Case report

Hamman-Rich syndrome

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ABSTRACT

Introduction: Acute interstitial pneumonia is a rare but important diagnosis, associated with a high mortality rate and important to identify early.

Case presentation: A 76 year-old individual presented to hospital with a two-week history of shortness of breath, fevers and a non-productive cough.

Treatment initially was for lower respiratory tract infection but returned to hospital three days later as her shortness of breath and peripheral oedema was worsening despite diuretic treatment. Arterial blood gas showed Type 1 Respiratory Failure (pO2 was only 10 kPa on 4 L per minute of oxygen). A computed tomography pulmonary angiography (CTPA) was performed to rule out a pulmonary embolism (PE), which showed multifocal diffuse areas of consolidations bilaterally involving all lobes. Bronchoalveolar lavage cellular analysis was also done.

The patient was treated as nonspecific interstitial pneumonia. This case study highlights this rare condition presenting similarly to common pulmonary conditions.

Discussion: The disease is often preceded by a flu-like prodromal illness lasting one to two weeks prior to presentation. Acute respiratory failure develops in previously healthy individuals without pre-existing lung disease. Diagnosis is also supported by high-resolution computed tomography (HRCT). The effects of high flow ventilation in patients with idiopathic pulmonary fibrosis are associated with improvement in respiratory parameters, improving the efficiency of breathing.

Conclusion: Acute interstitial pneumonitis can be a difficult diagnosis, associated with a high mortality rate up to 60%. It is also difficult to treat; however supportive treatment with high flow oxygen therapy along with pulsatile high dose Corticosteroids can aid recovery.

1. Introduction

Acute interstitial pneumonia is a rare diagnosis and one not often seen in clinical practice with a high mortality up to 60% in the first 6 months from diagnosis.

A 76 year-old lady presented to hospital with two-week history of shortness of breath, fevers and a non-productive cough. There was no history of a rash or arthritis.

She was initially treated as a lower respiratory tract infection (LRTI) but returned to hospital three days later as her shortness of breath and peripheral oedema was worsening despite furosemide therapy. On examination she had crackles at the left base and her arterial blood gas showed type 1 respiratory failure. Her pO2 was only 10 on 4 L per minute of oxygen, pH was 7.439 and pCO2 was 6.32 kPa. A computerised tomography pulmonary angiography (CTPA) was performed to rule out a PE, which showed multifocal diffuse areas of consolidations bilaterally, involving all lobes. Air bronchograms were present.

Chest radiograph (CXR) showed bilateral pulmonary congestion and differential diagnoses included eosinophilic lung disease or nonspecific interstitial pneumonia however as eosinophils were only mildly elevated, it was treated as the latter. This case study highlights a rare condition presenting with symptoms of common pulmonary conditions.

2. Presentation of case

2.1. History of presenting complaint

This was 76 year old lady of Pakistani origin who worked as an electrician exposing herself to silica.

The patient was admitted to hospital with shortness of breath, cough and fever over the last few days. The cough was non-productive, however as she was coughing a lot she developed chest pain. There was no history of a rash, coagulopathy or arthritis.

A chest radiograph (CXR) was performed which showed pulmonary

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congestion and right basal consolidation and was treated as an infective condition. The patient was discharged four days later with antibiotics and diuretics, with the plan to have a high resolution computed tomography (HRCT) scan, outpatient spirometry, followed by a chest clinic review as there seemed to be an underlying chronic lung pathology which needed to be investigated.

However, the patient was then readmitted three days later due to the worsening of her symptoms. A computerised tomography pulmonary angiography (CTPA) was performed which showed extensive peripheral opacities sparing the peri-hilar region and apico-basal gradient pattern. The findings were suggestive of eosinophilic lung disease or nonspecific interstitial pneumonia.

2.2. Relevant past medical history

The patient carried out electronic soldering as her profession. During her work she was exposed to silica. She was also a passive smoker as her husband whom she lived with, was a smoker.

2.3. Investigations

The bronchoalveolar lavage (BAL) from the right lower lobe laboratory analysis showed approximately 10mls of cloudy pink fluid. Microscopy result was benign respiratory epithelial cells, alveolar macrophages and scattered mixed inflammatory cells present. No malignant cells were seen. It is known in interstitial pneumonitis the diffuse alveolar damage is commonly caused by fibroblast invasion into the tissue and proliferation. TB culture and gram stain bacteriology from the BAL were also negative. However candida albicans was noted on mycology, which was thought to be likely a contaminant cause. Blood cultures and virology screen were also negative. However her (ANCA) perinuclear was mildly positive. Her serum ACE was 50u/l and IgE was elevated (512u/l). These results may occur in treated, inactive or relapsing microscopic polyangiitis (including its renal-limited variant), granulomatosis with polyangiitis and Churg-Strauss syndrome. Patients with systemic vasculitis in whom ANCA recur are more likely to relapse. It is also common in inflammatory bowel disease and other autoimmune diseases where its clinical significance is unclear. If ANA is present this may be a false positive result.

Bloods: on admission:

White cell count (WCC) 15 C-Reactive Protein (CRP) 77
7 days later WCC 8 CRP 29
34 days later WCC 18 CRP 42

The echocardiogram revealed pulmonary hypertension. Autoimmune serology were sent (antinuclear antibodies, antineutrophil cytoplasmic antibodies, extractable nuclear antigen antibodies, IgE antibodies, aspergillus antibodies and precipitins, anti Ro, anti La, anti ribonucleoprotein, anti Smith, anti Jo1 and anti SCL-70 antibodies including anti nuclear antibody (liver) gastric parietal cell IgG antibody, smooth muscle IgG antibody, liver/kidney microsomal antibody and mitochondrial antibody) were all negative. A bronchoscopy was performed to exclude TB and fungal infections.

Imaging:

The extensive consolidation in the right mid zone and left base has increased since the previous film. There is loss of volume in both lungs. Atypical infection as well as acute, rapidly progressive pulmonary fibrosing alveolitis should be suspected.

The extensive parenchymal changes in both lungs are noted. No significant difference is identified compared to a previous film.

CXR Poor inspiratory effort with small volume lungs. Extensive interstitial and airspace shadowing in the right mid zone and both lung
bases. There is a small left pleural effusion.

CXR Suboptimal aspiration with small volume lungs. There is consolidation in the right mid zone and left lower lobe. Small bilateral pleural effusions are present. A background of bilateral pulmonary congestion is present.

CT Pulmonary Angiogram:

CT imaging revealed:

Presence of extensive peripheral opacities of the lungs which are sparing the peri-hilar regions and show an apico-basal gradient pattern. The findings could be due to eosinophilic lung disease or non specific interstitial pneumonia (NSIP). Small bilateral pleural effusions seen. Reactive, borderline mediastinal lymph nodes seen. The heart size is normal and there is no pericardial effusion. The aorta and great vessels are normal in calibre. The central pulmonary arteries are patent with no evidence of embolus. The trachea and mainstem bronchi are patent. The oesophagus is normal in course and calibre. There is no pneumothorax. Scans through the upper abdomen are unremarkable. The osseous structures in the chest are intact. In comparison to CT PA of 37days prior there has been worsening of widespread patchy consolidation.

There are multifocal diffuse areas of consolidations bilaterally, involving all lobes. Air bronchograms are present. No pulmonary embolism.

No pleural/pericardial effusion.

No enlarged mediastinal or axillary lymph nodes. Small mediastinal lymph nodes noted.

These radiological findings were suggestive for eosinophilic lung disease or non-specific interstitial pneumonia (NSIP) as reviewed at the Lung Multidisciplinary Team meeting.

2.4. Differential diagnosis

Differential diagnoses included infective causes, aspiration, drugs, autoimmune conditions particularly vasculitis such as Churg-Strauss syndrome and acute interstitial lung disease.

Radiological differential diagnosis included acute respiratory distress syndrome (ARDS), Churg Strauss and cryptogenic organizing pneumonia (COP).

2.5. Treatment

On admission the patient was given a one week course of Co-amoxiclav which did not seem to improve the patient's cough. Therefore the patient was booked for follow-up in respiratory clinic with HRCT and outpatient spirometry.

One month later the patient returned to hospital with worsening of symptoms and was given two week course of intravenous (IV) Tazocin and Meropenem. The patient was discussed with the center of excellence in interstitial lung disease, who advised on stopping any possible triggers for interstitial pneumonitis (Aspirin and Omeprazole were
the only possible medications reported in the literature to trigger Acute Interstitial Pneumonia (AIP) and adding Linezolid and Vancomycin for possible resistant organisms.

Following the interventions above the patient received a pulse therapy with methyl-Prednisolone of 1g IV for three consecutive days, followed by hydrocortisone IV and a prolonged course of Corticosteroids (Prednisolone 60mg daily, weaned to 30mg daily over a three month period). The patient's oxygen requirements reduced and she made good progress with the physiotherapists.

2.6. Outcome and follow up

She was seen in the oxygen clinic three weeks after discharge requiring only 3L/min of oxygen 24 hours a day saturating at 98%. Another key element of the treatment consisted of high flow humidified heated oxygen therapy delivered via optiflow. This has helped prevent admission to ITU for intubation with a positive effect on acute hypoxemic respiratory failure and secretions management. Optiflow was delivered on the respiratory ward at a 60% Fio2, with a 60L/min flow and the patient's temperature was maintained at 37° celsius. Oxygen requirement improved over the 6 weeks admission to hospital, requiring 3L/min long term oxygen therapy (LTOT) on discharge. She had a further sleep study on 2L/min oxygen and was advised to continue Prednisolone 30mg daily for a further three months.

3. Discussion

Acute interstitial pneumonia also known as Hamman-Rich Syndrome, is a rare and severe form of idiopathic interstitial lung disease [1] originally described by Hamman and Rich in 1935. This disease is characterised by the following criteria [2]:

1) Acute onset of respiratory failure, similar to ARDS
2) Bilateral lung infiltrates on radiographs
3) Diffuse alveolar damage (DAD) on lung histopathology
4) The absence of an identifiable cause or predisposing condition

The disease is often preceded by a flu-like prodromal illness that lasts one to two weeks prior to presentation. The most common symptoms include dyspnoea, cough and fever [3]. Patients may also experience fatigue and myalgia. Acute respiratory failure develops in previously healthy individuals without pre-existing lung disease. The signs and symptoms of AIP include tachypnoea, dyspnoea, cyanosis, crackles and wheezes [2]. AIP mainly affects patients between the ages of 50 and 55 years, with an equal number of men and women affected [3] and no known risk factors [4].

Diagnosis requires clinical presentation of acute respiratory failure with histological finding of DAD from a lung biopsy [5]. In the early stages of DAD, hyaline membranes are formed. As the disease progresses, hyaline membranes are resorbed and fibroblasts begin to migrate into the alveolar septa and proliferate rapidly, leading to high Ki67 labeling index by immunohistochemistry. In later stages, interstitial thickening by fibroblasts is seen. Atelectasis, hyperplasia of type II pneumocytes, oedema within the alveolar septa and thrombi within small pulmonary arteries may also be seen [2].

If we compare to the cytology findings in this patient, the cytology showed alveolar macrophages and scattered mixed inflammatory cells. Diagnosis is also supported by HRCT. The main radiological finding is the presence of bilateral and generally symmetrical lung infiltrates, which vary from patchy to diffuse. HRCT findings, which are non-specific, include bilateral ground-glass opacities and/or bilateral airspace consolidation [2].

A review of thirty-six cases found ground glass abnormality, traction bronchiectasis and architectural distortion in all cases [6]. Other radiological features included: consolidation (92%), interlobular septal thickening (89%), thickened bronchovascular bundles (86%), nodular opacities (86%), honeycombing (14%) and lymphadenopathy (8%) [7,8]. In this case the patient did have generally symmetrical lung infiltrates and there was bilateral airspace consolidation involving all lobes. In addition honeycombing and mediastinal lymphadenopathy was seen in this patient's HRCT.

Pulmonary function tests show a restrictive pattern with reduced diffusing capacity of the lungs for carbon monoxide (D,CO) [9]. Peripheral neutrophilic leucocytosis is a common, but nonspecific, laboratory finding. Increased serum creatinine and reduced haematocrit levels may also be seen and are considered unfavorable prognostic factors [4].

Bronchoalveolar lavage (BAL) typically shows neutrophilia with occasional atypical type II pneumocytes and extracellular amorphous material, which represents fragments of hyaline membranes [1,5]. BAL may also be useful to differentiate AIP from other pneumonias; for example, the absence of eosinophils in the BAL fluid suggests against a diagnosis of acute eosinophilic pneumonia. Similarly, the absence of lymphocytosis and foamy macrophages may aid to exclude cryptocgenic organizing pneumonia and drug-induced pulmonary toxicity [1].

The biopsy specimen can also be used to exclude known causes of ARDS or DAD, which is essential before the diagnosis of AIP can be made. The main aetiologies to exclude include infections, connective tissue diseases and drug toxicities. Acute exacerbations of idiopathic pulmonary fibrosis should also be excluded. Clubbing is often seen in these patients, however this is not a feature of AIP [2].

The main focus in the treatment of AIP is supportive care including supplemental oxygen and mechanical ventilation. Previous case reports have described benefit from the use of high dose intravenous Corticosteroid therapy, however, its efficacy is unclear [5]. Alternative immunosuppressive therapies, such as Cyclophosphamide and Vincristine, and lung transplantation have also been reported in the literature with limited success and/or uncertain effectiveness [9–11].

The effects of high flow on ventilation in patients with idiopathic pulmonary fibrosis showed mean pressure to be significantly elevated. This was associated with improvement in respiratory parameters, including breathing rate and minute volume [12]. This aids with the relief of breathing-related work and increases efficiency of breathing [12].

However larger randomized controlled trials are needed to support these promising findings [12].

The particularity of this case consisted of a clinical and radiological diagnosis of AIP sustained by bronchoscopy results and a high serum IgE and eosinophilia levels. The diagnosis in this case is further supported, as there was a positive outcome after supportive and immunosuppressive treatment. A common characteristic for AIP, although for academic purpose a lung biopsy would have been useful, the patient's rapidly deteriorating clinical condition has made the historical diagnosis difficult.

Even with intensive treatment, the prognosis of AIP remains poor as seen in the published case reports, with more than sixty percent of patients dying within six months of presentation [10]. A study reported higher survival rates with early aggressive diagnostic approach [1], lung-protective mechanical ventilation, and the early administration of immunosuppressive therapy [3].

High-dose intravenous Methylprednisolone given in a ‘pulsatile’ manner (1–2 g once weekly or biweekly) has been used, but has no proven advantage over oral Corticosteroids [13].

4. Conclusion and learning points

1) Non-specific interstitial pneumonia can present similarly to that of an infective cause of lung pathology or thromboembolic cause. However a CT showing multifocal diffuse areas of consolidations bilaterally, involving all lobes should prompt the possibility of non-specific interstitial pneumonia. This is particularly important if patient is not improving with antibiotics.

2) Bronchoalveolar lavage typically shows neutrophilia with
occasional atypical type II pneumocytes and hyaline membranes, which can aid diagnosis.

3) The presence of increased serum creatinine and reduced haematocrit levels may be considered to be unfavorable prognostic factors in this condition.

4) The effects of high flow oxygen therapy on hypoxemic respiratory failure in the context of acute interstitial lung disease have prevented mechanical ventilation and led to a positive outcome.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmcr.2017.10.008.

References

[1] A. Bonaccorsi, A. Cancellieri, M. Chilosi, R. Trisolini, M. Boaron, N. Crimi, et al., Acute interstitial pneumonia: report of a series, Eur. Respir. J. 21 (1) (2003) 187–191.

[2] S. Mukhopadhysy, J. Parambil, Acute interstitial pneumonia (AIP): relationship to Hamman-Rich Syndrome, diffuse alveolar damage (DAD), and acute respiratory distress syndrome (ARDS), Semin. Respir. Crit. Care Med. 33 (5) (2012) 476–485.

[3] J. Bruminhent, S. Yassir, J. Pippim, Acute interstitial pneumonia (Hamman-Rich syndrome) as a cause of idiopathic acute respiratory distress syndrome, Case Rep. Med. (2011) 2011.

[4] A. Cancellieri, G. Dalpiaz, M. Maffessanti, A. Pesci, R. Pelverosi, M. Zompatori, Diffuse Lung Diseases, Springer, Milan, 2006.

[5] U. Costabel, R.M. du Bois, J.J. Egan (Eds.), Diffuse Parenchymal Lung Disease, Karger, Basel, 2007.

[6] K. Ichikado, M. Suga, N. Muller, H. Taniguchi, Y. Konno, M. Akira, et al., Acute interstitial pneumonia: comparison of HRCT findings between survivors and non-survivors, Am. J. Respir. Crit. Care Med. 165 (2002) 1551–1556.

[7] N. Mihara, T. Jokoh, K. Ichikado, O. Honda, M. Higasi, N. Tomiyama, et al., Can acute interstitial pneumonia be differentiated from bronchiolitis obliterans organizing pneumonia by HRCT? Radiat. Med. 15 (2000) 299–304.

[8] N. Tomiyama, N. Muller, T. Jokoh, J. Cleverly, S. Ellis, M. Akira, et al., Acute respiratory distress syndrome and acute interstitial pneumonitis: comparison of thin section CT findings, J. Comput. Assist. Tomogr. 25 (2001) 28–33.

[9] J.S. Pourleekis, K.K. Brown, C.D. Cool, D.A. Young, R.M. Cherniack, T.E. King, et al., Acute interstitial pneumonitis. Case series and review of the literature, Med. Baltim. 79 (6) (2000) 369–378.

[10] D. Bouros, A. Nicholson, V. Polychronopoulos, Bois R, Acute interstitial pneumonia, Eur. Respir. J. 15 (2) (2000) 412–418.

[11] D.S. Robinson, D.M. Geddes, D.M. Hansell, C.D. Shee, C. Corbishley, A. Murday, et al., Partial resolution of acute interstitial pneumonia in native lung after single lung transplantation, Thorax 51 (1996) 1158–1159.

[12] J. Braunlich, D. Beyer, D. Mai, S. Hammerschmidt, H.-J. Seyfarth, H. Wirtz, Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients, Respiration 85 (2013) 319–325.

[13] A. Gulsvik, F. Kjelsberg, A. Bergmann, S.S. Froland, K. Rootwelt, J. Vale, et al., Dose intravenous methylprednisolone pulse therapy as initial treatment in cryptogenic fibrosing alveolitis: a pilot study, Respiration 50 (1986) 252–257.