Received: 1 December 2020 | Revised: 26 May 2021 | Accepted: 31 May 2021

DOI: 10.1002/ccr3.4468

CASE REPORT

Clinical Case Reports Open Access WILEY

Adverse reaction of methylprednisolone pulse therapy: Acute respiratory distress syndrome

Fereshteh Ashtari[1] | **Rasool Soltani**[2] | **Shervin Shokouhi**[3,4] | **Ali Rismanbaf**[5] | **Somayeh Hajiahmadi**[6] | **Atousa Hakamifard**[4]

[1]Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

[3]Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4]Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[5]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

[6]Department of Radiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence
Atousa Hakamifard, Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: atousahakamifard@sbmu.ac.ir

Abstract

Methylprednisolone pulse therapy has significant anti-inflammatory effects in multiple sclerosis. Acute respiratory distress syndrome as a probable adverse effect of methylprednisolone pulse therapy in MS patients should be considered.

KEYWORDS

acute respiratory distress syndrome, ARDS, methylprednisolone, multiple sclerosis

1 | INTRODUCTION

Methylprednisolone pulse therapy is one of the most common treatments in exacerbation of multiple sclerosis. In this case report, we present a 25-year-old woman with a 5-year history of MS, who developed acute respiratory distress syndrome after methylprednisolone succinate pulse therapy.

Glucocorticoids are a class of corticosteroids first identified in the 1940s.[1] These agents have significant anti-inflammatory effects and were introduced as an effective multiple sclerosis (MS) treatment due to their beneficial effects on autoimmune diseases in the clinical practice.[1] Mechanisms that may be involved in the therapeutic effects of glucocorticoids in patients with MS include inhibitory effects on pro-inflammatory cytokines, inflammatory T cells, and phagocytic antigen-presenting cells, such as macrophages.[2] Today, the use of glucocorticoids in MS treatment is limited to manage the symptoms of exacerbations. Among the glucocorticoids, methylprednisolone pulse therapy (MPPT), 1 g daily intravenously (IV) for 3–5 days, is one of the most common and effective treatments of MS flare-ups. In addition to its beneficial effects, MPPT has several side effects including psychiatric abnormalities, sleep disorders, hyperglycemia, hypertension, hypokalemia, and peptic ulcer.[1,2] However, to our knowledge, pulmonary complications, including acute respiratory distress syndrome (ARDS), have not been reported as adverse drug reactions (ADR) for methylprednisolone pulse therapy in the treatment of MS exacerbation. In this case report, we present a patient with a 5-year history of MS who developed ARDS after methylprednisolone succinate pulse therapy for controlling disease flare. Written informed consent was obtained from the patient. This case report was approved by the ethics committee of Isfahan University of Medical Science.

2 | CASE REPORT

In May 2019, a 25-year-old woman with a 5-year history of relapsing-remitting MS being under treatment with glatiramer acetate (40 mg SC three times weekly) was referred to our hospital due to an exacerbation of MS. The patient's vital signs were stable (PR: 83/min, RR: 16/min, T: 37℃, and BP: 110/70 mm Hg) at the time of admission; however, paresthesia and paraparesis were detected on physical examination.

TABLE 1 Laboratory findings on the second day of methylprednisolone pulse therapy (MPPT)

Measure	First time MPPT	Second time MPPT
White blood cells (mm^3)	14900	23000
PMN (%)	78%	82%
Hemoglobin (g/dl)	11.7	12
Platelet (mm^3)	310000	267000
LDH	610	540
Creatinine (mg/dl)	0.8	0.7
CRP (gr/dl)	59	46

Abbreviations: CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; LDH, lactate dehydrogenase; PMN, polymorphonuclear.

Upon admission and evaluation, intravenous methylprednisolone succinate was started at a daily dose of 1 g for 3 days to control the exacerbated MS symptoms. On the first day of receiving methylprednisolone, the patient developed mild dyspnea, while her vital signs were stable and other aspects of physical examination including cardiac exam were unremarkable. On the second day, following the injection of methylprednisolone, she developed severe dyspnea, respiratory distress, decreased O_2 saturation (SpO_2) to 65% (Table 1). Consequently, because of respiratory failure, she was admitted to Intensive care unit and intubated for mechanical ventilation. Chest radiography and computerized tomography (CT) scan were performed with the results interpreted as bilateral lung involvement (Figure 1). According to a chest CT scan following pulse therapy, she received empiric IV cotrimoxazole (for possible *Pneumocystis jiroveci* pneumonia), meropenem, and vancomycin. Also, furosemide was initiated. However, endotracheal secretions gram staining and bronchoalveolar lavage (BAL) evaluation were with negative results. D-dimer's test was negative. Furthermore, no cardiac dysfunction was observed in echocardiography. On day 6, the patient was extubated with stable vital signs. Finally, on the 12th day, the patient was discharged.

In October 2019, the patient was again referred to our hospital due to MS flare-up. As in the previous episode,

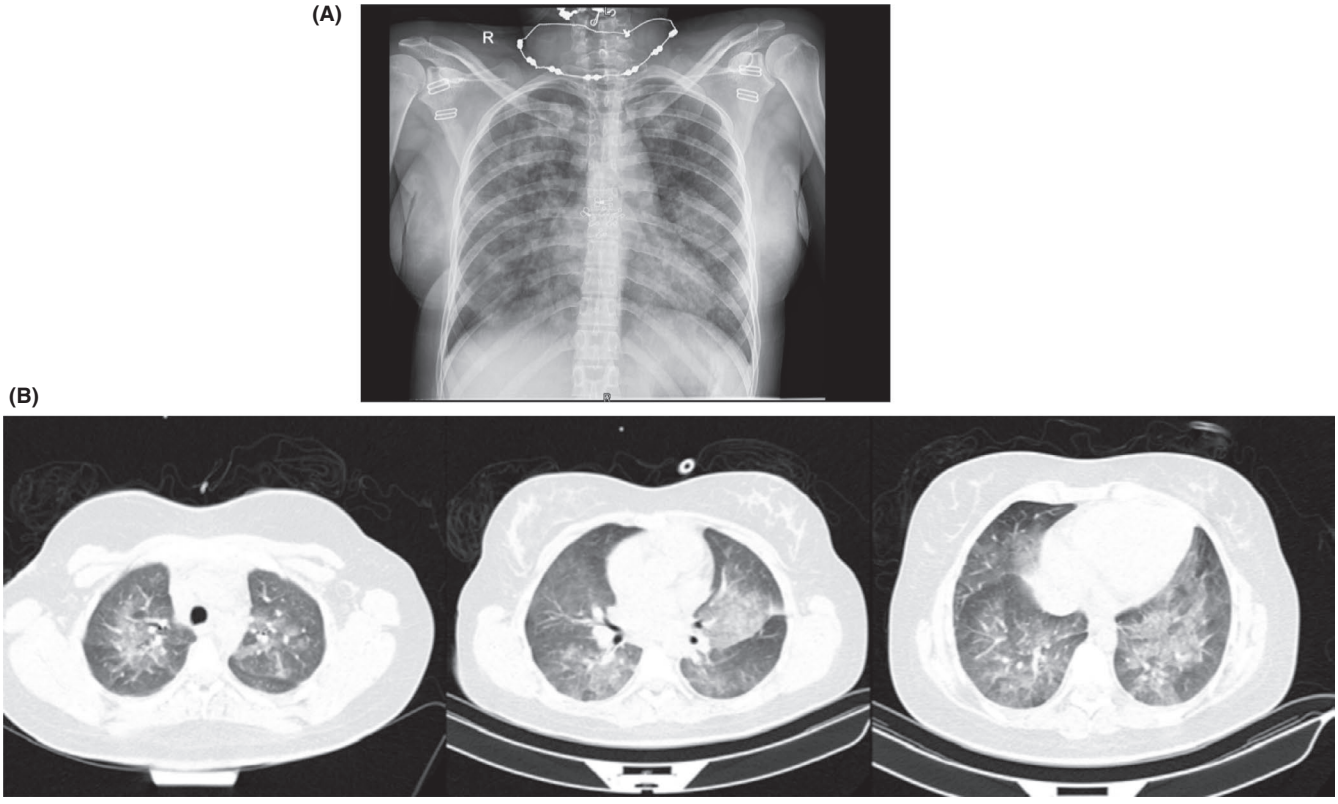

FIGURE 1 (A) Chest X-ray PA view shows multifocal parenchymal opacification. Cardiac size appears normal. (B) Axial CT scan lung window in upper, middle and lower zones of lung show diffuse bilateral ground-glass opacities in both lungs. Interlobular septal thickening and pleural effusion is not present

the patient was prescribed methylprednisolone succinate at a daily dose of 1 g for three days to control her exacerbation symptoms. The Chest X-ray was performed before pulse therapy (Figure 2) and was normal. On the second day of receiving methylprednisolone, severe dyspnea and reduced SpO_2 (80%) occurred again with similar chest CT results compatible with ARDS (Figure 3), hence, antibiotics were not prescribed. Supportive oxygen therapy with face mask and supportive care was initiated. Also, the methylprednisolone was discontinued and for eliminating alternative diagnoses as the cause of lung disease, the same workup was performed as in the previous hospitalization with the results of bronchoscopy and BAL gram staining for bacteria and *Pneumocystis jirovecii*, acid-fast staining, BAL fluid culture for bacteria and fungi and PCR for *Mycobacterium tuberculosis* and *Pneumocystis jirovecii* all being negative. We also checked the BAL specimen for respiratory viruses by PCR including respiratory syncytial virus, influenza, adenovirus, parainfluenza, coronavirus, and rhinovirus, all were negative. Serum galactomannan and aspergillus smear and culture in the BAL specimen were negative. We found no evidence of viral, fungal, or bacterial infection. In addition, the patient's echocardiography was normal. In the next visits for the patient when steroids were indicated, dexamethasone was used and no side effects were observed. The patient is off methylprednisolone pulse therapy for almost 11 months with no similar events. The patient is currently receiving glatiramer acetate (Figure 4).

3 | DISCUSSION

This case presents the possibility of ARDS following MPPT. ARDS is a consequence of an alveolar epithelium and capillary endothelium injury-producing diffuse alveolar damage. Septic shock, pancreatitis, and massive transfusion are examples that can cause this condition.[3,4] We know that drugs can also cause lung disease by injury to the airways or alveoli and create interstitial patterns in the lungs.[5] Often pathophysiologic mechanisms for ARDS including direct damage (by producing reactive oxygen) or indirect damage (by releasing inflammatory cytotoxic mediators) remain unknown for most of the drugs; hence most cases of drug-associated ARDS are considered probable or possible rather than definitive.[3]

Diffuse alveolar damage (DAD) is defined as a pathological finding for ARDS and clinically DAD is associated with diffuse pulmonary infiltration with respiratory failure. Till now some cases of DAD related to drugs have been reported.[5,6] To our knowledge, there is no previous report of such an adverse effect by MPPT. Of note, glucocorticoids are used in the treatment of ARDS or drug-induced lung injury in many cases.[7]

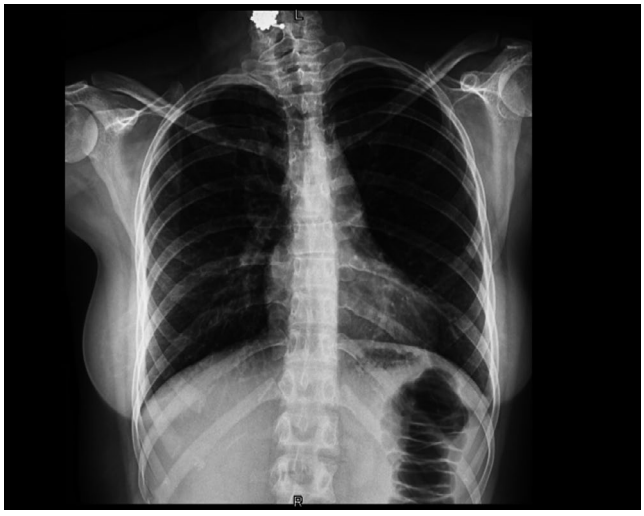

FIGURE 2 CXR before methylprednisolone pulse therapy

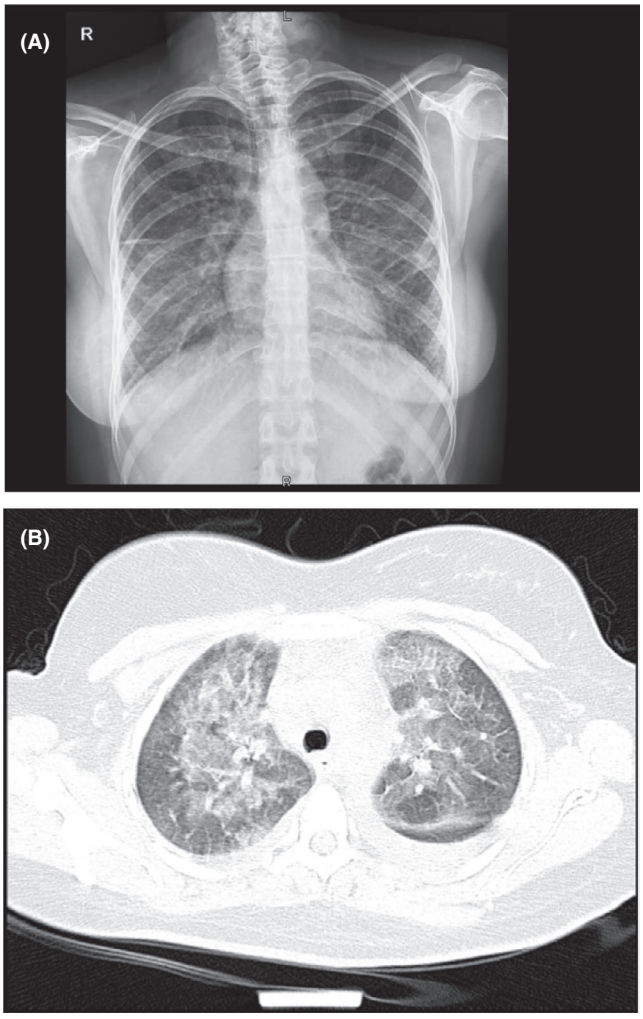

FIGURE 3 (A) Chest X-ray PA view shows reticular opacities with subtle ground-glass opacities. (B)-Axial CT scan lung window in upper and middle zones of lung shows: Multifocal ground-glass opacities and reticulation

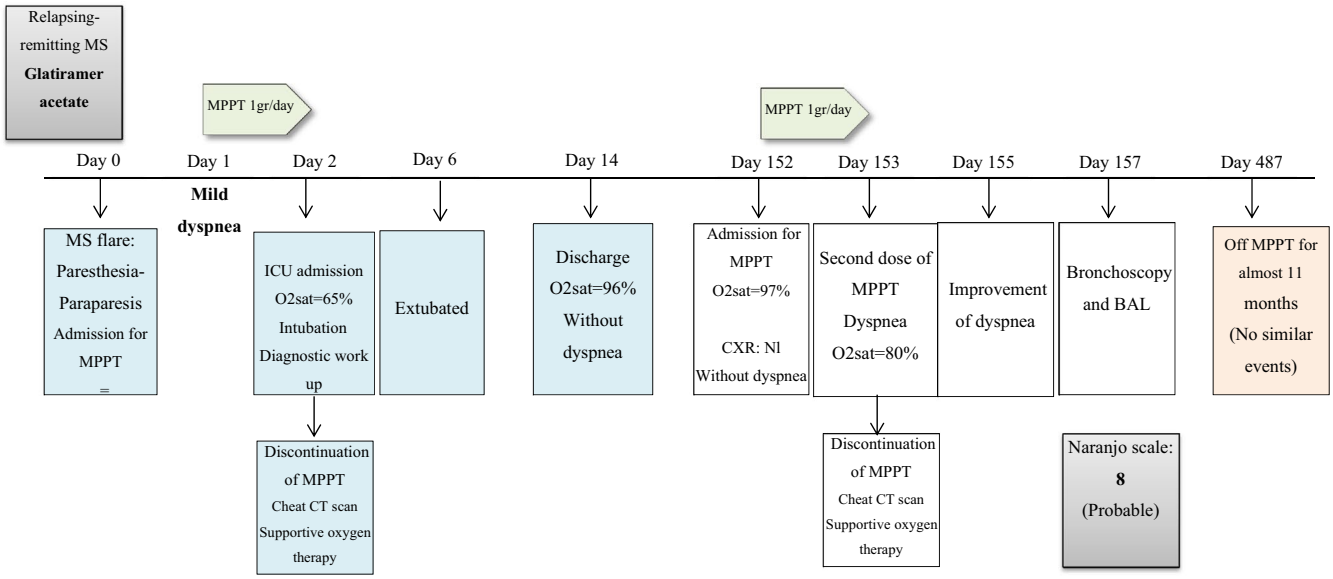

FIGURE 4 Timeline. The timeline containing the history and interventions provided the time course of the patient we presented

In our case, diffuse pulmonary infiltration with respiratory failure (ARDS, clinically DAD), the exclusion of other etiologies including PCP and other infectious agents, acute course of dyspnea with its relatively fast improvement following cessation of the MPPT and recrudescence with re-challenge make the diagnosis of possibility of adverse drug reaction (ADR) with MPPT. On the other hand, from the radiological point of view, it is necessary to mention few points: in a patient with acute symptoms, differential diagnosis of ground-glass opacities is broad such as atypical pneumonia, pulmonary edema, and either hydrostatic or increased permeability edema; diffuse alveolar damage, pulmonary hemorrhage and acute eosinophilic pneumonia. In the acute setting, appearance and distribution of ground-glass opacities are of limited use in narrowing differential diagnosis. Cardiogenic pulmonary edema usually presents with a history of acute cardiac events, so that physical examination reveals jugular venous distention and fine rales.[8] The normal echocardiography rules out the possibility of cardiac origin for pulmonary edema. No one was detected in our case.

We cannot accurately justify the exact mechanism of this complication, but MPPT may be the cause of direct lung endothelial damage in this case. Using Naranjo scale for estimating the probability of this adverse reaction,[9] the score 8 is obtained and interpreted as "probable" ADR. Therefore, ARDS should be considered as a probable ADR of high-dose glucocorticoids.

4 | CONCLUSION

This case presents ARDS as a probable ADR of methylprednisolone pulse therapy in MS patients. However, more studies and reports are necessary to confirm a causal relationship.

ACKNOWLEDGMENTS

Published with written consent of the patient.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

A.H; F.A; R.S; and S.S acquired data, analyzed and interpreted the data. A.H; R.S; A.R; and S.H assisted in drafting the manuscript. All authors have read, revised, and approved the final manuscript.

ETHICAL STATEMENT

This research was approved by the ethics committee of Isfahan University of Medical Sciences and written informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this case report article as no new data were created or analyzed in this study.

ORCID

Atousa Hakamifard https://orcid.org/0000-0001-9456-2239

REFERENCES

1. Krieger S, Sorrells SF, Nickerson M, Pace TW. Mechanistic insights into corticosteroids in multiple sclerosis: War horse or chameleon? *Clin Neurol Neurosurg*. 2014;1(119):6-16.
2. Namaka M, St-Laurent C, Vandenbosch R, Gill R, Ruhlen D, Melanson M. Corticosteroids and multiple sclerosis: to treat or not

to treat? pharmacists can be the front-line resource for MS patients. *Can Pharm J/Rev Pharm Canada*. 2005;138(6):1-3.
3. Dhokarh R, Li G, Schmickl CN, et al. Drug-associated acute lung injury: a population-based cohort study. *Chest*. 2012;142(4):845-850. https://doi.org/10.1378/chest.11-2103
4. Piantadosi CA, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med*. 2004;141:460-470.
5. Torok NI, Donaldson BL, Taji J, Abugiazya A, Assaly R. Diffuse alveolar damage and recurrent respiratory failure secondary to sertraline. *Am J Ther*. 2012;19(4):e132-e135. https://doi.org/10.1097/MJT.0b013e3181ed8363
6. Cleverley JR, Screaton NJ, Hiorns MP, et al. Drug induced lung disease: high-resolution CT and histological findings. *Clin Radiol*. 2002;57:292-299.
7. Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2019;7(7):CD004477.
8. Alwi I. Diagnosis and management of cardiogenic pulmonary edema. *Acta Med Indones*. 2010;42(3):176-184.
9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.

How to cite this article: Ashtari F, Soltani R, Shokouhi S, Rismanbaf A, Hajiahmadi S, Hakamifard A. Adverse reaction of methylprednisolone pulse therapy: Acute respiratory distress syndrome. *Clin Case Rep*. 2021;9:e04468. https://doi.org/10.1002/ccr3.4468