



Acute interstitial pneumonia triggered by strenuous exercise

Frosina Markoska^a, David Lestan^a, Matjaz Turel^a, Matevz Harlander^{a,b,*}

^a Department of Pulmonary Diseases, University Medical Centre Ljubljana, Zaloska cesta 2, 1000, Ljubljana, Slovenia

^b Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000, Ljubljana, Slovenia

ARTICLE INFO

Keywords:

Acute interstitial pneumonia
Exercise
Methylprednisolone
Mycophenolate mofetil

ABSTRACT

Acute interstitial pneumonia (AIP) is a rare and severe form of idiopathic interstitial lung disease. Treatment is primarily supportive with supplemental oxygenation and mechanical ventilation. Prognosis is poor, but long-term survival is possible after recovery from AIP. We present a case of a 48-years-old previously healthy female who was admitted due to acute shortness of breath and respiratory failure which started three days after she ran a half-marathon. After excluding infectious causes and connective-tissue diseases, a presumptive diagnosis of AIP was made based on clinical and radiological characteristics. The patient was successfully treated with high-dose corticosteroids and mycophenolate mofetil.

1. Introduction

Acute interstitial pneumonia (AIP), also known as Hamman-Rich Syndrome, is a rare and severe form of idiopathic interstitial lung disease originally described by Hamman and Rich in 1935 [1]. AIP describes an idiopathic clinicopathological condition, characterised clinically by an interstitial lung disease causing rapid onset of respiratory failure, which is distinguishable from the other more chronic forms of interstitial pneumonia [2]. The disease is identified by the acute onset of respiratory failure, bilateral lung infiltrates, diffuse alveolar damage (DAD) on lung histopathology and the absence of an identifiable cause or predisposing condition [3].

We present a case report of a patient with AIP seemingly triggered by strenuous physical exercise.

2. Case report

A 48 years old female without a history of chronic diseases or drug abuse and with a recently documented normal chest radiograph (Fig. 1) was admitted to the hospital due to acute shortness of breath, respiratory failure and suspected pneumonia. Three days before the first symptoms appeared she ran a half-marathon annually organised in Ljubljana, Slovenia. First symptoms included fever (up to 39 °C), chills and muscle pain. Initially, she received azithromycin, after which there was no improvement. Moreover, a dry cough appeared. After seven days she was referred to the hospital. Upon admission, we noted bilateral opacities on chest radiograph, increased CRP (155 mg/L) and a low level of

procalcitonin (0,06 mcg/L). Amoxicillin with clavulanic acid was started without success. Her condition quickly deteriorated. On the fourth day after admission, CT showed extensive bilateral ground glass opacities and alveolar consolidations (Fig. 2). Heart echography showed normal heart function. Bronchoscopically obtained microbiological samples were negative for pathogenic bacteria (including negative PCR for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* spp.), fungi, respiratory viruses (PCR negative for influenza A and B, RSV, parainfluenza, rhinoviruses, metapneumovirus, adenoviruses, coronaviruses, bocavirus and enteroviruses) and *Pneumocystis jirovecii*. The transbronchial biopsy was not attempted due to severe respiratory failure. Immuno-serological investigations (anti-ANA, anti-ENA panel extended for polymyositis/systemic sclerosis and myositis related antibodies, ANCA panel, anti-GBM, anti-dsDNA, RF, anti-CCP, levels of C3c and C4, total serum classic haemolytic complement (CH₅₀) test, alternative haemolytic complement (AP₅₀) test, mannose-binding lectin deficiency test, total and specific Ig levels) were negative.

The patient received intravenous therapy with piperacillin/tazobactam and methylprednisolone at an initial dose of 125 mg a day. After further respiratory deterioration (blood gas analysis on 60% venturi mask: pH 7.42, pO₂ 8.4 kPa and pCO₂ 5.4kPa; blood gas analysis on non-invasive ventilation using 35% O₂, PEEP 5 cm H₂O and pressure support 5 cm H₂O: pH 7.37, pCO₂ 6.6 kPa and pO₂ 9.0kPa) pulses of methylprednisolone (1000 mg for five days) were given, followed by gradual tapering. There was a partial improvement, but opacities remained (Fig. 3), and oxygen therapy was required. A therapeutic trial with mycophenolate mofetil (MMF) in the initial dose of 500 mg twice daily

* Corresponding author. Department of Pulmonary Diseases, University Medical Centre Ljubljana, Zaloska cesta 2, 1000, Ljubljana, Slovenia.

E-mail address: matevz.harlander@kclj.si (M. Harlander).

<https://doi.org/10.1016/j.rmcr.2020.101077>

Received 4 January 2020; Received in revised form 15 April 2020; Accepted 5 May 2020

Available online 7 May 2020

2213-0071/© 2020 The Authors.

Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Fig. 1. Normal chest radiograph that was taken after a bicycle accident approximately three months before the onset of the disease.

with an increase to 1000 mg twice daily was started. After that, her clinical and radiological picture started to improve gradually (Fig. 4). Oxygen therapy could be discontinued. A follow-up 12 months after the beginning of the disease showed significant regression of infiltrates on chest radiograph and CT (Fig. 5). Lung function tests showed normal FVC and FEV₁ (84% and 89%, respectively) and mild-moderate impairment of DLco (59%).

3. Discussion

AIP is a rare form of idiopathic diffuse lung injury that affects previously healthy individuals. In most cases, it is clinically indistinguishable from other causes of acute respiratory distress syndrome (ARDS). To confirm AIP, histological confirmation is required [4]. However, this likely leads to underdiagnosis of the condition, as respiratory failure is often prohibitive of lung biopsy. Our patient met the criteria for moderate acute respiratory distress syndrome (ARDS) [5], but it was not possible to perform biopsy due to respiratory failure. Nevertheless, an extended panel of examinations did not show alternative diagnosis in a previously healthy patient, so a presumptive diagnosis of AIP was made. Moreover, secondary ARDS is often accompanied with multiorgan failure while this is seldom seen in AIP [6]. Known causes of DAD are infections, connective tissue diseases, drugs, aspiration, non-infectious complications of organ transplantation and oxygen toxicity [4].

Another possible differential diagnosis in our case was cryptogenic organizing pneumonia (COP), also a disease of idiopathic origin. Clinical manifestations of COP can begin with a flu-like illness and often protracted dyspnoea, albeit there are also rapidly progressive cases. Because these symptoms are nonspecific, diagnosis is often delayed for more than 6 weeks [7]. Most common chest X-ray and CT patterns of COP are multiple alveolar opacities (typical COP), solitary opacity (focal COP) and infiltrative opacities (infiltrative COP). Opacities are usually peripheral or peribronchial, patchy and asymmetric, with air bronchograms and with a tendency to migration [8]. In AIP there are typically diffuse ground-glass opacities with a mosaic pattern and alveolar consolidations. Changes are usually bibasilar, but may also involve other areas [8]. In a study of diagnostic accuracy of high-resolution CT for the diagnosis of interstitial lung diseases, the diagnosis was correct in 79%

cases of COP and 65% cases of AIP [9]. While in our case COP could not be ruled out completely, the rapid onset of the disease, radiological features and slow response to corticosteroids were more compatible with the diagnosis of AIP.

We did not find any reports in the literature identifying exercise as a potential cause of ARDS/AIP. There are several reports of pulmonary oedema induced by marathon running [10]. In a study by Zavorsky et al., up to 46% of subjects (predominantly women) had chest X-ray signs of at least mild pulmonary interstitial oedema immediately after running a marathon [11]. Hemodynamic changes during exercise are thought to be the main cause – a theory supported by a documented fast resolution of oedema after the exercise [11]. On the other hand, mechanical stress or electrolyte disturbances may also play a role in some cases [10]. Strenuous exercise may influence the immune system. Initially, there are transient increases of pro-inflammatory cytokines and peripheral lymphocytosis, but this is followed by an increase of anti-inflammatory cytokines and lymphopenia. Moreover, exhaustive exercise can reduce the number of peripheral type-1 T-lymphocytes and their capacity to produce pro-inflammatory interferon- γ and increase the number of peripheral type-2 and regulatory T-lymphocytes, which produce anti-inflammatory cytokines (such as IL-4 and IL-10) [12]. Additionally, the natural killer cells activity may become depressed [13]. Dysregulation of normal hemodynamic or immunological response may have played a role in the development of the lung pathology in our case.

Treatment of AIP is primarily supportive with supplemental oxygenation and mechanical ventilation. In the published series of cases, most patients received high-dose corticosteroids. In some cases, cyclophosphamide was additionally used. Nonetheless, the prognosis remained poor. Avnon et al. collected data from 8 case series (in total 104 patients), which showed a mortality rate of 54,3% [14]. Based on the available data, the value of immunosuppressive therapy cannot be assessed. Some authors advocate the early introduction of corticosteroid therapy with the argument that corticosteroids therapy is likely ineffective in the fibrotic phase of AIP but might have a role in the inflammatory phase [15]. Recently, treatment with extracorporeal membrane oxygenation was successfully used as a bridge to recovery in AIP [16]. Long-term survival is possible after recovery from AIP, with documented



Fig. 2. Chest radiograph and CT three days after the admission (ten days after initiation of symptoms), showing symmetrical bilateral ground-glass opacities and alveolar consolidations in the dependent areas of the lung.

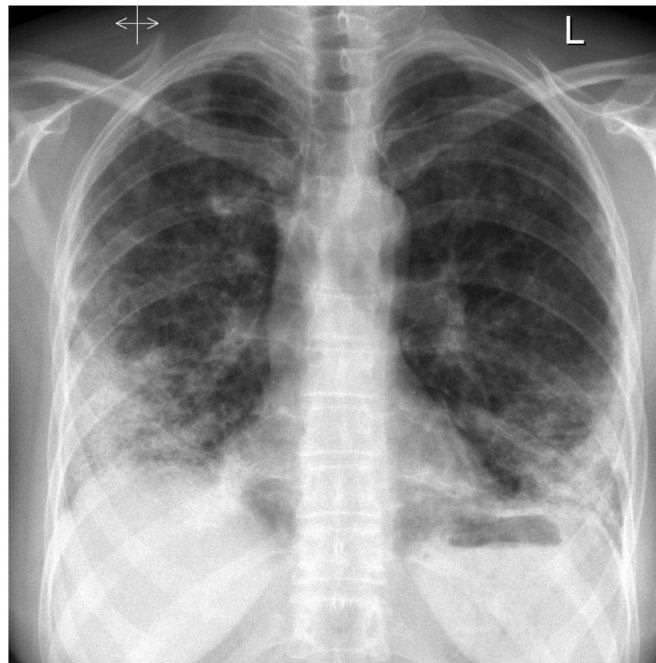


Fig. 3. Chest radiograph six weeks after presentation. Persistent infiltrates bilaterally are seen, showing limited improvement after high-dose corticosteroid therapy.

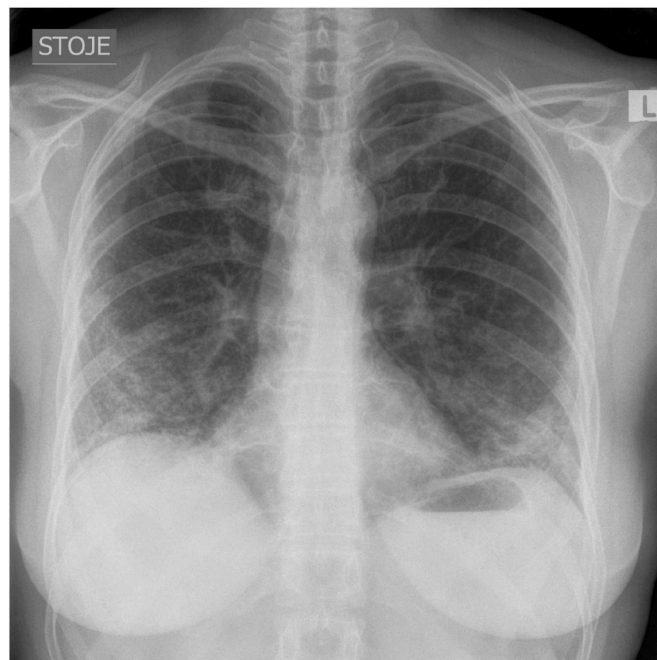


Fig. 4. Chest radiograph ten weeks after presentation, showing improvement after eight weeks of corticosteroids + mycophenolate mofetil.

survival up to 2–4 years after diagnosis [4]. Progression of pulmonary fibrosis was reported in most cases [4].

In our case, the patient was prescribed MMF after unsatisfactory recovery with corticosteroid therapy. There are no reports in the literature about the efficacy of this therapy in AIP. However, it is occasionally used in the treatment of nonspecific interstitial pneumonia (NSIP) as an add-on to corticosteroid therapy [17]. It is also used in the treatment of connective tissue disease-associated interstitial lung disease (CTD-ILD). In CTD-ILD, MMF was associated with improvement in

lung function (FVC and DLco) in patients with non-UIP HRCT pattern and with stabilisation of lung function in patients with UIP pattern [18]. Nonetheless, the efficacy of MMF needs to be confirmed in further studies. A recent small randomized placebo-controlled study that included patients with mild systemic sclerosis-related interstitial lung disease did not confirm benefits of MMF over placebo [19].

To summarise, we presented a case of a previously healthy patient who was admitted due to rapidly progressive interstitial pulmonary disease after running a half-marathon. A presumptive diagnosis of AIP



Fig. 5. Chest radiograph and CT after 1 year of follow-up, showing near-complete regression of infiltrations and minor residual fibrotic changes bilaterally.

was made given that lung biopsy was not considered safe. The patient was successfully treated with corticosteroids and mycophenolate mofetil.

Declaration of competing interest

F. Markoska reports no conflict of interests.

D. Lestan reports personal fees from Boehringer Ingelheim and Roche outside the submitted work.

M. Turel reports personal fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva outside the submitted work.

M. Harlander reports personal fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva outside the submitted work.

References

- [1] L. Hamman, A.R. Rich, Fulminating diffuse interstitial fibrosis of the lungs, *Trans Am Clin Climatol Assoc* 51 (1935) 154–163.
- [2] D. Bouros, A.C. Nicholson, V. Polychronopoulos, R. du Bois, Acute interstitial pneumonia, *Eur. Respir. J.* 15 (2) (2000 Feb) 412–418.
- [3] W.D. Travis, U. Costabel, D.M. Hansell, T.E. King, D.A. Lynch, A.G. Nicholson, 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.* 188 (6) (2013) 733–748.
- [4] S. Mukhopadhyay, 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 (2012 Sep 21) 476–485, 05.
- [5] ARDS Definition Task Force, V.M. Ranieri, G.D. Rubenfeld, B.T. Thompson, N. D. Ferguson, E. Caldwell, et al., Acute respiratory distress syndrome, *J. Am. Med. Assoc.* 307 (23) (2012 Jun 20) 2526–2533.
- [6] A. Qefatieh, C.H. Stone, B. DiGiovine, G.B. Toews, R.C. Hyzy, Low hospital mortality in patients with acute interstitial pneumonia*, *Chest* 124 (2) (2003 Aug) 554–559.
- [7] J.-F. Cordier, Cryptogenic organising pneumonia, *Eur. Respir. J.* 28 (2) (2006 Aug 1) 422–446.
- [8] S. Palmucci, F. Roccalva, S. Puglisi, S.E. Torrisi, V. Vindigni, L.A. Mauro, et al., Clinical and radiological features of idiopathic interstitial pneumonias (IIPs): a pictorial review, *Insights Imaging* 5 (3) (2014 Jun 22) 347–364.
- [9] T. Johkoh, N.L. Muller, Y. Cartier, et al., Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients, *Radiology* 211 (1999) 555–560.
- [10] J. Aoun, K. Dgayli, C. Abou Zeid, G. Wong, P. LaCamera, Pulmonary edema during the Boston marathon, *Respir Med case reports* 27 (2019) 100845.
- [11] G.S. Zavorsky, E.N.C. Milne, F. Lavorini, J.P. Rienzi, K.M. Lavin, A.M. Straub, et al., Interstitial lung edema triggered by marathon running, *Respir. Physiol. Neurobiol.* 190 (2014 Jan 1) 137–141.
- [12] D.M. Shaw, F. Merien, A. Braakhuis, D. Dulson, T-cells and their cytokine production: the anti-inflammatory and immunosuppressive effects of strenuous exercise, *Cytokine* 104 (2018 Apr) 136–142.
- [13] B.K. Pedersen, H. Ullum, NK cell response to physical activity: possible mechanisms of action, *Med. Sci. Sports Exerc.* 26 (2) (1994 Feb) 140–146.
- [14] L.S. Avnon, O. Pikovsky, N. Sion-Vardy, Y. Almog, Acute interstitial pneumonia–hamman-rich syndrome: clinical characteristics and diagnostic and therapeutic considerations, *Anesth. Analg.* 108 (1) (2009 Jan) 232–237.
- [15] G.Y. Suh, E.H. Kang, M.P. Chung, K.S. Lee, J. Han, M. Kitaichi, et al., Early intervention can improve clinical outcome of acute interstitial pneumonia, *Chest* 129 (3) (2006 Mar) 753–761.
- [16] G. Gonçalves-Venade, N. Lacerda-Príncipe, R. Roncon-Albuquerque, J.A. Paiva, Extracorporeal membrane oxygenation for refractory severe respiratory failure in acute interstitial pneumonia, *Artif. Organs* 42 (5) (2018 May) 569–574.
- [17] J. Lee, Y.H. Kim, J.Y. Kang, Y. Jegal, S.Y. Park, Korean interstitial lung diseases study group on behalf of KILDS. Korean guidelines for diagnosis and management of interstitial lung diseases: Part 3. Idiopathic nonspecific interstitial pneumonia, *Tuberc. Respir. Dis.* 82 (4) (2019 Oct) 277–284.
- [18] A. Fischer, K.K. Brown, R.M. Du Bois, S.K. Frankel, G.P. Cosgrove, E.R. Fernandez-Perez, et al., Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease, *J. Rheumatol.* 40 (5) (2013 May) 640–646.
- [19] G.S.R.S.N.K. Naidu, S.K. Sharma, M.B. Adarsh, V. Dhir, A. Sinha, S. Dhooria, et al., Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial, *Rheumatol. Int.* 40 (2) (2020 Feb 7) 207–216.