CASE BASED DISCUSSIONS

AIP, Jo-1 and ECMO

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CASE PRESENTATION: THE TRAINEE

A 56-year-old woman of South Indian origin presented with 2 weeks of cough, fever, malaise and dyspnoea ,with no response to amoxicillin. She was generally well with mild hypertension, type 2 diabetes controlled with metformin, hypothyroidism and vitamin D deficiency. There were no other relevant exposures, previous imaging, lung function or other investigations.

Initial observations: temperature 38.2°C, blood pressure 112/76 mm Hg, RR 24, SpO_2 94% on 3 L/min of O_2 via nasal cannulae. Examination of the chest revealed bilateral crackles.

Chest X-ray on admission showed bilateral patchy consolidation to the mid zones (figure 1A).

Initial test results are shown below:

White cell count 8.8×10^9/L (4–10).

C-reactive protein 141 (<5).

HIV negative.

Throat swab PCR negative for respiratory viruses.

With a working diagnosis of community-acquired pneumonia, treatment was initiated promptly with intravenous amoxicillin/clavulanic acid and clarithromycin, O_2 via nasal cannulae, intravenous crystalloids and paracetamol, and the patient was admitted to the acute admissions unit. Despite this, the patient failed to improve. Amoxicillin/clavulanic acid was changed to piperacillin/tazobactam, and she was transferred to the high dependency unit (HDU) 4 days after admission due to increasing O_2 requirements. Sputum examination was positive for *Candida* sp only.

INTENSIVE CARE ASSESSMENT

This patient deteriorated despite appropriate medical therapy. She was initially managed on HDU with high flow nasal O_2. However, her respiratory failure progressed rapidly, requiring invasive mechanical ventilation 5 days after admission. CT scan of the chest showed features consistent with ARDS (Acute Respiratory Distress Syndrome) (figure 1B).

There was little change over the following 4 days despite treatment with meropenem, clarithromycin and fluconazole. Ten days after admission, on day

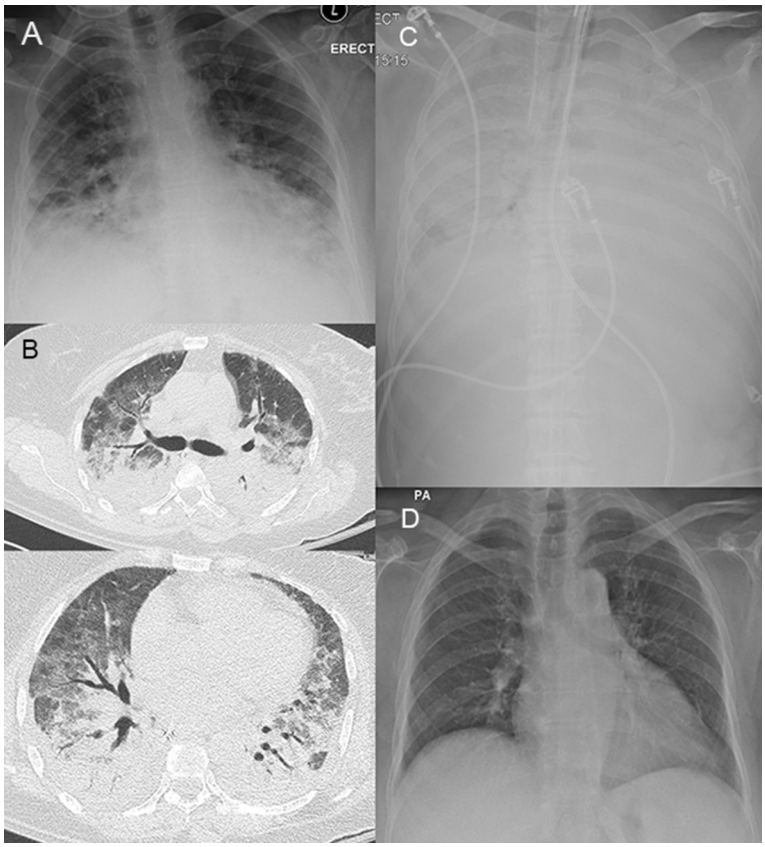

Figure 1 Radiology on admission, initiation of mechanical ventilation, initiation of ECMO, and discharge.

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5 of mechanical ventilation, gas exchange and lung mechanics rapidly deteriorated with a severe hypoxaemic respiratory acidosis (FiO_2 1, SpO_2 72%, $PaCO_2$ 14 kPa) despite paralysis and prone positioning, associated with vasoplegia (norepinephrine 0.7 μg/kg/min). Chest X-ray showed progressive bilateral opacification but no pneumothorax. It was felt that this patient was very unlikely to survive without extracorporeal membrane oxygenation (ECMO). She met UK adult veno-venous (VV) ECMO criteria, and following a meeting with the patient's family, 10 days after admission, VV-ECMO was initiated (figure 1C) with rapid stabilisation of physiological parameters. This allowed further investigation including bronchoalveolar lavage (BAL). CT brain and an echocardiogram were within normal limits.

Three weeks after admission and 11 days after starting ECMO, there had been no response to treatment with anti-infective agents, no positive microbiology or virology investigations, and no alternative diagnosis had been reached. A CT scan of the chest, abdomen and pelvis showed near complete collapse/consolidation of both lungs but no pathology below the diaphragm. Treatment with intravenous methylprednisolone was initiated followed by oral prednisolone with a transient improvement in lung compliance. Percutaneous tracheostomy was performed to allow sedation holds and aid in respiratory rehabilitation. Owing to a widespread National Health Service IT major incident, we only became aware of a positive Anti-nuclear antibody (ANA) (>1/640) and Extractable nuclear antigen (ENA) (anti-Ro, La and Jo-1 antibody positive) 6 weeks after admission.

RESPIRATORY/RHEUMATOLOGY ASSESSMENT

The patient's family provided a history of pain and stiffness in the hands for 2 weeks prior to admission. Examination of the hands revealed ragged cuticles but otherwise normal skin. There was no sclerodactyly or joint deformity. CK (Creatine kinase) was elevated transiently after admission to the intensive care unit, (ICU) prior to administration of steroids. This and the autoimmune profile suggested that the diagnosis was anti-synthetase syndrome (ASSD), a connective tissue disease (CTD) characterised by myositis, Raynaud's phenomenon, mechanic's hands, non-erosive arthritis and interstitial lung disease (ILD). The aminoacyl tRNA synthetases (ARS) are a family of enzymes that catalyse the formation of aminoacyl tRNA from an amino acid and its cognate tRNA prior to peptide synthesis in the ribosome. Eight anti-ARS autoantibodies have been identified including anti-histidyl (anti–Jo-1), anti-threonyl (anti–PL-7) and anti-alanyl (anti–PL-12). Anti–Jo-1 antibody is the most commonly detected. Patients with ASSD are often ANA negative, and anti-ARS autoantibodies may not be included in a standard ENA screen. As with our patient, the peripheral clinical signs are often subtle. Patients with ASSD often require intensive immune suppression. The National Institute for Health and Care Excellence in the UK has approved the use of rituximab in patients with ASSD and dermatomyositis or polymyositis.

This patient had severe ARDS requiring ECMO. She had multiple rounds of antibiotics, and no infective cause was identified despite bacterial, mycobacterial and fungal cultures of BAL fluid and extensive PCR, antigen and serological testing of blood and BAL. There may have been a temporary response to steroids. Her serology points to the diagnosis of acute interstitial pneumonia (AIP) secondary to ASSD. AIP or Hamman-Rich syndrome is a rare, rapidly progressive ILD with a high mortality.[1] AIP has the histopathological appearance of diffuse alveolar damage (DAD) that is indistinguishable from the pattern found in ARDS, and AIP can usefully be considered as idiopathic ARDS. Both AIP and DAD have been described in association with anti–Jo-1-mediated ASSD.[2–4]

Although there is no proven treatment for AIP, there is growing observational data on the use of immune suppression in rapidly progressive CTD-ILD.[2–7] Given how unwell this woman was, and how her prognosis was getting worse by the day, we felt we should start intensive, multimodality induction immune suppression immediately. We therefore initiated treatment with intravenous methylprednislone, intravenous immunoglobulin, intravenous cyclophosphamide and rituximab. There are reports of the successful use of all these therapies in ASSD-ILD,[2–7] although the evidence is generally limited to case series. Moreover, we have had some success using these drugs, in other patients with less severe ASSD-ILD. We also gave prophylactic cotrimoxazole, acyclovir and itraconazole.

INTENSIVE CARE ASSESSMENT

Twelve weeks after admission, the patient was still ECMO dependent, and there had been no significant improvement in lung compliance or radiology, despite treatment with prednisolone, cyclophosphamide every 2 weeks, monthly intravenous immunoglobulin and 2 g of rituximab. Treatment was complicated by three episodes of sepsis. Notwithstanding the lack of respiratory improvement, the patient started to rehabilitate. By 13 weeks, she was sitting out in a chair, on ECMO

RESPIRATORY/RHEUMATOLOGY ASSESSMENT

After 6 weeks of intensive immune suppression therapy, there was no tangible response. However, outpatients with ILD treated with cyclophosphamide may not start to improve until after the second or third monthly dose, and rituximab can also take several weeks to act. We agreed that we would have to allow at least 10 weeks of immune suppression before we could make an assessment of response. The patient developed a skin reaction of increasing severity with each infusion of cyclophosphamide, which was therefore changed to tacrolimus after the fourth dose. Although largely based on case series, there is a growing sense that tacrolimus is an effective maintenance therapy in ASSD-ILD[6], and we have previously used it successfully in rapidly progressive myositis-associated ILD, in combination with other drugs.

INTENSIVE CARE ASSESSMENT

After 14 weeks in hospital and nearly 9 weeks of intensive immune suppression, there were signs of recovery of pulmonary gas exchange despite little radiological improvement. On day 95 of ECMO, 15 weeks after admission to hospital, the patient was successfully decannulated from ECMO. A few days later, she began walking with her ventilator, and tracheal decannulation occurred 4 weeks later. The patient was discharged from ICU, following a 140-day stay, walking independently and with normal cognitive function.

RESPIRATORY/RHEUMATOLOGY ASSESSMENT

The rate of recovery of respiratory function after such a long period of profound respiratory failure and deconditioning was very surprising. Over the next 20 days on the respiratory ward, the patient was weaned off O_2. Although it is entirely possible her recovery was spontaneous and unrelated to immune suppression, we felt this was unlikely and continued maintenance therapy. She was discharged home on prednisolone, tacrolimus and cotrimoxazole. She was reviewed in our joint CTD lung clinic and critical care follow-up clinic and received

further doses of rituximab 6 and 12 months after her first treatment. Her chest X-ray following discharge showed significant improvement (figure 1D), with near normal spirometry (FEV_1/FVC: 1580/1710 (72%)=0.92).

TAKE HOME MESSAGE

AIP secondary to CTD is a potentially treatable condition if the patient can survive long enough for immune-modulatory therapy to take effect, but this may take several weeks. Advanced organ support strategies such as ECMO can make this possible in carefully selected patients accepting significant resource implications. Screening for ANA, anti Cyclic citrullinated peptides (anti-CCP) and autoantibodies, including antisynthetase and myositis-associated antibodies, in all patients presenting with unexplained severe respiratory failure recalcitrant to initial therapy may help in diagnosis, as peripheral clinical signs of systemic rheumatic diseases can be very subtle.

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REFERENCES

1 Travis WD, Costabel U, Hansell DM, *et al*. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013;188:733–48.
2 Jan K, Sriranganathan MK. Acute interstitial pneumonia as first presentation of anti-synthetase syndrome: an atypical case. *Oxford Medical Case Reports* 2018;2018:121–3.
3 Starsmore L, Lams B, Agarwal S, *et al*. S9 Acute inflammatory presentation associates with survival in interstitial lung disease and extracorporeal membrane oxygenation-requiring severe respiratory failure: a single centre case series. *Thorax* 2014;69:A7–8.
4 Zamora AC, Hoskote SS, Abascal-Bolado B, *et al*. Clinical features and outcomes of interstitial lung disease in anti-Jo-1 positive antisynthetase syndrome. *Respir Med* 2016;118:39–45.
5 Lega JC, Reynaud Q, Belot A, *et al*. Idiopathic inflammatory myopathies and the lung. *Eur Respir Rev* 2015;24:216–38.
6 Morisset J, Johnson C, Rich E, *et al*. Management of myositis-related interstitial lung disease. *Chest* 2016;150:1118–28.
7 Andersson H, Sem M, Lund MB, *et al*. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. *Rheumatology* 2015;54:1420–8.