersensitivity pneumonitis

Avoidance of the antigen is essential and prednisolone therapy may be required if there is severe or progressive disease.

When to consider a diagnosis of ILD

Case study 1

Mrs MP, 35 years of age, is a mother of three who presented to her GP with a 10 week history of progressive breathlessness associated with a dry cough, night sweats and malaise. She is a current smoker, with no past medical history and on no regular medications. She had no joint or eye symptoms and examination revealed her to be afebrile with oxygen saturations of 96%. There were no wheezes or crackles in her lungs and no other abnormalities on examination including no skin rashes. She was born in Australia, had never travelled overseas, and had no pets or any exposure to birds.

After trialling two courses of antibiotics with no response, a chest X-ray was performed revealing widespread interstitial changes and bilateral hilar enlargement. Inflammatory markers and renal function were within normal limits. A HRCT was performed and referral to a respiratory specialist was made. The HRCT showed bilateral hilar lymphadenopathy and bilateral pulmonary interstitial infiltrate. Lung function testing revealed a restrictive ventilatory pattern with a moderately reduced transfer factor. A bronchoscopy was performed with no bacterial or mycobacterial growth and the transbronchial biopsy being consistent with sarcoidosis. Due to the respiratory compromise, after lengthy discussion, Mrs MP was commenced on prednisolone at 0.5 mg/kg/day for 1 month with a view to further respiratory follow up. An ophthalmology review was also organised.

Case study 2

Mr DB, 61 years of age, presented to his GP with a 4 month history of progressive breathlessness associated with a dry cough. He is an exsmoker who quit 5 years ago with a 40 pack year history. Six months previously he had started on an angiotensin converting enzyme inhibitor (ACEI) for hypertension but he had no other medical history and was not on any other medications. He worked in an office and had no known exposure to asbestos.

Mr DB's ACEI was changed to an angiotensin receptor blocker with no improvement in the cough. He was then trialled empirically on inhaled corticosteroids (ICS) and salbutamol and a chest X-ray and lung function

tests were organised. He had no relief from the ICS or salbutamol. The chest X-ray showed diffuse interstitial opacities and lung function testing revealed a moderate restrictive ventilatory defect with a severely decreased transfer factor. A HRCT was performed and he was referred to a respiratory specialist. On examination he was afebrile, saturating 93% on room air, had clubbing and bibasal fine inspiratory crackles. The HRCT showed subpleural bibasilar interstitial changes with both 'honeycombing' and ground glass changes. Bronchoscopy was negative for infection and the transbronchial biopsy was nondiagnostic. Due to the presence of ground glass changes, he went on to have video assisted thoracic surgery with lung biopsy, which was consistent with IPF. After long discussion with the patient and his family it was decided he would undergo a course of pulmonary rehabiliation. Early referral was made to a lung transplant referral centre for discussion of lung transplantation and ongoing monitoring.

Case study 3

Mr PL, 81 years of age, was being managed by his GP for 3 months of progressive breathlessness. His past medical history included an ischaemic cardiomyopathy (left ventricular ejection fraction of 45%), coronary artery bypass graft surgery (x3) in 2003, hypertension and hypercholesterolaemia. Five months previously he had been commenced on amiodarone and warfarin for atrial fibrillation. Other medications included: perindopril, frusemide, spironolactone, aspirin and pravastatin. He was a life long nonsmoker and had no significant occupational exposures. Lung function testing in 2003 was normal. Despite optimal management of his heart failure, his breathlessness and interstitial changes on the chest X-ray persisted. A HRCT showed bibasal subpleural fibrosis with honeycombing and some ground glass changes. Lung function testing revealed a restrictive ventilatory pattern with a decreased gas transfer factor. He was referred to a respiratory specialist where ILD was diagnosed. After discussion with the patient, no invasive diagnostic procedures were performed and no specific treatments were instituted, with the differentials being IPF or amiodarone induced ILD. Amiodarone was ceased and he was monitored over the next 12 months. There was resolution of the ground glass changes on HRCT with no progression of the honeycombing and stabilisation of his lung function tests. A clinical diagnosis of amiodarone induced ILD was made and he was managed expectantly.

Summary of important points

- Interstitial lung disease is a term encompassing a diverse range of lung conditions that primarily affect the lung interstitium.
- ILD should be considered in any person presenting with breathlessness or cough along with abnormal chest radiology or lung function testing.
- High resolution computed tomography is the best imaging modality.
- Lung biopsy is often required for diagnosis.
- Referral to a respiratory specialist and involvement of multidisciplinary teams are the mainstays of management.
- Specific management varies according to the underlying diagnosis.
- General management strategies include: pulmonary rehabilitation, smoking cessation, oxygen therapy as required, and treatment of commonly associated diseases.

Authors

James Ward MBBS, is an advanced trainee in respiratory and sleep medicine, Department of Respiratory & Sleep Medicine, Austin Health, Victoria. james.ward@austin.org.au

Christine McDonald MBBS(Hons), FRACP, PhD, is Professor and Director, Department of Respiratory & Sleep Medicine, Austin Health and Melbourne University, Victoria.

Conflict of interest: none declared.

References

1. Demedts M, Wells AU, Anto JM, et al. Interstitial lung diseases: an epidemiological overview. Eur Respir J 2001;32:2–16S.
2. Ryu JH, Daniels CE, Hartman TE, Yi ES. Diagnosis of interstitial lung diseases. Mayo Clin Proc 2007;82:976–86.
3. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. N Engl J Med 2001;345:517–25.
4. Behr J, Thannickal VJ. Update in diffuse parenchymal lung disease 2008. Am J Respir Crit Care Med 2009;179:439–44.
5. American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165:277–304.
6. Raghu G, Brown KK. Interstitial lung disease: clinical evaluation and keys to accurate diagnosis. Clin Chest Med 2004;25:409–19.
7. Flaherty KR, King TE Jr, Rghu G, et al. Idiopathic interstitial pneumonia. What is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004;170:904–10.
8. Wells AU, Hirani N. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63:v1–58.
9. Holland A, Hill C, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax 2008;63:549–54.
10. Collard HR, Tino G, Noble PW, et al. Patient experiences with pulmonary fibrosis. Respir Med 2007;101:1350–4.
11. Behr J, Kolb M, Cox G. Treating IPF – all or nothing? A PRO-CON debate. Respirology 2009;14:1072–81.
12. Raghu G. Improving the standard of care for patients with idiopathic pulmonary fibrosis requires participation in clinical trials. Chest 2009;132:330–3.

correspondence **afp@racgp.org.au**