

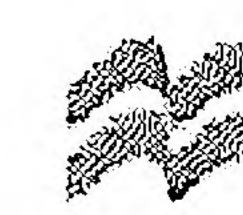
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Case report

Massive pleural effusion attributed to high-dose cyclophosphamide during conditioning for BMT

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Summary:

A 37-year-old male developed massive pleural effusion leading to respiratory failure and electromechanical dissociation within 24 h after the second dose of 4200 mg cyclophosphamide (CY) during conditioning for allogeneic bone marrow transplantation for chronic myelogenous leukemia. After resuscitation and bilateral pleural drainage he recovered within 1 day. Subsequently, total body irradiation was given and with a delay of 1 day the transplantation procedure was continued without major complications. No explanation for this idiosyncratic reaction other than the administration of high dose CY in combination with mesna rescue was found. This reaction has not been reported before in the literature.

Keywords: pleural effusion; cyclophosphamide; bone marrow transplantation

A 37-year-old man suffering from Philadelphia chromosome positive chronic myelogenous leukemia in first chronic phase was admitted for bone marrow transplantation with marrow from his HLA-identical, MLC-negative sister. At admission the patient had no complaints and physical examination and laboratory findings were completely normal. A double-lumen catheter was introduced in the left subclavian vein without complications. Twenty-four hours later conditioning therapy was started with demethoxydaunorubicin 77 mg by continuous intravenous infusion over 48 h (day -12 and -11). Hyperhydration (3 l NaCl 0.45% glucose 2.5%/24 h) and alkalinization (1 l NaHCO₃ 4.2%/24 h) was started at day -7 and continued until day -1. Cyclophosphamide (Endoxan[®], Asta, Bielefeld, Germany) 4200 mg on each of 2 consecutive days was given in a 1-h infusion by peripheral venous infusion. Mesna rescue was administered (at each time point 1400 mg) with cyclophosphamide (days -6 and -5) and 3, 6, 9 and 12 h thereafter. At days -2 and -1 total body irradiation

(TBI) was given in two equal fractions of 450 cGy each. Infection prophylaxis consisted of cotrimoxazole 960 mg two times daily/2 × weekly, ciprofloxacin 500 mg two times daily, aciclovir 400 mg four times daily, amphotericin-B inhalations 5 mg two times daily. Ondansetron 8 mg was given two times daily. On day -4, 21 h after the last CY he complained of pain in his right shoulder radiating to the right arm. Physical examination showed no abnormalities, body temperature was 37.2°C and laboratory findings were all normal. The pain persisted and 24 h later he experienced chest pain which was not related to respiration. Within 8 h he developed progressive dyspnea. Temperature and pulmonary examination remained normal. A chest X-ray showed bilateral pleural effusion without intrapulmonary signs. Arterial blood values were pO₂: 6.9 kPa (N = 10.6–13.3 kPa), pCO₂: 5.9 kPa (N = 4.5–6.0 kPa), pH 7.48 (N = 7.38–7.43), bicarbonate 33.2 mmol/l (N = 22–26 mmol/l). Since overhydration was considered, treatment with diuretics and oxygen was initiated (120 mg furosemide i.v., 4 l O₂/min). Three hours later he deteriorated with severe dyspnea, tachypnea and tachycardia. Blood pressure was 125/82 mmHg, pulse 138/min. No pulsus paradoxus was observed. Percussion of the lungs revealed increasing pleural effusion. On auscultation respiration was reduced over the right lung compared to left. Auscultation of the heart and lungs was completely normal. Electrocardiography showed sinus tachycardia (140/min), with reduced size of the complexes in comparison with previous ECGs. Arterial blood analysis with 4 l/min oxygen supplementation showed: pO₂ 10.3 kPa, pCO₂ 6.8 kPa, pH 7.44 and bicarbonate 34.5 mmol/l. Ultrasound of the heart showed normal left and right ventricular function without pericardial effusion. Massive bilateral pleural fluid was seen. During echocardiography the patient suffered cardiopulmonary arrest with electromechanical dissociation. Resuscitation was started immediately. After 30 min cardiac output was restored and the patient regained consciousness. Perfusion scintigraphic investigation of the lungs showed bilateral defects confluent with the pleural effusions, but no signs of embolism.

Pleural drainage was performed and 5 l of transparent pleural fluid were evacuated. Biochemical analysis revealed protein content: 2.68 g/l; LDH 32 U/l; amylase 3 U/l; glucose 52 mmol/l (serum glucose 38 mmol/l); triglycerides 0.24 mmol/l; leukocytes 0/field; erythrocytes 4/field. Viro-

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logical investigations revealed CMV early antigen and antigen negative; respiratory, adeno-, and enteroviruses all negative. All cultures for bacteria and fungi were negative. Digital subtraction angiography after pleural drainage excluded pulmonary embolism.

After drainage respiratory failure resolved. The patient was extubated 10 h after resuscitation. The drains produced no significant amounts of fluid after 16 h and were removed. Chest X-rays showed only minimal residual pleural fluid on the left side which completely resolved after 3 days, and no intrapulmonary abnormalities.

Because of the rapid recovery, we decided to proceed with the conditioning regimen. TBI was given without further complications (4.5 Gy on each of 2 consecutive days). A T cell-depleted marrow graft¹ was given 1 day after the last irradiation. On day 15, his granulocyte count was $>500 \times 10^6/l$ and he became transfusion independent. He developed mild grade II graft-versus-host disease of the skin and liver. On day 21 he was discharged in good condition. Now, 6 months after BMT he is clinically well without any pulmonary abnormalities and in remission from CML.

Discussion

We hypothesize that the high dose cyclophosphamide alone or in combination with mesna was responsible for the reaction described. All prophylactic medication given during conditioning was continued after the incident without adverse effects. An interaction between cyclophosphamide and one of these agents can not be completely ruled out. We found no evidence of an infectious agent. Overhydration was unlikely. The bodyweight was stable before the incident and fluid balance was adjusted. He had no symptoms of peripheral edema and no signs of intrapulmonary overhydration or congestive heart failure. Diuretics did not improve his condition nor prevented further progression.

Diffuse myocardial injury with progressive congestive heart failure is a well known subacute complication of high-dose cyclophosphamide therapy. In such patients myocarditis has been documented with typical pathologic findings. Fibrinoid pericarditis is also a common finding. The incidence of this complication varies between 7–25%. A correlation has been established between incidence and total dose of cyclophosphamide administered.^{2–5} Angelucci *et al*⁶ described eight thalassemic patients with cardiac tamponade caused by pericardial effusion with physiochemical characteristics of transudate after high-dose CY. They concluded that the absence of myocardial lesions and complete resolution of the syndrome after fluid removal strongly indicated that the pericardial membranes played the main part of the pathogenesis of the syndrome.

In the patient described, no myocardial or pericardial involvement was seen but the underlying mechanism may be similar. Ozkaynak *et al*⁷ observed a high incidence of pleural effusion in children with veno-occlusive disease

(VOD) after conditioning with busulphan and cyclophosphamide. In this patient no busulphan was used and no signs of VOD were present.

Mesna has been well tolerated by all our patients up to now. High-dose mesna (>60 mg/kg per dose) can produce gastro-intestinal side-effects, eg nausea, vomiting and diarrhea, and all of these symptoms are difficult to distinguish from side-effects produced by CY. The dose we use as CY rescue was only 20 mg/kg. No data are available on pleural effusion during mesna therapy in combination with oxazaphosphyrines such as CY. In more than 150 patients conditioned with a regimen consisting of Ida, CY and TBI we have never seen acute cardiac or acute pulmonary toxicity during or after administration of demethoxydaunorubicin.⁸ Demethoxydaunorubicin (42 mg/m²) is administered as a continuous infusion over 48 h. A relation between demethoxydaunorubicin and pleural effusion has never been reported in the literature. The time between administration of the drug and the first symptoms (6 days) does not make a direct causal relation very likely. A late interaction, however, between metabolites of demethoxydaunorubicin and high-dose cyclophosphamide could be possible.

In patients with chest pain and progressive dyspnea after administration of high-dose CY the possibility of massive pleural effusion should be considered, with pleural drainage as a life-saving procedure.

References

- Schattenberg A, De Witte T, Preijers F *et al*. Allogeneic bone marrow transplantation for leukemia with marrow grafts depleted of lymphocytes by counterflow centrifugation. *Blood* 1990; **75**: 1356–1363.
- Appelbaum FR, Strauchen JA, Graw RG Jr *et al*. Acute lethal carditis caused by high-dose combination chemotherapy. A unique clinical and pathological entity. *Lancet* 1976; **i**: 58–62.
- Goldberg MA, Antin JH, Guinan EC *et al*. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood* 1986; **68**: 1114–1118.
- Gottdiener JS, Appelbaum FR, Ferrans JV *et al*. Cardiotoxicity associated with high dose cyclophosphamide therapy. *Arch Intern Med* 1981; **141**: 758–763.
- Buja M, Ferrans VJ, Graw RG Jr. Cardiac pathologic findings in patients treated with bone marrow transplantation. *Hum Pathol* 1976; **7**: 17–45.
- Angelucci E, Mariotti E, Lucarelli G *et al*. Sudden cardiac tamponade after chemotherapy for marrow transplantation in thalassaemia. *Lancet* 1992; **339**: 287–289.
- Ozkaynak MF, Weiberg K, Kohn D *et al*. Hepatic veno-occlusive disease post-bone marrow transplantation in children conditioned with busulphan and cyclophosphamide: incidence, risk factors and clinical outcome. *Bone Marrow Transplant* 1991; **7**: 467–474.
- Raemakers J, De Witte T, Schattenberg A *et al*. Prevention of leukemic relapse after transplantation with lymphocyte depleted marrow by intensification of the conditioning regimen with a 6-day continuous infusion of anthracyclines. *Bone Marrow Transplant* 1989; **4**: 167–171.