Pleuro-Pulmonary Complications of Rheumatoid Arthritis

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Word Count: 2548 (main article excluding figures legends and references)

Authors’ Statement:
All authors have read the submitted manuscript and acknowledge it as their own work that has not been submitted elsewhere for consideration of publication. None of the authors have any conflicts of interest to declare in relation to the submitted work. No funding was received in relation to the submitted work. Consent to publication has been sought and granted by the families of the patients whose cases are described in the submitted work.

Key Words: rheumatoid arthritis, pleural empyema, pneumothorax, pleural effusion
INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease whose distinctive feature is the development of symmetrical polyarthritis. It has a prevalence of approximately 1% in the general population, predominating in females and peaking between the ages of 30 and 50 years; and is found worldwide although some ethnic groups show an increased propensity for the disease. The burden of illness in these patients is manifest in a mortality rate over twice that of age-matched individuals in the general population, with poor prognostic factors including rheumatoid factor seropositivity, anaemia of chronic disease, presence of anti-CCP antibodies and extra-articular manifestations. Since Ellman and Ball [1] first described lung disease in association with RA, various pulmonary manifestations including pleural effusions, lung nodules, obstructive lung disease and vasculitis have been described in the literature. In addition to problems caused by the disease, immunosuppressants and other medications used to treat RA can be directly pneumotoxic, predispose to opportunistic infection, and impair wound repair or healing. Clinical features associated with RA-associated lung disease include male gender, rheumatoid factor seropositivity, severe articular disease, subcutaneous nodules and other extra-articular manifestations.

Progressive nodular and pleural lung disease associated with RA represents a particular clinical challenge. The nodules are often multiple and involve both lungs, varying in size from a few millimetres to several centimetres. A propensity for the lung peripheries and fissures with an ability to become necrotic and rupture results in complications such as recurrent secondary pneumothorax, bronchopleural fistula formation with sizeable air leak, haemorrhage, pulmonary abscess formation and empyema. The inflammation, fibrous visceral peel formation (with trapped lung) and non-compliant parenchyma associated with rheumatoid lung mean achieving key clinical objectives such as closure of the air leak, obliteration of the pleural space, eradication of infection, and effective pleurodesis may prove impossible. An additional tendency for the pleuro-pulmonary complications of RA to recur can result in disease that requires repeated intervention and is resistant to standard therapy. This case series illustrates the challenges that may occur in severe pleuro-pulmonary disease associated with RA, alongside a review of the literature relating to this area of practice.
CASE 1

A 51 year old woman presented to A&E in June 2008 with acute confusion. Her medical history included seropositive rheumatoid arthritis diagnosed 10 years previously and managed with leflunomide 20mg daily and prednisolone 2.5mg daily. Plain chest radiograph demonstrated opacification of the right hemithorax with CT confirming a large right pleural effusion, mediastinal lymphadenopathy and multiple pulmonary nodules presumed secondary to rheumatoid lung disease. The effusion was drained under ultrasound guidance and the patient treated for microbiologically-confirmed empyema with antibiotics. Follow-up CT in July showed a small right pneumothorax that required drainage one week later in the context of worsening dyspnoea and increasing size. Interval CT after a fortnight demonstrated minimal residual pneumothorax and as the patient was asymptomatic further intervention was deemed inappropriate.

In September 2008 the patient presented again with dyspnoea on minimal exertion. CT demonstrated a large right hydropneumothorax associated with a ruptured pulmonary nodule and following drain insertion for symptom relief the patient was referred for surgical intervention. A right VATS exploration with talc pleurodesis was performed; fluid culture was negative and biopsies confirmed rheumatoid pleuritis and nodular disease. Recovery was uneventful and the patient went home after eight days with wide-bore drain and Heimlich valve in-situ to manage ongoing air leak.

At outpatient follow-up over the next three months persistent air leak from a bronchopleural fistula meant the drain was left in position. This was eventually complicated by chronic empyema and breakdown of the subscapular VATS port site, requiring a prolonged course of oral ciprofloxacin. In the context of persistent pyopneumothorax and air leak an unsuccessful attempt was made in February 2009 to resolve the problem with a chest drain change, chemical pleurodesis (doxycycline and povidone-iodine) and application of negative pressure to the drain. The patient was left with an ongoing air leak and 20% residual pneumothorax with wide-bore drain and Heimlich valve in-situ.

Over the next year the patient had her right-sided chest drain changed three times (twice for dislodgement, once for blockage), as well as suffering a left-sided pneumothorax secondary to another
ruptured rheumatoid nodule that resolved with simple drainage. In an attempt to reduce the risk of infection her prednisolone and leflunomide were stopped. Despite this, the patient required recurrent treatment for persistent pleural space infection. On the last of these occasions she required ICU admission for septic shock where in the context of multi-organ failure including difficult ventilation due to bilateral bronchopleural fistulae the patient passed away, two years after her first presentation.

CASE 2

A 64 year old man was referred to respiratory clinic in May 2008 with progressive dyspnoea. He had been diagnosed with rheumatoid arthritis in 1976 and was managed with methotrexate 7.5mg weekly, leflunomide 20mg daily and prednisolone 5mg daily. Other medical problems included significant cardiac disease with atrial fibrillation, bioprosthetic aortic valve replacement and dual chamber pacemaker in-situ; and a diagnosis of right basal pleural thickening of uncertain aetiology made in 1998. CT demonstrated right lower lobe bronchiectasis with thick-walled segmental cavitation indicative of recurrent or persistent infection, alongside widespread pleural thickening with punctuated calcification suggesting chronic pleuritis. As there were no symptoms or biochemical markers of infection the patient was managed conservatively.

He was subsequently admitted in October 2008 with a week-long history of cough, dyspnoea and fever. Plain chest radiograph showed a right-sided hydropneumothorax that drained purulent fluid on drain insertion. After one week of intravenous antibiotics the chest drain continued to bubble and after CT (Figure 1) confirmed persisting hydropneumothorax the patient was referred for surgery. Rigid bronchoscopy, right-sided thoracotomy and decortication were performed; the post-operative period was difficult with persistent air leak and vasopressor requirement. Intraoperative samples grew *Aspergillus* and intravenous antifungals were added to ongoing antibiotic therapy. Three weeks after surgery the patient was discharged on oral antibiotics and antifungals; however, a persistent right pneumothorax and contiguous lower lobe cavity required a wide-bore drain to be left in position. The patient was readmitted a week later with rigors and restarted on intravenous antimicrobials, alongside weaning off methotrexate and steroids in discussion with his rheumatologist. Further surgical review concluded that rheumatoid pleurisy alongside significant air leak from the right lower lobe cavity and
bronchopleural fistula would prevent successful pleurodesis and re-expansion of the lung. The patient was allowed home with chest drain in-situ once his symptoms and inflammatory markers settled.

At subsequent follow-up over the next year the patient remained stable from a respiratory perspective. Repeat imaging including cross-sectional studies demonstrated an unchanged trapped right lung with thick-walled right lower lobe cavitation, bronchopleural fistula and persistent pneumothorax. He continued to be managed with a shortened wide-bore chest drain attached to a colostomy bag with de-airing holes; management options including thoracic window formation or muscle flap to fill the defect were discussed and either declined or deemed inappropriate due to concerns regarding fitness for general anaesthetic. The patient passed away from sequelae of his cardio-respiratory disease two years after his initial referral.

CASE 3

A 55 year old woman was referred to respiratory clinic in September 2005 after a plain chest radiograph demonstrated an incidental left-sided hydropneumothorax. She had seropositive rheumatoid arthritis diagnosed in 1987 requiring multiple joint replacements and cervical spine surgery; alongside other auto-immune conditions including Sjogren’s syndrome, vitiligo and hypothyroidism. She was on methotrexate 15mg weekly and anti-TNFα therapy (adalimumab) with concurrent isoniazid prophylaxis. Cross-sectional imaging in 2003 had demonstrated lung nodules presumed secondary to rheumatoid disease whilst the patient reported drainage of a left-sided pleural effusion in 2004. Ultrasound-guided aspiration of the left hydropneumothorax obtained cloudy fluid with pH > 7.2 and glucose > 4 mmol/L; whilst bacterial culture was negative. In the absence of systemic symptoms conservative management was pursued. Routine follow-up over the next two years was uneventful with stable appearance of the left hydropneumothorax on serial imaging.

In January 2008 the patient presented acutely with malaise and dyspnoea. Plain chest radiograph demonstrated an enlarged left hydropneumothorax that subsequently drained purulent fluid. Her adalimumab and methotrexate were stopped and broad spectrum antibiotics commenced for six weeks. The patient required readmission in late March with dyspnoea and discharge from the previous
drain site. Pleural fluid from January had cultured *Mycobacterium kansasii* and in discussion with microbiology the patient started oral rifampicin, ethambutol and clarithromycin. An ultrasound-guided chest drain was inserted for residual left pleural effusion and a surgical opinion sought, where it was felt early intervention might prove beneficial given a persistent hydropneumothorax, empyema and bronchopleural fistula identified on CT (Figure 2).

In early April the patient had flexible (fiberoptic) bronchoscopy, left rib resection and wide-bore chest drain insertion before being transferred back to her local respiratory unit for ongoing in-patient care. Unfortunately the chest drain became dislodged after two weeks and in the context of accumulating pleural fluid and rising inflammatory markers the patient was referred for further surgical input. A VATS exploration, drainage and washout of the pleural cavity was performed with drain left in-situ on discharge and a plan to complete twelve months of anti-mycobacterial treatment.

Over the next eighteen months the patient required two further admissions to treat complications of chronic pleural infection despite remaining off immunosuppression. Serial imaging demonstrated gradual improvement in the persistent left hydropneumothorax with drain in-situ although plans for thoracic window formation were prevented by the patient’s limited functional reserve. A steady physical decline culminated in admission in late 2010 when in the context of type 2 respiratory failure, sepsis and cardiac ischaemia the patient passed away.

**DISCUSSION**

This case series demonstrates the difficulties that can occur with severe pleuro-pulmonary disease associated with RA and escalating management approaches, as well as the morbidity and mortality associated with this process. It is difficult to be certain about the proportion of patients with RA who develop pulmonary manifestations as many may be asymptomatic or never have relevant investigations. Whilst RA is three times more common in females it is males who proportionally develop more pulmonary complications, a key observation as recent data suggests the incidence of RA-associated lung disease is on the rise [2] and represents a major cause of morbidity and mortality in these patients [3, 4].
Post-mortem series suggest that RA-associated pleural disease may occur in between 38 and 73% of patients over a lifetime [3, 5, 6]; whilst observational work has estimated the annual incidence of pleural effusion formation in patients with RA at 0.34% for women and 1.54% for men [7]. The development of pleural disease can occur alongside or precede the first signs of joint involvement [8, 9] and like other connective tissue diseases may have a genetic predisposition [10]. Despite being the most common intra-thoracic manifestation of RA the majority of patients will never develop symptoms of pleural disease; only a reported 20% of individuals with RA experience pleurisy at any point in time [9] whilst overt clinical evidence of pleural disease is found in less than 5% of patients with RA [11, 12].

The presence of a pleural effusion in a patient with RA should prompt diagnostic investigation with ultrasound-guided thoracocentesis being the first-line test. Pleural fluid in RA is usually exudative, non-odorous and often turbid with a low pH (<7.3) and glucose (<50mg/dL or 2.8mmol/L); whilst more long-standing effusions may become chyliform [13, 14]. The presence of rheumatoid factor in pleural fluid reflects serum levels and is highly suggestive of a RA-associated aetiology, whilst the cytological appearance may be characteristic [7, 15, 16]. If the clinical history and thoracocentesis fail to confirm a diagnosis medical thoracoscopy or VATS and pleural biopsy may be necessary, particularly when there is concern regarding occult malignancy or infection. In cases of rheumatoid pleuritis both the “gritty” frozen macroscopic appearance of the pleura and histopathology are classically diagnostic [17, 18]. Most rheumatoid effusions are ultimately self-limiting with over two-thirds resolving within four months of their diagnosis [9].

RA-associated pleural effusion shares many biochemical and macroscopic features with empyema and the clinical history should be considered alongside appropriate microbiological studies before treating for infection. The risk of developing empyema in association with RA is unclear [9, 17, 19] but is certainly higher with immunosuppression and disease-modifying anti-rheumatic drugs (DMARDs); patients on anti-TNFα therapy are at risk of Mycobacterial infection and should be specifically screened for this. The presence of other RA-associated pulmonary pathology, such as bronchiectasis
or rheumatoid lung nodules, may predispose to infection by providing a portal of entry to the pleural space – for instance through rupture and formation of a bronchopleural fistula [20]. It may be necessary to review any prescribed immunosuppression; whilst conventional wisdom dictates that treating RA reduces the risk of progressive pulmonary disease, excessive immunosuppression may make treating an infection impossible. Furthermore, continuing any drug with an anti-inflammatory effect may negatively impact on the likelihood of successful pleurodesis following treatment for empyema or pneumothorax [21, 22], with talc preferable to complete pleurectomy, decortication or other chemical agents. There is increasing evidence linking specific drugs, notably leflunomide, with accelerated pulmonary nodulosis [23, 24, 25, 26] that may complicate management further.

Surgical intervention may be necessary in rheumatoid lung disease for reasons including the investigation of lung nodules or pleural effusion; and treatment of pneumothorax, empyema or symptomatic pleural thickening. There is no consensus guidance on how to approach these cases and consequently clinical decision making is based on the experience of the individual responsible clinician. The difficulty in managing these cases has long been recognised, with the formation of fibrous peel in association with chronic rheumatoid pleuritis making it difficult to divide away the lung during decortication and close any sites of air leak [27]. Whilst the surgical treatment of primary and secondary spontaneous pneumothorax using thoracotomy or VATS is highly efficacious in the general population [28, 29], this may not apply in RA-associated pleuro-pulmonary disease where the underlying lung can be grossly abnormal. Although guidelines for the management of both pneumothorax and empyema recommend small-bore chest tube drainage as part of standard first-line therapy [30, 31] it has been suggested that a more aggressive strategy utilising early surgical intervention with a concerted effort to re-expand the lung, obliterate the pleural space and facilitate pleurodesis might benefit patients already identified as having abnormal pleura secondary to RA [32].

This case series describes the management and longer-term outcome in a complex group of patients with RA who can, as a consequence of their underlying disease and the medications used to treat it, develop a range of pleuro-pulmonary complications that are resistant to conventional therapy. Whatever therapeutic approach is taken the patient must be counselled on the increased risk of
complications and failure of any intervention; the clinical team should also be prepared with alternative options that might prove necessary – these may include long-term chest drain insertion or thoracic window formation with or without delayed closure for control of persistent air leak or empyema – to maximise potential success in managing the patient.

**TEACHING POINTS**

- Pleural involvement with RA is common with most patients likely to remain asymptomatic or recover spontaneously. Significant manifestations include nodule formation and rupture causing bronchopleural fistulae and/or secondary pneumothorax; lung abscess; and empyema.
- Complex RA-associated pleuropulmonary disease can be difficult to treat given its tendency to recur; the physical characteristics of the underlying lung; and an immunosuppressed state that predisposes to chronic infection and poor healing.
- Complex and symptomatic RA-associated pleuropulmonary disease is associated with significant morbidity and mortality. Patients should be counselled on the increased risk of complications and failure for any therapeutic intervention; whilst clinicians should consider what long-term options are available in case initial management is unsuccessful.

**ACKNOWLEDGEMENTS**

The authors thank Dr Milan Bhattacharya (Milton Keynes Hospital, UK) and Dr Najib Rahman (Churchill Hospital, Oxford, UK) for their assistance in the preparation of this article. Above all, we thank the families of the patients whose cases are described for their support and understanding during the treatment of their relatives and writing of this article.
REFERENCES


LEGENDS FOR FIGURES:

FIGURE 1:
CT imaging (case 2) demonstrating right hydropneumothorax with multiple pulmonary nodules of varying size secondary to rheumatoid disease visible bilaterally.

FIGURE 2:
CT imaging (case 3) with left hydropneumothorax and drain in-situ, alongside a large cavitating right rheumatoid pulmonary nodule raising concern for the development of bilateral pleuropulmonary disease.
CT imaging (case 2) demonstrating right hydropneumothorax with multiple pulmonary nodules of varying size secondary to rheumatoid disease visible bilaterally.

180x180mm (72 x 72 DPI)
CT imaging (case 3) with left hydropneumothorax and drain in-situ, alongside a large cavitating right rheumatoid pulmonary nodule raising concern for the development of bilateral pleuropulmonary disease.