

CONCISE COMMUNICATION

Late-onset anaphylactic reactions following i.v. cyclophosphamide pulse in a patient with systemic sclerosis and systemic lupus erythematosus overlap syndrome

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ABSTRACT

Late-onset anaphylactic reaction is a rare adverse effect of i.v. cyclophosphamide pulse (IVCY), which is caused by cyclophosphamide metabolites. We herein report a case of scleroderma and lupus overlap syndrome who developed anaphylactic reactions 3 h to 4 days after IVCY. Long time lapses between IVCY and appearance of symptoms are compatible with type I hypersensitivity to cyclophosphamide metabolites, appearing as late-onset anaphylactic reaction. Albeit unusual, this is an important anaphylactic reaction to be aware of following IVCY.

Key words: cyclophosphamide, interstitial lung disease, late-onset anaphylactic reactions, systemic lupus erythematosus, systemic sclerosis.

INTRODUCTION

Cyclophosphamide (CY) is an immunosuppressive and antineoplastic agent widely used for the treatment of systemic rheumatic diseases and malignant neoplasms. Common undesirable toxic effects of CY include bone marrow suppression, infertility and hemorrhagic cystitis. On the other hand, various type I and III hypersensitivity reactions to CY have been reported, including urticaria, angioedema, anaphylactic reactions with cutaneous, respiratory and vascular manifestations, and cutaneous vasculitis.^{1–3} Importantly, there also have been reports of late-onset type I hypersensitivity to CY in patients with malignant neoplasms, which occurs several hours to several days after the infusion and is associated with acute allergic reaction to CY metabolites, such as phosphoramidate mustard and 4-hydroxycyclophosphamide.⁴ Although immediate anaphylactic reactions related to i.v. CY pulse (IVCY) have been reported in systemic lupus erythematosus (SLE) patients,^{5,6} there is no report of late-onset type I hypersensitivity in patients with collagen vascular diseases. We herein present a case of late-onset type I hypersensitivity following IVCY in a patient with systemic sclerosis (SSc)/SLE overlap syndrome.

CASE REPORT

A 46-year-old Japanese woman with diffuse cutaneous SSc/SLE overlap syndrome presented to us in December 2004. Laboratory work-up at presentation revealed hypocomplement-

emia, positive antinuclear antibody of 1:2560 with a speckled pattern, elevated anti-dsDNA antibody, anti-topoisomerase I antibody and anti-U1-RNP antibody. Anti-Sm antibody was not present. Her serological test results showed slightly elevated KL-6 (526 U/mL; normal, <500) and normal surfactant protein-D (SP-D, 106 ng/mL; normal, <110) values. Chest computed tomography (CT) revealed patchy ground-glass opacity in the lower lobes of both lungs, compatible with interstitial lung disease (ILD) related to SSc. Since November 2009, 5 years after first presentation, she progressively developed dyspnea and chest CT showed worsening of her ILD. In March 2010, arterial blood gas test and pulmonary function test showed hypoxia with a decreased level of PaO₂ (65.7 mmHg), decreased vital capacity (VC; 1.30 L: 49.7% of the predicted value) and low diffusion capacity of the lung for carbon monoxide (D_{LCO}; 5.26 mL/min per mmHg: 31.2% of the predicted value). In addition, the disease activity of ILD was confirmed based on the increased serum levels of KL-6 and SP-D (1642 U/mL and 136 ng/mL, respectively). Therefore, in April 2010, we decided to start monthly IVCY (a test dose of 350 mg/m² at the first month followed by monthly IVCY at a dose of 500 mg/m²) with moderate dose of prednisolone (30 mg/day) for her SSc-related ILD. During and after the first IVCY, there was no adverse effect related to the therapy. However, 4 days after the second IVCY, she felt feverish and experienced dyspnea and mild wheezing. She then developed generalized macular erythema, pruritus and muscle pain (Fig. 1). Repeated blood cultures were all negative. These symptoms subsided spontaneously in 24 h but recurred after subsequent pulses, with the

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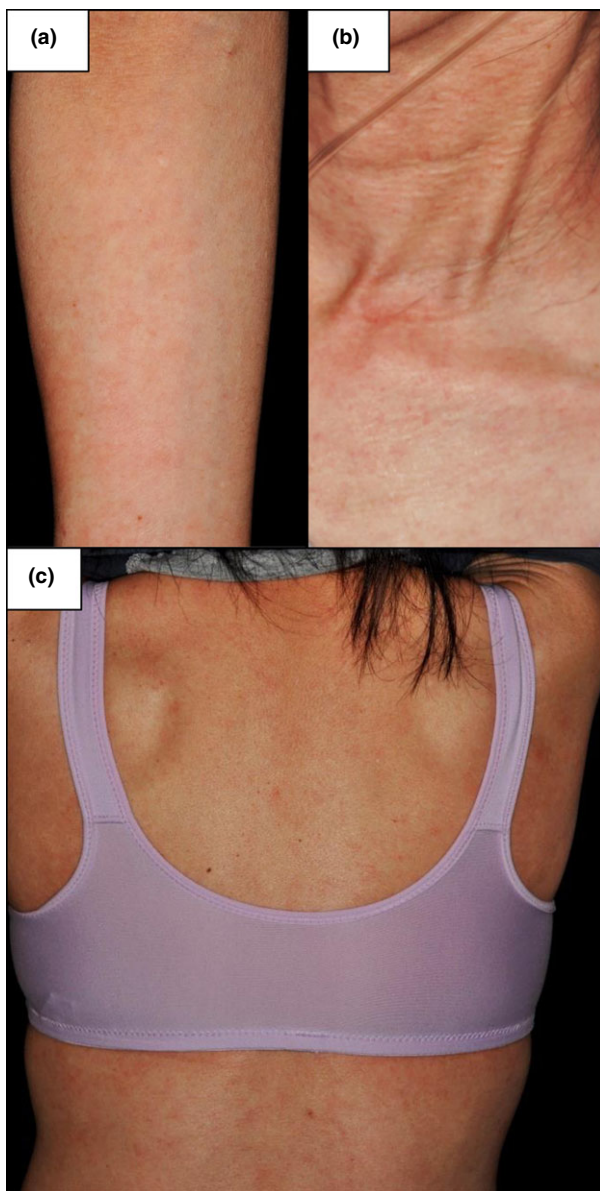


Figure 1. Cutaneous manifestations at the first episode of adverse reactions. Bean-sized faint erythema disseminated on the patient's (a) forearm, (b) neck and (c) trunk.

time lapse between infusion and appearance of symptoms getting shorter and these symptoms getting severer. Three hours after the fifth IVCY, she suddenly deteriorated with marked tachycardia, hypotension, respiratory distress and diffuse maculopapular rash, suggesting that she was in a preshock state (Fig. 2). Her blood systolic pressure decreased by 48 mmHg from baseline to 78 mmHg, and her pulse rate increased by 38 b.p.m. to 145 b.p.m. At that time, arterial blood gas test showed decreased PaO_2 (44.2 mmHg). The patient immediately received diphenhydramine, methylprednisolone (125 mg i.v.) and i.v. fluids. The blood pressure stabilized without vaso-

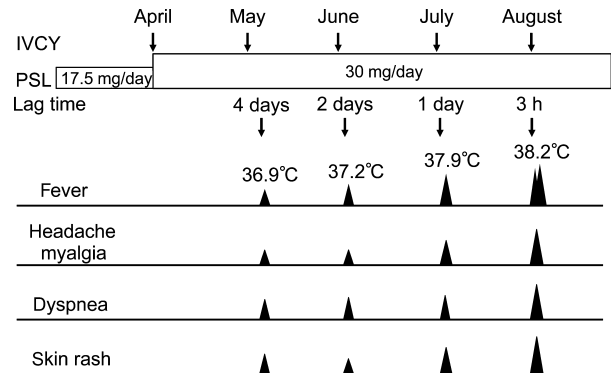


Figure 2. Time course of anaphylactic symptoms during i.v. cyclophosphamide pulse (IVCY) therapy. Degree of anaphylactic reactions became stronger and time lapse between IVCY and appearance of anaphylactic symptoms became shorter as the number of IVCY increased. PSL, prednisolone.

pressors, and other symptoms gradually resolved within 24 h. These series of events made us notice the relationship between these anaphylactic reactions and IVCY because her symptoms appeared only after IVCY. Despite the extraordinarily long time lapse between CY infusion and appearance of these anaphylactic reactions, these events were consistent with late-onset anaphylactic reactions caused by type I hypersensitivity to CY metabolites. Although prick tests and i.d. skin tests with suspected drug or metabolites were not performed for fear of anaphylactic shock induction, we diagnosed her, based on the characteristic clinical courses, as having late-onset anaphylactic reactions related to IVCY. Although monthly IVCY were effective, confirmed by improvement of dyspnea, VC and D_{LCO} on pulmonary function test (1.75 L and 5.80 mL/min per mmHg representing 66.5% and 34.5% of the predicted values, respectively), chest CT manifestations, and decreased serum KL-6 and SP-D levels after the fifth IVCY (1510 U/mL and 85 ng/mL, respectively), we did not perform further IVCY to prevent the induction of anaphylactic reactions. Even after recovering from the preshock state, serum biomarkers kept similar levels. Her ILD had been well controlled with mizoribine (300 mg/day) as a p.o. maintenance immunosuppressive therapy for 1.5 years until there was an increased frequency of dry cough accompanied by increased biomarkers (1621 U/mL and 107 ng/mL for KL-6 and SP-D, respectively) and deterioration in respiratory function (1.49 L and 5.34 mL/min per mmHg, representing 57.2% and 31.8% of the predicted values for VC and D_{LCO} , respectively) in 2011. After that, her ILD was successfully treated with rituximab.⁷

DISCUSSION

Although CY has been reported as a possible causative drug of late-onset anaphylactic reactions, it is clinically difficult to notice the relationship between late-onset anaphylactic reactions and IVCY because there is a long time interval between CY infusion and appearance of symptoms. In our case,

although skin allergy tests were not performed, anaphylactic reactions appeared to be associated with CY infusion because re-administration of CY reproduced these reactions and the degree of reactions got stronger as the number of IVCY increased. Given that mild clinical symptoms related to type I allergic reaction are occasionally similar to manifestations of collagen vascular diseases and easily confused with exacerbations of the underlying diseases, it is important to be aware of late-onset allergic reactions when IVCY is performed for patients with those diseases.

Clinical delay in late-onset anaphylactic reactions is thought to reflect the time to metabolize the drug and then generate metabolite-dependent allergens.⁸ Popescu *et al.*⁴ demonstrated the positive immediate skin test results of CY metabolites, such as 4-hydroxycyclophosphamide and phosphoramidate mustard, but not CY itself, in all of the five patients with late-onset type I hypersensitivity, including four patients with 8–16 h of delay and a patient with 10 days of delay, indicating that immunoglobulin E-mediated allergic reaction to these two metabolites is a major mechanism underlying late-onset anaphylactic reactions. Given that 4-hydroxycyclophosphamide and phosphoramidate mustard reach peak levels within 0.5–3 h and 3–6 h after IVCY, respectively,⁹ there may be other mechanisms due to underlying autoimmune diseases, such as altered metabolism of CY in the liver, to induce these reactions several days after IVCY. Importantly, although serum levels of aspartate aminotransferase and alanine aminotransferase before IVCY were within normal limits (23 and 15 U/L, respectively), they were slightly reduced before the third IVCY (14 and 9 U/L, respectively) and kept the reduced levels thereafter. These results may support the idea that repeated IVCY therapies ameliorated altered CY metabolism due to the patient's autoimmune disease, leading to earlier appearance of allergic reactions afterwards.

Another problem related to adverse reactions after IVCY is that it is difficult to distinguish late-onset type I hypersensitivity from type III hypersensitivity occurring several hours to a few days after administration of the allergens and anaphylactoid reactions showing a quite similar clinical picture to that of anaphylaxis due to non-allergic hypersensitivity reactions. The former two types of allergic reactions are different from each other in that type III hypersensitivity does not trigger anaphylaxis, while type I hypersensitivity does, though some symptoms such as urticarial rash, macular erythema, muscle pain and arthralgia are common manifestations. Regarding discrimination between anaphylactic and anaphylactoid reactions, escalating intensity of her symptoms suggests that her reactions were of an allergic nature. Although high-grade fever is not a common symptom in anaphylactic reactions, presence of pyrexia does not necessarily deny the possibility that her

reactions were due to type I hypersensitivity because pyrexia is not a rare symptom in patients with type I hypersensitivity related to CY.^{4,8,10} Taken together, her symptoms seemed to be typical type I allergic reactions from the beginning, but the longer time interval between CY infusion and appearance of symptoms hindered diagnosis and she finally developed severe anaphylactic reactions. Given that most patients treated with IVCY are under an immunosuppressive condition due to CY and concomitant immunosuppressants, we need to know that the first clinical symptoms of type I hypersensitivity following IVCY may be largely modified and different from typical type I hypersensitivity reactions.

In summary, we presented late-onset anaphylaxis due to IVCY in a patient with SSc/SLE overlap syndrome. These unusual features of anaphylaxis should be taken into consideration when IVCY therapy is conducted in patients with collagen vascular diseases.

CONFLICT OF INTEREST: None.

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