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Acute respiratory failure during first cyclophosphamide infusion in a patient with systemic lupus erythematosus

We here present a case of acute respiratory failure during the first-time infusion of cyclophosphamide (CP) in a 40-year-old woman with systemic lupus erythematosus (SLE). She had been diagnosed with SLE 6 years earlier, but had been unwilling to receive medical treatment despite persistent symptoms. Eventually, her daily functioning was impaired by slowly progressive dyspnea. The lung diffusion capacity was reduced to 57%, and a chest radiogram revealed sequelae after right-sided pleurisy, but no interstitial infiltrates. The emergence of proteinuria and hematuria indicated renal involvement and she reluctantly accepted a combination of mycophenolate mofetil (MMF) and corticosteroid. However, after 4 months of treatment no significant improvement was noted and six fortnightly CP infusions at a fixed dose of 500 mg were planned [1]. After receiving approximately 250 mg of CP in the time span of 30 min, our patient developed severe respiratory failure within minutes. No co-medications were administered. She was immediately transferred to an intensive care unit (ICU) for ventilator support and a full clinical evaluation including echocardiography was negative, except for single-organ respiratory failure. High-resolution computed tomography (HRCT) 2 days after CP infusion revealed diffuse interstitial infiltrates (■ Fig. 1). Serum tryptase level was normal and there had been no urticarial rash. Laboratory results from day 2 in the ICU were as follows: CRP 206 mg/l (normal: <10 mg/l), white blood cell count

29.2×10⁹/l (normal: 3.5–10.0×10⁹/l) and markedly elevated lactate dehydrogenase (LDH) at 896 U/l (normal: 105–205 U/l). A bronchoalveolar lavage (BAL) was performed and microscopy of the BAL fluid revealed abundance of leucocytes but no bleeding. Bacterial cultures and PCR tests for atypical and viral pneumonia were all negative. Acute CP lung toxicity was suspected and high-dose methylprednisolone (500 mg daily) was given for 4 days. Additional empiric antibiotic therapies with cefuroxime and ciprofloxacin were initiated to treat a potential undiagnosed infection. The clinical condition improved and the lung infiltrates partially regressed. However, as methylprednisolone was tapered to 250 mg the lung infiltrates progressed, and a 4-day course of high-dose immunoglobulin infusions was given, with the intent to obtain further immunosuppression with minimal risk of exacerbating a possible infectious process. Our patient gradually recovered and after a total of 17 days in the ICU she was transferred to a general ward. The corticosteroid was slowly tapered and she was discharged from the hospital after 2 months with MMF, hydroxychloroquine, and low-dose steroid. Repeat HRCT after 7 months showed almost complete resolution of the lung infiltrates (■ Fig. 2), but diffusion capacity remained mildly impaired compared to her baseline level. At present, 2 years later, the patient is doing well without any sign of SLE activity.

CP is a nitrogen mustard-like alkylator originally developed for treatment

of malignant tumors [2]. Lung toxicity caused by CP has mainly been recognized through case reports, but often other drugs, oxygen therapy or radiation therapy may have contributed to the lung toxicity and the true incidence of CP lung toxicity is, therefore, difficult to estimate. Surveillance chest radiograms in 588 lung cancer patients who received busulphan, CP, or placebo failed to demonstrate radiological abnormalities in the CP arm [3]. Consistently, the pivotal study by the Euro-Lupus Nephritis Trial group introducing the six fortnightly and fixed-dosed 500 mg CP regimen did not report any lung toxicity [1]. A review of patients treated at the Mayo Clinic between 1974 and 1994 only identified 6 cases of clear CP-induced lung toxicity, while other causes of lung injury could not be excluded in additional 29 patients [4]. Further analysis of the 6 patients revealed two types of lung toxicity: early onset pneumonitis and late onset pneumonitis with fibrosis. Late onset pneumonitis occurred in 5 patients and was diagnosed between 18 months and 13 years after starting CP therapy. These patients had slow progressive dyspnea unresponsive to corticosteroids and three succumbed to respiratory failure. One patient had early-onset pneumonitis with onset 6 months after starting CP and recovered on corticosteroids [4]. Our patient showed similarities to the early onset pneumonitis, but the hyperacute onset of respiratory failure has to the best of our knowledge not been reported previously. The mechanism by which CP causes lung



Fig. 1 ▲ High resolution computed tomography 2 days after cyclophosphamide infusion revealed diffuse interstitial infiltrates

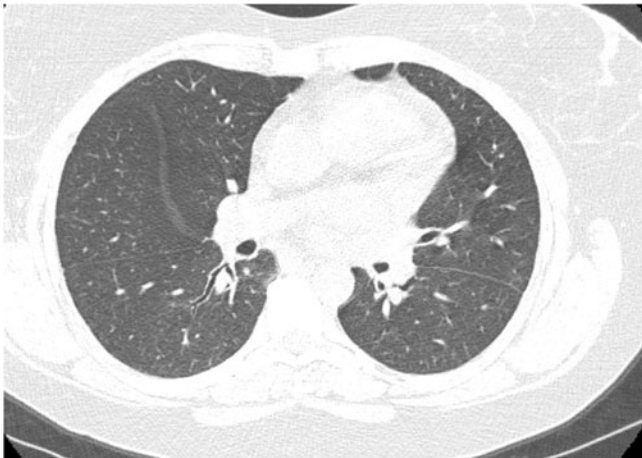


Fig. 2 ▲ Repeat high resolution computed tomography after 7 months showed almost complete resolution of the lung infiltrates; however, the diffusion capacity remained mildly impaired compared to her baseline level

injury is not well understood. In human lung tissue from patients with CP lung toxicity a mixture of inflammatory cells, activated fibroblasts, abnormal alveolar cells, and collagen fibers have been described [5, 6]. We administered high dose immunoglobulin infusions to our patient in a provisional attempt to reduce immunological lung damage.

Our patient started MMF therapy 4 months prior to CP exposure. MMF was discontinued at the initiation of CP treatment. Although MMF has sporadically been associated with insidious lung toxicity, the reported intervals from beginning of therapy to pulmonary symptoms were 10 and 42 days [7, 8]. The absence of blood in the BAL fluid excludes diffuse alveolar hemorrhage, which is an impor-

tant differential diagnosis in SLE patients [9]. There were no acute progressive pulmonary symptoms or interstitial lung infiltrates on chest x-ray immediately prior to CP infusion and on the day of CP infusion CRP was <10 mg/l leading us to believe that our patient suffered an extremely rare form of hyperacute CP lung toxicity rather than acute lupus pneumonitis.

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Acute respiratory failure during first cyclophosphamide infusion in a patient with systemic lupus erythematosus

Abstract

We present a report of what we believe was an extremely rare case of hyperacute respiratory failure caused by first time exposure to cyclophosphamide in a 40-year-old woman with systemic lupus erythematosus. The patient was extensively evaluated for alternative etiologies with negative results. Treatment with methylprednisolone and high doses of human immunoglobulin resulted in gradual improvement of the patient's condition. We review the literature with regard to cyclophosphamide-induced lung toxicity.

Keywords

Lung diseases · Immunoglobulin · Methylprednisolone · Respiratory insufficiency · Dyspnea

Akutes Lungenversagen nach erstmaliger Cyclophosphamidinfusion bei systemischem Lupus erythematosus

Zusammenfassung

Vorgelegt wird das u. E. extrem selten vorkommende Ereignis eines hyperakuten Lungenversagens nach erstmaliger Cyclophosphamidexposition bei einer 40-Jährigen mit systemischem Lupus erythematosus. Mögliche alternative Ätiologien wurden umfassend evaluiert, ohne positives Ergebnis. Nach Behandlung mit Methylprednisolon und humanem Immunglobulin in hohen Dosen kam es zu einer allmählichen Verbesserung des Zustandes der Patientin. In Bezug auf durch Cyclophosphamid induzierte pulmonale Toxizität wird die Literatur gesichtet.

Schlüsselwörter

Lungenerkrankungen · Immunglobulin · Methylprednisolon · Ateminsuffizienz · Dyspnoe

Contributions. PS and TCE wrote and contributed equally to the manuscript. TR co-authored and revised the manuscript. JBF provided and analyzed radiological data.

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Compliance with ethical guidelines

Conflict of interest. P. Schjelderup, T.C. El-Galaly, J.B. Frøkjær, and T. Ring state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

Consent was obtained from all patients identifiable from images or other information within the manuscript.

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Ausschreibung Dr.-Holger-Müller-Preis-2014 Erforschung, Verhütung und Bekämpfung seltener Krankheiten

Für weitere Auskünfte steht Ihnen
Frau Anne-Marie Flad
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gerne zur Verfügung.

*Quelle: Care-for-Rare Foundation,
www.care-for-rare.org*

Die Care-for-Rare Foundation am Dr. von Haunerschen Kinderspital der Ludwig-Maximilians-Universität München lobt den Dr. Holger Müller Preis 2014 in Höhe von 5.000 Euro aus. Der von der Dr. Holger Müller Stiftung zur Verfügung gestellte Preis soll eine herausragende wissenschaftliche Arbeit auf dem Gebiet der seltenen Erkrankungen auszeichnen. Als selten gilt eine Erkrankung, wenn nicht mehr als 5 von 10.000 Menschen betroffen sind. Es werden grundlagenwissenschaftliche und klinische Arbeiten berücksichtigt.

Für die aktuelle Ausschreibungsperiode kann ein wissenschaftliches Manuskript eingereicht werden, welches in der Zeit zwischen dem 30. September 2013 und dem 15. Dezember 2014 veröffentlicht oder zur Veröffentlichung angenommen wurde.

Dr. Holger Müller arbeitete 20 Jahre als Chefarzt des Labors am Klinikum Göppingen. Er war ein erfahrener Mediziner, der seinen Beruf mit Leib und Seele ausfüllte. Nach seinem Tod Ende 2008 wurde die Dr. Holger Müller Stiftung zur Erforschung, Verhütung und Bekämpfung seltener Krankheiten errichtet. Der Dr. Holger Müller Preis richtet sich insbesondere an jüngere Wissenschaftlerinnen und Wissenschaftler, um ihr Engagement für Menschen mit seltenen Erkrankungen zu würdigen und zu fördern.

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Die vollständigen Bewerbungsunterlagen sind bis zum 15. Dezember 2014 (Ausschlussfrist) elektronisch einzureichen. Einzelheiten finden Sie auf www.care-for-rare.org.

Die feierliche Preisverleihung wird im März 2015 in Esslingen stattfinden.