Respiratory Medicine Case Reports 26 (2019) 212–214

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Interstitial pneumonia induced by cyclophosphamide: A case report and review of the literature

Panpan Qian[a,b,1], Chun hong Peng[b,1], Xianwei Ye[b,*]

[a] ZunYi Medical University, Zunyi, Guizhou Province, China
[b] Department of Respiration and Critical Care Medicine, Guizhou Provincial People's Hospital, Guiyang, Guizhou Province, China

ARTICLE INFO

Keywords:
Side effect
Interstitial pneumonia
Toxicity
Cyclophosphamide

ABSTRACT

Introduction: Recently, interstitial lung disease significantly increases and it is difficult to treat. Cyclophosphamide(CP) is one drug administrated in interstitial lung disease, which can also cause pulmonary fibrosis and lung function lesion. This article present a case which exacerbated interstitial pneumonia after treatment by CP, aiming to enhance the understanding of the side effects of CP and standardize usage of the CP.
Case presentation: A patient of nephrotic syndrome administrated with CP suffered respiratory insufficiency requiring mechanical ventilation. Computed tomography (CT) imaging was compatible with interstitial pneumonia(IP). After treating with multimodal combination therapy (corticosteroids, immune globulins), the patient survived. The clinical characteristics of CP-related lung toxicity and/or pulmonary fibrosis should be paid more attention to avoid the serious outcomes.
Conclusion: Although interstitial lung disease induced by CP is rare, with the current widespread usage of CP increases the risks of diffuse interstitial pneumonia and pulmonary fibrosis, which need to be noted in time to get early treatment.

1. Introduction

Interstitial lung disease (ILD), involving in pulmonary interstitial, alveolar and/or bronchioles, manifested as progressive dyspnoea, hypoxemia with image of the lungs diffuse lesions. Drug-induced interstitial pneumonia is caused by the drug, affecting the bronchioles, alveolar cavities, small pulmonary vessels and leading to pulmonary interstitial fibrosis, which has been reported in recent years. The drugs include anti-tumor, antibiotics, cardiovascular drugs, anti-rheumatic drugs, targeted drugs, biological agents and so on [1] Cyclophosphamide (CP) is an alkylating agent widely used for the treatment of malignancies, renal diseases, multiple rheumatic diseases [2]systemic lupus erythematosus [3,4]. and interstitial lung disease [5,6]. CP is associated with a range of significant toxicities that make its usage problematic. The injury of normal tissues is the major limitation of using CP, which gives rise to numerous side effects [7]. Here, we report a patient with lung function failure related with usage of CP.

2. Case presentation

A 42-year-old non-smoking female patient with diagnosis of Nephrotic syndrome, no clinical manifestations of other systems damage, anti-nuclear antibodies, anti-neutrophil cytoplasmatic antibodies, complement factors, circulating immune complexes and immune globulin dosage confirmed no abnormalities. she was treated with prednisone and CP(0.1g oral qod) for 2 months, then admitted to the hospital due to fever, dry cough and progressive dyspnoea. She denied history of chronic respiratory disease. Ten days before admission, CT examination of the lungs revealed extensive abnormalities in both lungs with diffuse ground glass abnormalities in both the upper and lower lobes (Fig. 1ab). Fungal infection was considered for the diffusion Lung lesion from CT image. Then, flucon Oxazole (200mg per day) was administrated intravenously. Meanwhile, the treatment of control of blood pressure, protection of liver and kidney functions were also taken. However, the symptoms did not improve, with fever continous and wheezing aggravating. Blood gas analysis showed that PH7.47, PaCO2: 34 mmHg, PaO2: 48 mmHg, HCO3-: 24.7mmol/L. No microorganisms were detected on the BAL fluid and sputum culture. PPD,G

* Corresponding author. Department of Respiration and Critical Care Medicine, Guizhou Provincial People's Hospital, 83 Zhongshan East Road, Guiyang City, Guizhou Province, China.
E-mail address: yxw1205@163.com (X. Ye).
[1] Pan-pan Qian and chun hong Peng are co-first authors, contributed equally to this paper.

https://doi.org/10.1016/j.rmcr.2019.01.014
Received 22 October 2018; Received in revised form 16 January 2019; Accepted 16 January 2019

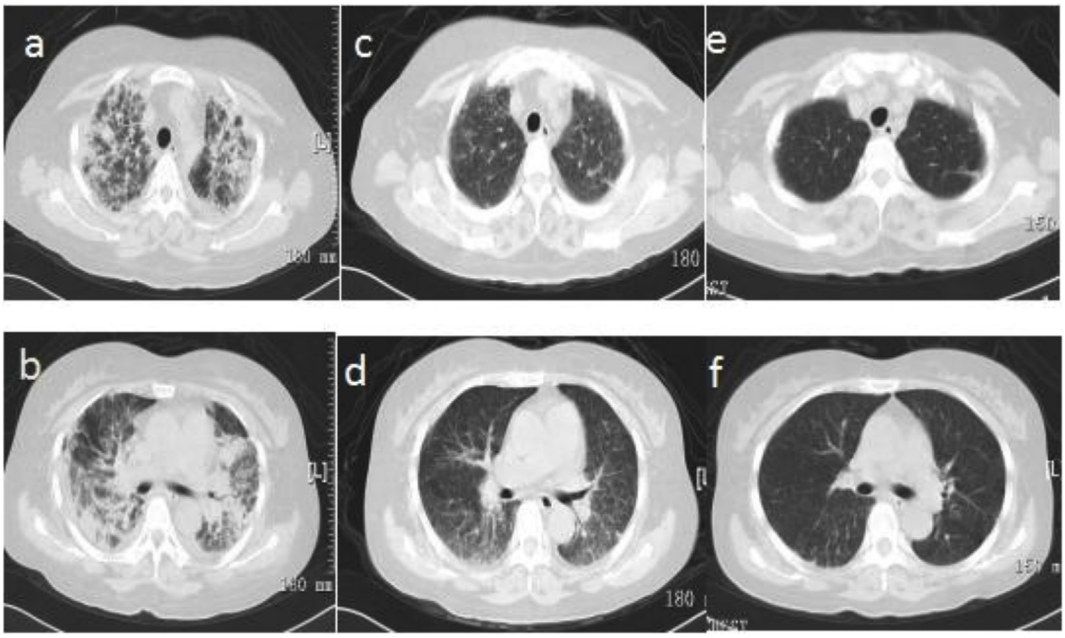

Fig. 1. CT images of the chest in the lung window:Figure (ab) Pulmonary diffuse lesions: diffuse multiple nodules of both lungs, patchy, ground-glass density lesions. Figure (cd) a variety of combination therapy after 1 month review chest CT lung pattern enhancement, lung biopsy-like high density was significantly more than the former suction, double lung glass shadows absorption. Figure (ef) Only a minor cine-ray after more than one year of follow-up.

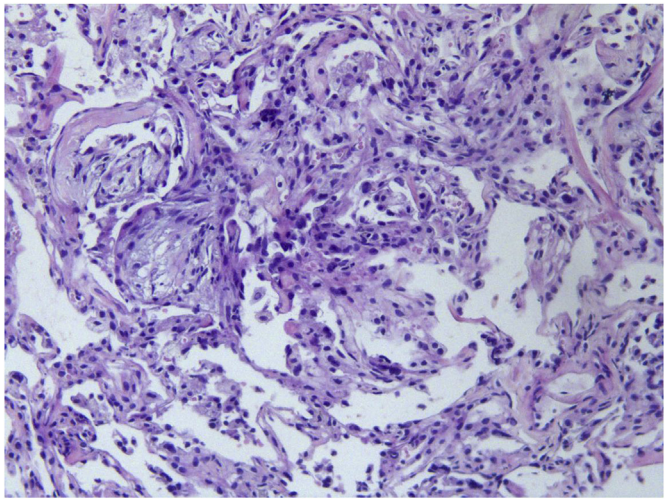

Fig. 2. The microscopic view of the lung tissue (fiber bronchoscope lung biopsy, staining Hematoxylin Eosin) revealing with the alveolar septa are thickened, hyperplasia of fibrous tissue with lymphocytic inflammatory infiltrate.

test antinuclear antibody, ANCAs test proved negative. In view of the fact that screening for autoimmune and systemic diseases revealed no aberrations, fiber bronchoscope lung biopsy (right upper lobe) was performed. The microscopic view of the lung tissue (staining Hematoxylin Eosin) revealing with the alveolar septa are thickened, hyperplasia of fibrous tissue with lymphocytic inflammatory infiltrate (Fig. 2). There were no arguments for concomitant vasculitis, infection or malignancy. The Chest X-ray showed that pulmonary lesions were significantly worse than before and diffuse function was severely reduced, inflammatory cell infiltration in the lung biopsy. Considering the exacerbation of lung lesion, uneffection of antibiotic, and the usage of CP, drug-related interstitial pneumonia was dignosised.

Then, stopping the usage of CP, immune globulins and methylprednisolone(40mg) were given to relieve the inflammation. After these administration, the temperature dropped quickly and the symptom was significantly improved with SpO2 elevating to more than 90%. The interstitial pneumonia on chest X-ray and follow-up CT gradually dissolved. 1 month after discharge, chest CT showed that the ground glass abnormalities and consolidation with only minor residual parenchymal changes (Fig. 1cd). After discharge, the patient received oral methylprednisolone tablets 16 mg per day, and gradually reduced to the required withdrawal. Follow-up more than 1 year showed that there were no uncomfortable symptom and no residual pulmonary obvious abnormalities (Fig. 1ef).

3. Discussion

CP is widely used as an anti-tumor and immunosuppressive agent which have pulmonary toxic side effects. Drug-induced pulmonary disease may manifest as a variable clinical pattern, including subacute or chronic interstitial pneumonitis, pulmonary fibrosis, eosinophilic pneumonia, pulmonary edema and so on. The following steps are necessary for diagnosis: drug exposure, clinical and imaging methods, reclusion other disease and improvement after drug withdrawal [14]. The diagnosis of the disease still lacks a specific method, most importantly, other pulmonary interstitial disease should be ruled out. The causes of IP in the immune-compromised host treated with cytotoxic agents may include opportunistic infection, drug-induced pulmonary disease, and pulmonary involvement by the malignancy. The diagnosis of the patient in the case was ruled out other infection diseases and immune system diseases. After CP withdrawal and the usage of methylprednisolone, the symptom and chest image significantly better.

Mechanisms of pulmonary damage by drugs include direct toxicity and indirect effects through enhancement of inflammatory reactions. Clinical features are similar to other categories of cytotoxic agents and the most common clinical syndrome is chronic pneumonitis/fibrosis [8]. Many anticancer drugs can be muta-genic, teratogenic, and carcinogenic [15]. The toxicity of CP come from its metabolism, CP can generate high reactive oxygen species(ROS) and free radicals [16,17], which damage the cellular DNA and mitochondrial, lysosomal membrane. CP exposure can induce oxidative stress-mediated disruption of redox balance, then generates biochemical and physiological disturbances [18,19]. The cellular mechanisms by which CP causes lung

injury are poorly unclear.

The pulmonary damage is related to drug cumulative dose. CP-induced lung disease has been previously described in 9 patients receiving continuous low dose for a total period ranging between 1 and 52 months [11]. Such fibrosis has not been described with high dose intermittent therapy [20]. To reduce total dosage, duration of CP usage is often shorter than 12 months and intravenous regimens are preferred for a reduction by up to two-thirds of total cumulative dose, thereby reducing risks of some toxicity [21]. Clinicians should carefully monitor for adverse effects during treatment and even during the years thereafter. If interstitial pneumonia occurs, CP should be promptly discontinued and immune globulins should be administrated to reduce the pulmonary inflammation and fibrosis [22]. Corticosteroids and immunoglobulin can be combined for treatment.

4. Conclusion

As a widely used cytotoxic drug in clinical practice, CP can be used in the treatment of ILD, Although interstitial lung disease induced by CP is rare, early diagnosis and treatment can get great improvement for patient.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

The work was supported by Guiyang Science and Technology Plan Project of Guizhou Province of China (Grant No.20151001).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.01.014.

References

[1] A. De Weerdt, A. Dendooven, A. Snoeckx, J. Pen, M. Lammens, P.G. Jorens, Prognosis and treatment of FOLFOX therapy related interstitial pneumonia: a plea for multimodal immune modulating therapy in the respiratory insufficient patient, BMC Canc. 17 (1) (2017) 586.

[2] K.A. Teles, P. Medeiros-Souza, L. FAC, B.G. Araújo, L. RAC, Cyclophosphamide administration routine in autoimmune rheumatic diseases: a review, Rev. Bras. Reumatol. Engl. Ed. 57 (6) (2017) 596–604.

[3] P. Perini, M. Calabrese, L. Rinaldi, P. Gallo, The safety profile of cyclophosphamide in multiple sclerosis therapy, Expert Opin. Drug Saf. 6 (2) (2007) 183–190.

[4] W.E. Uber, S.E. Self, A.B. Van Bakel, N.L. Pereira, Acute antibody-mediated rejection following heart transplantation, Am. J. Transplant. 7 (9) (2007) 2064–2074.

[5] K. Broad, J.E. Pope, The efficacy of treatment for systemic sclerosis interstitial lung disease: results from a meta-analysis, Med. Sci. Monit. 16 (9) (2010) RA187–R190.

[6] H. Barnes, A.E. Holland, G.P. Westall, N.S. Goh, I.N. Glaspole, Cyclophosphamide for connective tissue disease-associated interstitial lung disease, Cochrane Database Syst. Rev. 1 (2018) CD010908.

[7] R.M. Bukowski, The need for cytoprotection, Eur. J. Cancer 32A (Suppl 4) (1996) S2–S4.

[8] J.A. Cooper, D.A. White, R.A. Matthay, Drug-induced pulmonary disease. Part 1: cytotoxic drugs, Am. Rev. Respir. Dis. 133 (2) (1986) 321–340.

[11] K.F.W. Abdel, R.E. Ayash, C. Allam, P.A. Salem, Pulmonary fibrosis after prolonged treatment with low-dose cyclophosphamide. A case report, Oncology 40 (3) (1983) 174–176.

[14] P. Bonniaud, M. Georges, N. Favrolt, P. Camus, Drug-induced interstitial lung diseases, Rev. Prat. 64 (7) (2014) 951–956.

[15] M. Sorsa, K. Hemminki, H. Vainio, Occupational exposure to anticancer drug–potential and real hazards, Mutat. Res. 154 (2) (1985) 135–149.

[16] Y. Mythili, P.T. Sudharsan, E. Selvakumar, P. Varalakshmi, Protective effect of DL-alpha-lipoic acid on cyclophosphamide induced oxidative cardiac injury, Chem. Biol. Interact. 151 (1) (2004) 13–19.

[17] P.T. Sudharsan, Y. Mythili, E. Selvakumar, P. Varalakshmi, Lupeol and its ester exhibit protective role against cyclophosphamide-induced cardiac mitochondrial toxicity, J. Cardiovasc. Pharmacol. 47 (2) (2006) 205–210.

[18] I.A. al-Nasser, In vivo prevention of cyclophosphamide-induced Ca2+ dependent damage of rat heart and liver mitochondria by cyclosporin A, Comp. Biochem. Physiol. Mol. Integr. Physiol. 121 (3) (1998) 209–214.

[19] P.T. Sudharsan, Y. Mythili, E. Selvakumar, P. Varalakshmi, Lupeol and its ester inhibit alteration of myocardial permeability in cyclophosphamide administered rats, Mol. Cell. Biochem. 292 (1–2) (2006) 39–44.

[20] T.X. O'Connell, M.C. Berenbaum, Cardiac and pulmonary effects of high doses of cyclophosphamide and isophosphamide, Cancer Res. 34 (7) (1974) 1586–1591.

[21] D.T. Boumpas, H.A. Austin, E.M. Vaughn, et al., Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis, Lancet 340 (8822) (1992) 741–745.

[22] V. Molina, S. Haj-Yahia, I. Solodeev, Y. Levy, M. Blank, Y. Shoenfeld, Immunomodulation of experimental pulmonary fibrosis by intravenous immunoglobulin (IVIG), Autoimmunity 39 (8) (2006) 711–717.