

# TEMPORARY HEART FAILURE ASSOCIATED WITH LONG-TERM DAILY ORAL CYCLOPHOSPHAMIDE USE IN A PATIENT WITH WEGENER'S GRANULOMATOSIS

## UZUN SÜRELİ ORAL SİKLOFOSFAMİD KULLANIMINA BAĞLI GEÇİCİ KALP YETMEZLİĞİ GELİŞEN BİR WEGENER GRANÜLOMATOZU HASTASI

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### Dear Sir,

Wegener's Granulomatosis (WG) is a necrotising, granulomatous small-vessel vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) typically affecting the upper and lower airways and, in some cases, the kidneys (1, 2). Involvement of vital organs, such as severe pulmonary or renal involvement, requires aggressive immunosuppressive treatment (2). Cyclophosphamide (Cyc), an immunosuppressive agent, is often used when vital organs are involved (2). Cyc therapy has severe side effects, some of which are bone marrow suppression and associated infections, hemorrhagic cystitis, gonadal damage and malignancy (3, 4). Cardiomyopathy may occur in some patients treated with high-dose intravenous Cyc in a short period, and is shown to be dose related (5, 6). To the best of our knowledge, Cyc cardiotoxicity resulting from long-term daily oral cyclophosphamide use has not been previously reported. It is often described as an acute fatal event related to high dose iv infusion and, in survivors, it resolves within several weeks with no sequelae (7). No evidence has been reported on cardiotoxicity due to cumulative Cyc usage (8). Here, we describe a case of heart failure associated with long-term daily oral cyclophosphamide. A 39 year-old woman with a diagnosis of WG was admitted to hospital with complaints of dyspnea and cough. Diagnosis of WG was made seven months previously when she presented with cough and dyspnea on exertion. Her cytoplasmic ANCA (cANCA) was positive. She had pulmonary nodules. Transbronchial biopsy revealed granulomatous inflammation. The patient was treated with methylprednisolone 1 mg/kg po and Cyc 15 mg/kg/month iv. There was a progression in the pulmonary nodules and an increase in the serum cANCA level after the second dose of iv pulse Cyc. Therefore iv Cyc regimen was switched to an oral daily regimen at a dose of 150 mg/day, and oral methylprednisolone regimen was continued. Additionally, pulse methylprednisolone was given at a dose of 1000 mg intravenously once a month.

On her current admission, she was on methylprednisolone 12 mg/day and Cyc 100 mg/day. The cumulative Cyc dose she received was 23 g (350 mg/kg). She complained of dyspnea and nonproductive cough for a month. Her blood pressure was 120/80 mmHg and heart rate was 120 beats/minute. She was afebrile. The remainder of her physical examination was unremarkable except for rhonchi during expiration. Complete blood cell count and biochemical analysis were within normal ranges. Erythrocyte sedimentation rate was 44 mm/hour and C-reactive protein level was 54 mg/dl (range 0-6 mg/dl). Electrocardiography (ECG) revealed sinus tachycardia (110 beats/minute). Chest radiography revealed bilateral pulmonary nodules which were smaller compared to baseline. She did not have evident cardiomegaly on her chest x-ray.

Echocardiography (ECHO) showed deteriorated left ventricular (LV) systolic function with global hypokinesia and an LV ejection fraction (LVEF) of 48%. There was no valvular deformity or pericardial fluid. Left ventricular end-systolic diameter was 3.2 cm and end-diastolic diameter was 4.2 cm, and both were within normal ranges. Dynamic magnetic resonance imaging (MRI) of the heart was performed, and there were no findings suggestive of cardiac involvement of WG. Cyc cardiotoxicity was suspected and Cyc was switched to azathioprin. On her follow-up, thirty days after discontinuation of Cyc, repeat ECHO revealed an LVEF of 65% and normal systolic movements of the LV wall. Cough and dyspnea had resolved. Her lungs were clear to auscultation and cardiac examination was unremarkable.

Here, we presented a patient with WG but no prior history of hypertension, heart failure or diabetes mellitus, who developed cardiotoxicity due to oral cyc therapy. She had received a large cumulative dose of cyclophosphamide through venous and oral routes over seven months. Cyc has been previously reported to be associated with the development of acute cardiomyopathy and heart failure in patients with cancer receiving high-dose Cyc in a short

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period for preoperative bone marrow transplantation regimens (e.g., 180 mg/kg over 4 days) (7, 9). It was suggested that the incidence of cardiotoxicity due to high dose Cyc (>1.55 g/m<sup>2</sup>/day) was 25% in adults, and Cyc doses based on body surface area rather than body weight correlate better with the development of cardiotoxicity (6). Histopathologic examination of the heart has revealed increased heart weight, myocardial necrosis with hemorrhagia, vascular endothelial damage and intracapillary microthrombi in patients with acute Cyc cardiotoxicity (10). Similarly, autopsy studies have revealed myocardial edema, fibrosis and cellular hypertrophy (11).

In our case, myocarditis and cardiac involvement of WG were excluded by the demonstration of a normal myocardium with dynamic MRI. Normal cardiac MRI findings suggest that long-term daily cyclophosphamide therapy may have caused ultrastructural changes and functional impairment in the heart, without causing macroscopic changes to be detected by MRI. Cyclophosphamide cardiac toxicity with daily oral cyc treatment has not been previously reported. However, our patient improved dramatically after cessation of the Cyc with no increase in the glucocorticoid dose. The ejection fraction increased from 48% to 65%, and cough resolved. There was no other condition likely to be the cause of heart failure. Therefore, we attributed heart failure to the large cumulative Cyc dose used. The rapid recovery after discontinuation of Cyc suggests that it might not have been causing severe damage. Fortunately, the patient recovered rapidly, however this precluded a cardiac biopsy. Patients with WG are often given long-term daily Cyc. When these patients present with dyspnea and cough, if relapse of WG is excluded, cardiac functions should be explored and potential Cyc cardiotoxicity should be considered.

**Authors' contributions:** Conceived and designed the experiments: TA, BG. Performed the experiments: MDD, ŞH, MAÖ. Analyzed

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