

Hands On

Practical advice on management of rheumatic disease



LUNG DISEASE IN PEOPLE WITH ARTHRITIS

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EDITORIAL

Respiratory disorders are common in general practice. Most practices now have spirometers and the diagnosis and management of lung disorders has advanced considerably within primary care.

The link between rheumatological conditions and the lung is poorly understood in primary care. Many GPs will not be aware of any of the possible lung complications of rheumatoid arthritis, for example. My aim in commissioning this Hands On report was to increase GPs' knowledge and awareness of these lung complications and, with that, their ability to diagnose and manage these conditions in primary care and enable the patient to be cared for closer to home, as Lord Darzi would suggest.

I was particularly keen to raise the awareness of the lung complications of disease-modifying anti-rheumatic drugs (DMARDs), especially methotrexate as this is commonly used and monitored in primary care. GPs' knowledge of the possible complications is poor. Methotrexate can cause fatal lung disease: patients are often mismanaged because there is a delay in the diagnosis of a serious lung complication – the symptoms are confused with those of viral infections and influenza.

The author, Dr Chris Warburton, is a respiratory physician who shares a monthly clinic with rheumatology consultant colleagues in order to manage those patients who have both inflammatory arthritis and lung problems.

Louise Warburton

Lung disease in people with arthritis can be simply divided into:

- lung disease related to the arthritic disease itself
- lung disease related to the treatment of that arthritic disease
- lung disease unrelated to the presence of arthritic disease.

In most subjects the respiratory manifestations of arthritic disease occur well after the development of the arthritis itself; however in a minority of cases the lung disease may be the presenting feature of a multisystem connective tissue disease. It is important for healthcare professionals to be aware of this.

Lung disease related to the presence of arthritic disease

There are no lung diseases directly related to the presence of osteoarthritis (although any lung disease may coexist with this or other conditions – see below), but there are specific associations between other types of arthritis and lung disease.

Rheumatoid arthritis

There are a number of lung diseases which are more common in people with rheumatoid arthritis (RA) than the general population. These include diseases of the airways, the pleura and also the lung parenchyma itself.

Disease of the airways

Subjects with RA commonly have symptoms of, and investigations which demonstrate, airways disease. Commonly such subjects complain of symptoms of cough, sputum production and shortness of breath.

Historically airways diseases in RA have been separated into the clinical entities of bronchiectasis and obliterative

bronchiolitis,¹ although it is now felt that these two conditions are probably part of the same syndrome and both are probably present to a greater or lesser extent in those subjects with appropriate symptoms.

Predominant bronchiectasis

Subjects with predominant bronchiectasis will have the symptoms mainly of daily cough and sputum production, with intermittent flares of more severe symptoms termed exacerbations. Pathologically bronchiectasis is dilatation of the small- and medium-sized airways in the lung which encourages colonisation of those airways with bacteria. When such bacteria proliferate, the immune system within the lung mounts an inflammatory response, causing the volume of sputum production to rise and the sputum to change in colour (becoming yellower or greener). During these exacerbations subjects may become breathless, or more breathless if they already have this symptom.

Diagnosis of bronchiectasis may be made on clinical grounds if cough and daily sputum production are present along with the finding of coarse inspiratory crackles on physical examination. These symptoms and physical findings are however non-specific and demonstration of dilated airways on high-resolution (thin section) computerised tomography (HRCT) is usually required for diagnosis.

Treatment of bronchiectasis may not be required if daily symptoms are minor and exacerbations are infrequent, although exacerbations are usually treated with antibiotic therapy. If exacerbations are frequent or daily symptoms are severe then treatment usually includes daily physiotherapy techniques to encourage expectoration of sputum and more aggressive antibiotic therapy. The latter may include intravenous antibiotics for exacerbations, daily nebulised antibiotic therapy or rotational oral antibiotics. Evidence would suggest that low-dose macrolide antibiotics such as erythromycin, azithromycin and clarithromycin (in doses lower than antibacterial ones) have a beneficial effect on symptoms and exacerbation rates when given long-term to subjects with bronchiectasis.²

Predominant obliterative bronchiolitis

Obliterative bronchiolitis (OB) affects the smaller airways in the lungs and causes obstruction to airflow through these airways with trapping of air within the lungs. Patients with a pure form of this condition generally present with progressive breathlessness, but cough and sputum production are usually not present. Simple spirometry will demonstrate bronchial obstruction (a reduction from the normal 0.75 in the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC)). More detailed lung function testing will demonstrate an increase in the measured lung volumes such as residual volume (RV) and total lung capacity (TLC). There will be a reduction in the gas transfer capacity of the lungs. Reversibility of the bronchial obstruction to bronchodilators is variable but usually minimal. Despite this the mainstay of treatment remains bronchodilator therapy.

The lung function abnormalities are indistinguishable from those of smoking-related lung disease (chronic obstructive pulmonary disease – COPD), and deciding what the cause of such lung function abnormalities is in a smoker with RA can be difficult. The treatment in this situation is a combination of smoking cessation and bronchodilator therapy.

In a minority of cases subjects with OB can progressively lose airway function and become increasingly breathless, eventually developing respiratory failure which can progress to cor pulmonale (right heart failure as a consequence of chronic hypoxaemia and pulmonary hypertension). Studies³ of the use of immunosuppressant therapy to try to prevent decline in lung function over time have been few and generally non-placebo-controlled, although corticosteroids may demonstrate some benefit. Treatment of respiratory failure in this situation is the same as for any other cause: long-term oxygen therapy and treatment of any heart failure with diuretics.

Disease of the pleura

Pleurisy with pleural effusion is the commonest respiratory manifestation of RA. It may be asymptomatic; however it may present with breathlessness, fever and pleuritic chest pain. The effusion is inflammatory, and biopsy of the pleura itself generally just shows chronic inflammation. The investigation and management of RA-related pleural effusion is the same as for pleural effusions of any other cause. This involves drainage if the effusion is large and symptomatic along with techniques to prevent recurrence such as pleurodesis if the effusion is recurrent.

In some circumstances empyema (infection of the pleural effusion) may occur. This complication requires drainage of the infected fluid and antibiotic therapy.

Diseases of the lung parenchyma (interstitial lung diseases)

A number of patterns of disease of the lung parenchyma have been described in association with RA. All essentially involve a combination of inflammation and scarring (fibrosis) of the lung tissue and are termed interstitial lung diseases.

The exact labelling of these conditions is usually defined using either the pattern of shadowing on HRCT scanning of the thorax or the actual pathology on lung biopsy, and includes entities termed usual interstitial pneumonitis (UIP), non-specific interstitial pneumonitis (NSIP), organising pneumonia (OP) and hypersensitivity pneumonitis (HP), among others.

Previous studies have estimated that around 20% of subjects with RA attending secondary care clinics will have evidence of interstitial lung disease, although not all of these will be symptomatic.⁴ The main symptom produced by interstitial lung disease is breathlessness on exertion, although cough can also present as an early symptom.

The finding of inspiratory crackles on auscultation of the chest in a subject with RA should alert the clinician that

further investigations are indicated. These investigations should include HRCT scanning of the thorax and detailed lung function testing.

Generally interstitial lung disease will cause a restrictive pattern on lung function testing, with reduction in lung volumes (FEV1, FVC, RV and TLC) along with a reduction in the gas diffusion capacity of the lung. HRCT scanning will define the presence, the extent and the pattern of the interstitial lung disease present. Most commonly the lung fibrosis occurs in the bases of the lung, initially in the subpleural region but spreading to other areas as the disease progresses.

Management of interstitial lung disease in subjects with RA initially involves surveillance. A significant proportion of such subjects will not develop progressive disease, and therefore their management will be that of their underlying arthritis. It is felt that disease-modifying anti-rheumatic drugs (DMARDs) may in fact protect against progressive lung disease in some subjects.⁵

TABLE 1. Patient with rheumatoid arthritis and respiratory symptoms
<p>History – pattern of symptoms</p> <ul style="list-style-type: none"> • Cough? • Sputum? • Breathlessness? • For how long? • Worsening? • Relevant therapies? • Smoking history?
<p>Physical examination</p> <ul style="list-style-type: none"> • Hyperexpanded lungs (hyperresonant with reduced breath sounds)? • Inspiratory crackles? – could be fibrosis or bronchiectasis • Inspiratory squawks (high-pitched multifocal inspiratory sounds)? – sometimes heard in obliterative bronchiolitis
<p>Chest x-ray</p> <ul style="list-style-type: none"> • May show fibrosis • Hyperinflated lung fields may suggest obliterative bronchiolitis • Often normal even with significant lung disease
<p>Spirometry</p> <ul style="list-style-type: none"> • Obstructive – suggests obliterative bronchiolitis or bronchiectasis • Restrictive – may suggest fibrosis (usually physical signs present)
<p>Referral for specialist advice</p> <ul style="list-style-type: none"> • Detailed lung function tests • High-resolution computerised tomography • Lung biopsy (only if uncertainty)

For those subjects who do develop progressive interstitial lung disease and progressive lung inflammation and fibrosis with reducing lung function their management is best delivered using a joint approach between chest physician and rheumatologist. Options for treatment to reduce the rate of progression of lung disease include oral steroids and other immunosuppressant drugs such as azathioprine and cyclophosphamide. Such treatments are helpful in some; however a small proportion of patients will still deteriorate and develop respiratory failure and cor pulmonale. The management of subjects with these conditions has been described above.

Scleroderma

Lung disease in scleroderma takes two main forms: interstitial lung disease leading to lung fibrosis and pulmonary hypertension. Both of these conditions usually present with breathlessness on exertion.

Lung fibrosis

As in RA, the lung fibrosis of scleroderma generally occurs at the lung bases initially and spreads to other areas as it becomes more severe. It also requires monitoring initially as in some patients the disease is not progressive.

If progressive disease does occur, studies have suggested that both intravenous cyclophosphamide and oral mycophenolate mofetil can reduce lung function decline over time.⁶ Intravenous cyclophosphamide is usually delivered as monthly infusions, often as a hospital day patient, whereas oral mycophenolate can be given on a shared-care basis between hospital and primary care in a similar manner to oral azathioprine. Steroids should be used with caution in scleroderma due to the risk of renal crisis.⁷ Scleroderma renal crisis is the rapid development of renal failure associated usually with accelerated hypertension. Treatment usually entails aggressive anti-hypertensive therapy along with other supportive measures, including acute haemodialysis where necessary.

Pulmonary hypertension

Pulmonary hypertension is defined as a rise in the blood pressure within the pulmonary circulation and occurs in a significant proportion of subjects with scleroderma. It is diagnosed definitively by catheterisation of the right heart and direct measurement of pressures within the right heart and pulmonary artery. Trans-thoracic echocardiography may suggest in some subjects that pulmonary hypertension is present but most large studies of this modality suggest that there are significant false-positive and false-negative rates. More recent studies have suggested that the blood level of B-type natriuretic peptide (BNP) or its precursors and cardiac magnetic resonance imaging may be useful non-invasive modalities for diagnosis.

Once diagnosed, treatment of pulmonary hypertension is only provided in a small number of nationally funded National Pulmonary Hypertension Centres (see 'Further information'). Treatment usually includes pulmonary vasodilator therapy of which there are several types, such as sildenafil, bosentan and prostacyclin.

Other conditions

Some of the other rheumatological arthritic conditions are associated with lung disease. Most of these lung diseases are described above, namely pulmonary hypertension, lung fibrosis and pleurisy.

Pulmonary hypertension can be found in subjects with mixed connective tissue disease (MCTD) and systemic lupus erythematosus (SLE).

Lung inflammation and fibrosis may be found in subjects with SLE, Sjögren's syndrome, MCTD and polymyositis. In all of these conditions the lung fibrosis tends to occur most commonly in the lower lobes of the lung. In contrast, in subjects with ankylosing spondylitis lung fibrosis when it occurs tends to affect the upper lobes of the lung.

Pleurisy with pleural effusion may also occur in subjects with SLE and Sjögren's syndrome.

In SLE and antiphospholipid syndrome (Hughes syndrome), subjects may present with respiratory symptoms due to their predisposition to develop venous thromboembolic disease with pulmonary embolism.

In addition, some subjects with SLE may develop myopathy of the diaphragms leading to reduced lung volumes and the so-called 'shrinking lung syndrome'. This condition usually presents with breathlessness.

Lung disease related to the treatments used in arthritis

There are three main categories of lung disease which relate to the treatments used in arthritic disease. These include an increased risk of pyogenic lung infection in subjects treated with immunosuppressant drugs, methotrexate-induced pneumonitis and the risk of tuberculosis in subjects treated with the newer biological therapies.

Pyogenic lung infection

Most of the DMARDs can theoretically increase the risk of pyogenic lung infection (i.e. pneumonia and bronchitis). This effect can be exacerbated in subjects who have existing lung disease (whether related or unrelated to their arthritic disease). For example there is often concern when a subject with bronchiectasis and symptomatic arthritis requires disease-modifying therapy.

In most cases however the risks are more theoretical than real, and a pragmatic approach to management of these patients is to commence the immunosuppressant therapy for their symptomatic arthritis and simply monitor the effect on their lung symptoms. In a minority of cases a detrimental effect on symptoms will be experienced and the therapy will need to be modified or changed.

Methotrexate-induced pneumonitis

Methotrexate (MTX), one of the DMARDs, has a number of side-effects including pneumonitis.

MTX-induced pneumonitis is an acute inflammatory condition of the lungs which causes relatively abrupt onset of breathlessness which may be associated with cough and fever. It most commonly occurs within the first 12 months of MTX therapy and can be very severe with marked hypoxia at presentation and severe exercise limitation. Death can occur from this drug side-effect. Lung function testing demonstrates a reduction in lung volumes with reduced gas diffusion. CT scanning of the chest demonstrates inflammatory shadowing (often described as ground glass change as it has this appearance on lung window settings on HRCT) and in some cases established lung fibrosis. Treatment includes stopping the MTX, and severe cases are often treated with corticosteroids, although the evidence for this treatment is largely anecdotal rather than scientific.

In a subject with arthritis who is on MTX and who is found to have lung fibrosis, it is often difficult to know whether this relates to the drug treatment itself or the underlying arthritis. In such cases the views of a chest physician should be sought. Provided there is no progression in the lung fibrosis over time then it is probably safe to continue with the MTX therapy. In most cases where lung function declines over time, however, most physicians would stop the MTX therapy even if the classical inflammatory features of MTX pneumonitis are not present.

Tuberculosis

In subjects treated for their arthritis with the newer biological therapies such as etanercept, infliximab and adalimumab, there is a significant risk of reactivation of tuberculosis in those subjects with latent tuberculous disease.⁸ Latent tuberculosis is present in a significant proportion of middle-aged and elderly patients who have been exposed to tuberculosis but have not undergone treatment for it. Clues to its presence would include calcified foci on plain chest x-ray.

In these subjects tuberculosis prophylaxis is generally given using one or more antituberculous antibiotics for a period of 3–6 months before the biological therapy is commenced.

In all subjects on biological therapy a high index of suspicion for tuberculosis developing and a low threshold for investigation should be maintained at all times. The British Thoracic Society have published guidelines to assist health-care professionals dealing with this issue.⁹ These guidelines cover appropriate screening, options for referral, investigation and treatment for tuberculosis in subjects on biological therapy.

Lung disease unrelated to the presence of arthritic disease

Not all lung disease which occurs in patients with arthritis is related to the arthritis itself. Lung disease of any nature may coexist with any type of arthritis. These diseases are independent of each other in terms of aetiology; however the therapies given for either the lung disease or the arthritis may impact significantly on the other.

An example of this would be the use of non-steroidal anti-inflammatory therapy given for arthritis to an asthmatic who may be intolerant of these drugs, or the inability of a patient to use metered dose inhalers for their smoking-related COPD due to significant arthritis of the hands.

In a subject therefore with lung disease which is unrelated to their arthritis, it is imperative to ensure that any new drug therapies considered for either the lung disease or the arthritis do not adversely affect or are adversely affected by the other condition.

Summary

When healthcare professionals are presented with a subject with both arthritis and lung disease, they must remember that lung disease may occur very commonly in subjects with arthritis. They must decide whether the lung disease and the arthritis are directly related or whether they are simply independent diseases. They must consider whether any therapies given for the arthritis have caused the lung disease, and they must take care with the prescription of any new medications for either disease to ensure that it will not adversely affect the other.

Lung disease directly related to arthritis generally presents with non-specific symptoms such as cough, sputum production and breathlessness. Physical examination will guide initial investigations of the lung disease. Arthritis may be associated with a broad range of conditions which affect all parts of the respiratory system including the airways, the lung parenchyma, the pleura and the pulmonary circulation.

General practitioners should always offer influenza vaccination annually and a pneumococcal vaccination to any patient suffering from inflammatory arthritis or connective tissue disorder, even if they are not on immunosuppressant therapy.

Further information

National Pulmonary Hypertension Centres

England and Wales

- Hammersmith, Royal Brompton and Royal Free Hospitals, London
- Freeman Hospital, Newcastle upon Tyne
- Royal Hallamshire Hospital, Sheffield
- Papworth Hospital, Cambridge

Scotland

- West Glasgow Hospital

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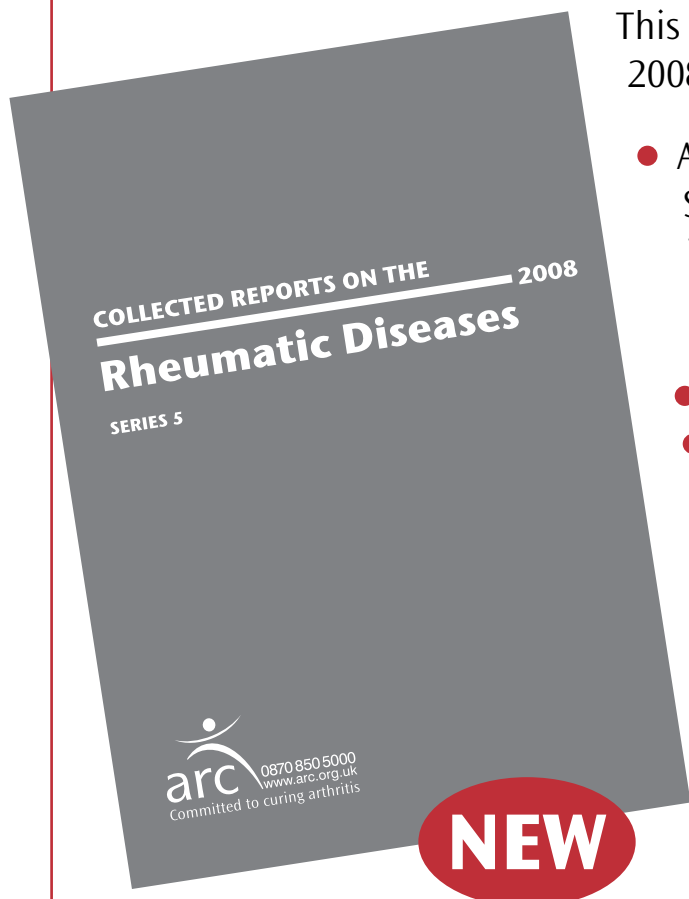
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