Case report

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

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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 \cite{1} Cyclophosphamide (CP) is an alkylating agent widely used for the treatment of malignancies, renal diseases, multiple rheumatic diseases \cite{2} systemic lupus erythematosus \cite{3,4}, and interstitial lung disease \cite{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 \cite{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. 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 administered 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 continuous and wheezing aggravating. Blood gas analysis showed that PH 7.47, PaCO2: 34 mmHg, PaO2: 48 mmHg, HCO3-: 24.7mmol/L. No microorganisms were detected on the BAL fluid and sputum culture. PPD,G
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. 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.

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 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 the patient.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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

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