Case Presentation

Patient 1. A young woman with rheumatoid arthritis and acute respiratory failure

Background
A 33 year-old obese Chinese female, non-smoker, with longstanding history of rheumatoid arthritis (RA) since childhood sequentially requiring systemic steroids, penicillamine, oral gold, plaquenil, and 4 years earlier, leflunomide (Arava®), was admitted directly to the ICU for acute onset of high fever and oxygenation failure. There had been a prodrome of fever, non-productive cough, shortness of breath, vomiting and diarrhoea for a few days prior to admission. Her chest examination revealed diffuse crepitations throughout both lungs. 

Investigations
Her chest x-ray on admission showed bilateral diffuse consolidative changes (Figure 1A). Her white cell count was 1.72 \(10^9/L\) with total neutrophil count of 1.31 \(10^9/L\) and lymphocyte of 0.25 \(10^9/L\). The platelet count was 107 \(10^9/L\). Her CRP, procalcitonin and renal function tests were all normal. Her liver function tests were normal except for a SGOT of 109 U/l. The ESR was 35 mm/h. A subsequent chest CT showed extensive ground glass consolidation in both lungs sparing only the dorsal and apical regions consistent with acute pneumonitis (Figure 1B). The working diagnosis was fulminant community-acquired pneumonia versus leflunomide-induced interstitial pneumonitis. Leflunomide was promptly discontinued. Cholestyramine was given to accelerate the clearance of leflunomide.

Workup for Infection
She was pan-cultured on admission for high fever and was promptly started on broad-spectrum antibiotics including a beta-lactam, a macrolide, and anti-PCP and anti-fungal therapy based on microbiology consultation. She developed an episode of hypotension on Day 3, for which stress dose steroids and intravenous immunoglobulin were added for possible fulminant sepsis. One dose of G-CSF was given on Day 4 for persistent leukopenia, followed by good sustained recovery of her white cell count in the ensuing days. The lymphopenia persisted till Day 11. All microbiologic workup turned out to be negative: sputum and blood cultures, sputum for acid fast bacilli smear and PCR, urinary antigen for Legionella and Streptococcus, serologic titres for mycoplasma, nasopharyngeal aspirate for influenza A and B, and serum CMV pp65. All her immune markers were also negative.

Stormy Course in Respiratory Support
The patient required BIPAP support on Day 1 immediately upon ICU admission because of poor oxygenation. A FIO\(_2\) of 50% on BIPAP could achieve an oxygen saturation (SpO\(_2\)) of 80-85% only. Over the following week, her oxygenation remained very
marginal with SpO₂ achievable above 90% at FIO₂ of ≥ 70%. Mild exertion or coughing would precipitate marked oxygen desaturation down to 70s%. On Day 11, as the patient’s oxygenation deteriorated despite being on BIPAP, with SpO₂ barely above 90% on FIO₂ 80%, the patient was intubated and tracheostomy was performed. Ventilatory support showed a PEEP level of 15 cm together with a FIO₂ of about 60% to achieve a SpO₂ of 90-91%. On Day 18, the patient was commenced on bi-level ventilation for her fulminant ARDS with severe oxygenation failure.

Empiric Corticosteroids
The patient’s fever peaked on Day 2 but gradually came down (possibly from stress dose steroids) over the next few days and henceforth remained afebrile. On Day 9, in view of the totally negative microbiologic workup, multi-system presentation, leukopenia, lymphopenia, and the diffuse pneumonitis, the diagnosis of leflunomide-induced ARDS was felt to be likely. Pulse steroids in the form of daily methylprednisolone 500 mg for 2 days was given for the worsening respiratory failure and fulminant ARDS, followed by pharmacologic doses of steroids with gradual tapering over the next few weeks.

Inhaled Nitric Oxide
On Day 22, a repeat CT scan of the chest showed worsening ground glass consolidation with reticular shadows consistent with evolving pneumonitis. On Day 23, in view of the patient’s worsening oxygenation failure requiring FIO₂ of 85%, inhaled nitric oxide (iNO) was initiated to enhance gas exchange and for fear of oxygen toxicity. iNO at 5 parts per million (ppm) was administered via the InoVent. Within 12 hours of iNO administration, the patient demonstrated pleasing response with improvement in the SpO₂ thus enabling tapering down of FIO₂. By Day 25, the patient’s FIO₂ came down to as low as 50-55%. iNO was brought down gradually to 1 ppm and eventually off after a total course of 6 days. FIO₂ requirements remained stable off iNO. On Day 34, the FIO₂ requirements were 35-40% only. On Day 38, a repeat CT chest showed partial resolution of the alveolar process and lessening of the interstitial reticular markings.

The Road to Recovery
Her clinical course was otherwise only complicated by Klebsiella-related ventilator-associated pneumonia which responded to prolonged course of antibiotics. On Day 40, the patient was switched from IV steroids to oral prednisolone at 60 mg qd. By Day 45 she was able to sustain spontaneous breathing most of the day. By Day 55, the patient was completely off the ventilator, and was soon discharged from the ICU. The patient finally went home after a hospital stay of 3 months.

Final Diagnosis
Leflunomide-induced ARDS

Patient 2. An elderly woman with acute respiratory failure following VATS lung biopsy

Background
A 78 year-old Chinese female, nonsmoker, with history of hypertension and paroxysmal atrial fibrillation on warfarin and amiodarone (Cordarone®) 100 mg bd, was electively admitted to the hospital for wedge lung biopsy under video-assisted thoracoscopy. There had been a history of insidious onset of exertional dyspnoea and recent chest x-ray and CT finding of bibasilar subpleural infiltrates more on the left than right, with some suggestion of honeycomb lung in the left base (Figure 2A and 2B). Pre-operative myocardial perfusion scan was normal, and so were her chest examination and resting oximetry reading. VATS wedge biopsy of the left lower lobe was performed on Day 2. Intra-operatively, pleural fibrosis and lung nodularity were noted on palpation. Histology of the resected lung showed interstitial fibrosis with chronic inflammatory infiltrate consistent with usual interstitial pneumonitis. All stains for micro-organisms were negative.
lower zones. (Figure 2C) In view of the rapidly deteriorating condition and likely non-infectious pneumonitis, the patient was given pulse steroids in the form of methylprednisolone 500 mg qd for 3 days from Day 4 through Day 6 followed by prednisolone 50 mg qd beginning on Day 7. Diuretics were also given for possible fluid overload. From Day 7 through Day 9, the patient was put on spontaneous breathing with oxygen at 8 L+30%, achieving rather marginal O2 saturation of 90-94%. On Day 10, the patient appeared rather fatigued and tachypnoeic with a respiratory rate of 40, and required resumption of BIPAP. On Day 11, she was transferred to the ICU for intubation and invasive ventilation using PEEP levels of 10 cm H2O and FiO2 of 85%. However, her oxygenation failure remained profound requiring bi-level ventilation and FiO2 up to 100%. A bronchoalveolar lavage did not reveal any infectious aetiology for her oxygenation failure. Serum immune markers were normal. The working diagnosis was fulminant ARDS secondary to acute and chronic lung injury from amiodarone. Amiodarone was discontinued.

**Empiric Treatment of Amiodarone-induced ARDS**

High dose steroids were continued. Oxygen radical scavenger therapy was started using vitamin C, vitamin E, pentoxifylline, and N-acetylcysteine. One dose of anti-tumour necrosis factor-alpha antibody was also given for possible cytokine storm associated with the acute lung injury. By Day 13, FiO2 requirement came down to 75%-85% at a PEEP level of 10 maintaining a SpO2 of 91%, by Day 15 FiO2 down to 55% with a SpO2 of 92%, and Day 16 FiO2 down to 45% with a SpO2 of 91-92%, consistent with encouraging clinical response. However, she continued to demonstrate heightened respiratory drive with persistent tachypnoea up to 40 and marked use of accessory muscles despite full ventilatory support and generous doses of sedation. Her ICU course was further complicated by rather difficult-to-control atrial fibrillation, subcutaneous emphysema, right pneumothorax, steroid-induced diabetes, and critical illness polyneuropathy. The patient was eventually off the ventilator on Day 30, discharged from ICU on Day 34, and discharged home on Day 78.

**Final Diagnosis**

Amiodarone-induced ARDS

**Discussion**

**Definition of ARDS**

The acute respiratory distress syndrome (ARDS), first described in 1967, is characterised by diffuse inflammation of the lung’s alveolar-capillary membrane in response to various pulmonary and extra-pulmonary insults such as aspiration, pneumonia, sepsis, trauma, or pancreatitis. The 1994 American-European consensus on the definition of ARDS is acute onset of

1. Hypoxaemia, with a PaO2/FiO2 ratio of 200 mmHg or less,
2. Bilateral infiltrates on a frontal chest radiograph, and
3. Pulmonary artery wedge pressure < 18 mmHg or no clinical evidence of left atrial hypertension.

Patients with ARDS invariably require mechanical ventilation and prolonged ICU stay. Mortality rates remain high at 35-60%. Management strategies for ARDS have focused on combating the inciting insult, ventilatory optimisation and at times cautious use of steroids.

**Drug-induced ARDS**

Drug-induced lung diseases can manifest in various clinico-pathological entities as shown in Table 1, based on the cellular mechanism of lung injury as well as the tempo of disease presentation, ranging from slowly progressive pneumonitis/fibrosis to acute respiratory failure arising from either diffuse alveolar damage (DAD), non-cardiogenic pulmonary oedema or alveolar haemorrhage. The aetiologic link to a certain drug can be difficult, and is usually based on a history of drug exposure, histological evidence of lung damage, and exclusion of other causes of lung injury, especially the exclusion of active infection. In the milder cases, radiographic findings of subtle ground glass opacities and mild fibrosis can be elusive on conventional chest x-ray and may only be seen on CT scanning.

Despite our clinical impression to the contrary, noncardiogenic pulmonary oedema, and to lesser extent, ARDS, are common clinical manifestations of drug-induced lung diseases. The former can be mild and self-limited, with rapid recovery following the use of oxygen and diuretic therapy, and discontinuation of the culprit drug. However, the more severe form, usually presenting as fulminant ARDS, as resulting from Ara-C, nitrofurantoin, or amiodarone, can be life-threatening and may require ventilatory support and administration of steroids. Drug-induced ARDS is by and large a diagnosis by exclusion; every effort has to be made to exclude other important causes of ARDS, including sepsis, fulminant pneumonia and aspiration.

**Leflunomide-induced ARDS**

Leflunomide (Arava®) is a disease-modifying anti-rheumatic drug for the treatment of rheumatoid arthritis (RA). The drug had been considered relatively safe for quite a few years since its launch in the U.S. and E.U. in the late 1990s, with common adverse events being nausea, diarrhoea, headache, deranged liver enzymes, rash, alopecia, respiratory infections and hypertension.

However, within a few months after its release in Japan in September 2003, 48 cases of interstitial lung disease (ILD) were found among 4395 patients registered for use in Japan, including 16 fatal cases, giving rise to an incidence of 1.1%, and a fatality of 30%. A stormy course of acute respiratory failure from leflunomide leading to fatality was described despite the use of high dose steroids. Pathological findings at autopsy were that of DAD. DAD manifested as widespread patchy ground glass opacities and/or consolidation also appearing to be the predominant presenting finding radiographically.

There does appear to be a difference in the susceptibility to leflunomide-induced lung toxicity between different ethnic/geographic groups. Subsequent to the Japanese findings, Canadian investigators conducted a retrospective population-based case control epidemiologic study reviewing more than 60,000 Canadian patients with RA on leflunomide between 1998 and 2003 and found a much lower rate of leflunomide-
induced ILD, with the hospitalisation rate for ILD being 8.1 per 10,000 per year (0.08%)12. This discrepancy between Japan and the western countries in the incidence of lung toxicity was also tacitly echoed in a consensus statement written by a multi-disciplinary panel of rheumatologists and general practitioners across the U.K. in late 2004. The consensus statement, published in early 2005, amidst the publicity aroused by the Japanese clinicians/investigators, did not include lung toxicity on their list of adverse events13.

A recent multivariate logistic regression risk analysis of the large Japanese registry revealed the following risk factors for leflunomide-induced lung injury: preexisting ILD, with odds ratio (OR) of 8.17, loading dose administration (OR 3.97), smoking history (OR 3.12) and low body weight (OR 2.91)14. Fatality was most observed in those with severe hypoxaemia requiring mechanical ventilation, high C-reactive protein level, hypoalbuminaemia, and persistent lymphopenia14. Nevertheless, de novo cases of leflunomide-induced lung injury in the absence of the above-mentioned risk factors do occur, as in our patient (Patient 1) and as reported in the literature2.

Current Japanese recommendation places leflunomide as a second-line drug not to be used in smokers, or those with low body weight or with preexisting ILD. Loading dose should not be given14. Careful monitoring for drug toxicity is warranted, and when lung injury develops, accelerated drug elimination using cholestyramine and early use of steroids constitute the mainstay of treatment8.

**Amiodarone-induced ARDS**

The pulmonary toxicity associated with amiodarone therapy is a major factor limiting the widespread use of this very effective anti-arrhythmic agent. Amiodarone-induced lung disease occurs in about 5-10% of patients receiving the drug15, manifesting itself in the form of subacute onset of dyspnoea and CT findings of diffuse interstitial thickening (known as subacute interstitial pneumonitis or fibrosis), or as nodular areas of subpleural consolidation with histological features of bronchiolitis obliterans organising pneumonia, or as acute onset of dyspnoea and fever with CT findings of dependent consolidation typical of ARDS16.

The pharmacokinetic properties of amiodarone predispose the lung to amiodarone toxicity. Firstly, amiodarone is lipophilic with a large volume of distribution, hence the long elimination half-life at 45-60 days and likely storage in organs with high lipid content such as fat, lung and liver15. Secondly, amiodarone’s principal metabolite, desethylamiodarone, accumulates in peripheral tissues providing a sustained reservoir, to the extent that concentrations measured in unfractionated lung parenchyma significantly exceed that of the heart, setting up the lungs up for toxic effects of amiodarone17.

Mechanisms underlying lung toxicity have been poorly understood, likely because of the heterogeneity of amiodarone lung syndromes and corresponding histopathological findings. Two prevalent hypotheses have been (1) adaptative-immune-mediated hypersensitivity reaction based on findings of an inflammatory response similar to inhalation of organic dust15, and (2) direct drug-induced phospholipidosis17, arising from a direct toxic effect of the drug, and characterised by the histopathological findings of “foamy” changes in the alveolar macrophages15. The role of free radicals in the pathogenesis of amiodarone toxicity was further implicated in in vitro and in vivo models of amiodarone lung15, 18.

However, beginning in the mid-to-late 1980s, it became increasingly apparent that the mechanism of lung injury may differ between chronic amiodarone lung disease and acute amiodarone-mediated lung injury. In the former, risk groups have been identified as those who are elderly with pre-existing lung condition on doses of > 400 mg per day17. In the latter, which usually presents as an acute and rapidly deteriorating, and at times fatal, illness, the risk factors revolve around concomitant injury rendering the lung liable to amiodarone’s acute toxic damage. These injuries include angiography19, cardiothoracic surgery20, and lung surgery21,22 with the most common intraoperative denominator being high inspired oxygen concentrations23,24. Patients with preexisting amiodarone lung were found to be at high risk of developing ARDS after cardiothoracic operations20. Patients without surgery but ventilated in the ICU have also been found to be at risk of development amiodarone-induced ARDS25.

Management of amiodarone-induced ARDS is largely supportive. Steroids have been used empirically. In our patient, given the severe ARDS requiring high concentrations of oxygen to support the patient’s oxygenation, empiric use of anti-oxidant therapy was given to minimise further oxygen toxicity. The empiric use of anti-TNF alpha was to combat the likely cytokine storm arising from activation of the alveolar macrophages.

**Pharmacotherapy for ARDS**

Research efforts devoted to identifying the magic bullet for combating ARDS have largely been unproductive. In the Cochrane review of 33 randomised clinical trials involving over 3000 patients, no pharmacotherapy was found to show convincing improvement in survival in patients with ARDS. Use of early high-dose steroids in ARDS was deemed not justifiable26. The use of corticosteroids in late-phase ARDS remains controversial. An earlier, much quoted, small trial of 24 patients showed improved survival when given moderate dose steroids at day 7 or more after the onset of ARDS, during the so-called fibroproliferative phase of ARDS27. A recent multicentre trial of 180 patients however showed higher mortality when given corticosteroids at 14 days or more after the onset of ARDS28. Two recent meta-analyses also arrived at conflicting conclusions: the Australian researchers concluded that the use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes29, while the U.K. researchers concluded that despite a suggestion of reduced mortality and increased ventilator-free days with steroids after the onset of ARDS, a definitive role of corticosteroids in the treatment of ARDS in adults has not been established30. Hence, effective pharmacologic therapy for established ARDS remains controversial and extremely limited.
**Ventilatory Strategy for ARDS**
The key advances in the management of ARDS in the past decade lie largely in our better understanding of the mechanisms underlying ventilator-associated lung injury (VALI), which could further exacerbate the ongoing insult to the lung. One important contributor of VALI is regional alveolar overdistension (volutrauma)\(^3\). Lung-protective strategy using low-tidal volumes at 6 ml per kg of predicted body weight have been proven in the ARDSNET study of over 800 patients to improve ARDS mortality from 40% to 31%.\(^\text{31,32}\) Hypercapnoea is deemed acceptable in this context. Another contributor of VALI is repetitive alveolar collapse with shearing (atelectrauma)\(^3\). However, despite the interest in the use of high levels of PEEP for addressing the problem of atelectrauma and for alveolar recruitment, the clinical studies of high PEEP levels have not been conclusive\(^3\). Current recommendation on recruitment, the clinical studies of high PEEP levels addressing the problem of atelectrauma and for alveolar mechanics\(^3\). Lung-protective strategy using low-tidal volumes at 6 ml per kg of predicted body weight have been proven in the ARDSNET study of over 800 patients to improve ARDS mortality from 40% to 31%.\(^\text{31,32}\) Hypercapnoea is deemed acceptable in this context. Another contributor of VALI is repetitive alveolar collapse with shearing (atelectrauma)\(^3\). However, despite the interest in the use of high levels of PEEP for addressing the problem of atelectrauma and for alveolar recruitment, the clinical studies of high PEEP levels have not been conclusive\(^3\). Current recommendation on the use of PEEP targets at PEEP levels which can be shown to improve rather than exacerbate the lung mechanics\(^3\).

**Unconventional Support for ARDS**
Two unconventional therapeutic modalities for ARDS have been hotly debated in the past decade: inhaled nitric oxide (iNO) and prone positioning. Both modalities have been aimed to address the key pathophysiological derangement of ARDS: mismatching of ventilation (V) and perfusion (Q) leading to gas exchange impairment. iNO serves as a selective pulmonary vasodilator, offering the theoretical advantage of improving perfusion in areas of better ventilation, thereby enhancing V/Q matching. Over 10 randomised trials on iNO have been conducted in the past decade. Meta-analyses in 2003 and in 2007 both showed no significant effect of iNO on hospital mortality, duration of ventilation or ventilator-free days\(^3\). There was however improvement in the oxygenation index which persisted till day 4 of therapy. Renal toxicity was noted. Routine use of iNO is not recommended. Some clinicians may still consider iNO as a temporarising role for those with severe hypoxaemic failure. Pharmacotherapy for ARDS remains very limited.

While iNO may not be readily available in a medical centre, the application of prone positioning can be achieved at the bedside of any ICU. The concept of prone positioning (PP) as a treatment for ARDS arises from the finding of atelectatic lungs in the dependent dorsal regions in a supine patient with ARDS. The reversal from supine to prone positioning allows opening up of the atelectatic lungs, more favourable lung mechanics, better V/Q matching and less VALI\(^3\). Two recent meta-analyses seemed to have arrived at similar conclusions about the clinical efficacy of PP: PP did not improve survival despite an improvement in oxygenation\(^3\). PP is therefore not recommended as routine treatment for ARDS. However, a sustained improvement in oxygenation may support the use of PP in patients with severe hypoxaemia\(^3\).

**Conclusion**
ARDS represents a severe form of acute lung injury requiring intensive care support. The two cases of fulminant drug-induced ARDS presented here represent triumph in combating a critical condition using conventional as well as unconventional wisdom. As drug-induced ARDS is largely a diagnosis by exclusion, thorough search for other possible aetiologies is a must. Clinicians who regularly use these two drugs, leflunomide and amiodarone, need to keep watchful vigilance on the development of lung toxicity in those patients taking these drugs. Concomitant exposure to other possible pulmonary toxins, such as high-flow oxygen, needs to be avoided as much as possible. Ventilatory support using low tidal volume and optimal PEEP is considered the standard of care. Inhaled nitric oxide and prone positioning are not supported by the literature but nevertheless may serve a temporarising role for those with severe hypoxaemic failure. Pharmacotherapy for ARDS remains very limited.

<table>
<thead>
<tr>
<th>Clinicopathological entity</th>
<th>CT findings</th>
<th>Examples of drugs</th>
<th>Prognosis</th>
<th>Respiratory failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Bilateral GGO* and poorly defined centrilobular nodules</td>
<td>Methotrexate, gold therapy, cyclophosphamide, nitrofurantoin, antidepressants</td>
<td>Favourable with use of steroids</td>
<td>Yes but infrequently</td>
</tr>
<tr>
<td>Eosinophilic pneumonitis</td>
<td>Peripheral alveolar infiltrates</td>
<td>Methotrexate, sulfasalazine minocycline, para-aminosalicylic acid, nitrofurantoin, NSAIDs</td>
<td>Favourable with use of steroids</td>
<td>Yes but infrequently</td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia</td>
<td>Irregular linear opacities and GGO in subpleural distribution</td>
<td>Amiodarone, chemotherapy</td>
<td>Poor, fibrosis likely</td>
<td>Usually subacute</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
<td>Bilateral GGO</td>
<td>Methotrexate, interferons, etanercept</td>
<td>Favourable with use of steroids</td>
<td>Yes but infrequently</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>Diffuse air-space consolidation</td>
<td>Bleomycin, busulphan, mitomycin</td>
<td>Poor; death in 50-60% patients</td>
<td>Yes typically</td>
</tr>
<tr>
<td>Non-cardiogenic pulmonary edema</td>
<td>Dependent air-space consolidation</td>
<td>Cytosine arabinoside, beta2 agonists, blood products, narcotics</td>
<td>Favourable</td>
<td>Yes typically</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
<td>Diffuse air-space consolidation</td>
<td>Oral anticoagulants, fibrinolytic agents, platelet glycoprotein inhibitors</td>
<td>Favourable</td>
<td>Yes typically</td>
</tr>
<tr>
<td>Bronchiolitis obliterans organizing pneumonia</td>
<td>Patchy GGO, consolidation and linear opacities</td>
<td>Busulfan, cyclophosphamide, amiodarone, nitrofurantoin, methotrexate</td>
<td>Favourable with use of steroids</td>
<td>Usually subacute</td>
</tr>
</tbody>
</table>

\(^*\text{GGO} = \text{Ground glass opacities}\)
References