

Impedance cardiography in the diagnosis of capillary leak syndrome caused by doxorubicin therapy in a patient with myeloma multiplex

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Abstract

Cytotoxicity of drugs can be a cause of cardiorespiratory disorders connected with chemotherapy. Doxorubicin is an antibiotic from the group of anthracyclines effective in antineoplastic therapy of solid and hematopoietic tumors. The most common cause of therapy ceasing is its cardiotoxicity. However, a lung injury connected with its cytotoxic activity to pulmonary endothelium (capillary leak syndrome) can be an equally serious complication. In the case presented, rapid, multi-profile diagnostics with the use of impedance cardiography, a modern noninvasive tool of hemodynamic monitoring, led to the recognition and effective treatment of a rare clinical syndrome. (Cardiol J 2010; 17, 1: 88–91)

Key words: dyspnoe, anthracyclines, doxorubicin, impedance cardiography, multiple myeloma

Introduction

Noncardiogenic pulmonary edema (NCPE) is a rare and barely known clinical syndrome caused by toxic injury of the lungs connected with chemotherapy. It is characterized by breathing disorders, chest discomfort, hypoxemia and a gradual deterioration of a patient's general condition, with a lack of heart failure evidence [1, 2]. Capillary leak syndrome (CLS) can be one of the causes of cardiorespiratory disorders connected with pharmacotherapy and it is connected with pulmonary endothelial damage and leakage of pulmonary capillary vessels [1]. Doxorubicin (adriamicin, adriblastin) is a cytostatic antibiotic from the group of anthracyclines, frequently used in the treatment of solid and hemato-

poietic tumors. Anthracyclines are very effective. But their use is limited due to serious adverse effects, especially the most frequent: cardiotoxicity [3]. The case we present exemplifies another severe complication of doxorubicin therapy connected with its pulmotoxicity and is a significant clinical problem requiring rapid and specific treatment.

Case report

A 71 year-old male suffering from myeloma multiplex Ig A (stage III) was admitted to the Department of Internal Diseases and Hematology of Military Medical Institute for the second cycle of chemotherapy (VAD, vincristine, doxorubicin,

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dexamethasone). On admission, the patient was in a rather good general state, afebrile, complaining about general weakening, decreased exercise tolerance, symmetric crural oedemas. Physical examination showed discreet crepitations on the base of the lungs, regular heart rhythm 110/min, blood pressure 100/80 mmHg, mild crural oedemas. Anomalous results of laboratory tests were as follows: normocytic anemia: red blood cells 3.28 mln/mm³ (normal values: 3.50–5.50 mln/mm³), hemoglobin 9.9 g/dL (11–18 g/dL), hematocrit 29.3% (35–55%). Moreover, renal dysfunction features were observed: creatinine level 2.2 mg/dl (0.4–1.5 mg/dL), urea 92 mg/dL (21–43 mg/dL), without electrolyte disorders. Electrocardiogram revealed sinus tachycardia 120/min, no arrhythmias, no ischemic features. On the third day of hospitalization planned chemotherapy was initialized and it was continued as intravenous infusions for four following days: vincristine 0.4 mg/day, doxorubicin 16 mg/day, dexamethasone 40 mg/day. In this period, the patient did not reveal any new complaints and there was no progression of renal dysfunction in laboratory tests. On the second day after chemotherapy, in the early morning, the patient reported progressive weakening, dyspnoea and limb shivering. Physical examination showed tachycardia about 110/min (with additional premature beats), blood pressure 100/60 mm Hg, normal vesicular murmur, without crepitations and crural oedemas modestly bigger than on admission day. About midday, the patient's clinical state aggravated gradually: dyspnoea increased rapidly, breathing rate was about 20–30/min, tachycardia was 120–140/min and hypotension 70/50 mm Hg.

Lungs auscultation revealed a discreet, symmetrical decrease in breath sounds, without any other abnormalities, oxygen saturation about SatO₂ = 90–96%. In view of a potential cardiac cause of the sudden worsening of the patient's state, continuous monitoring was recommended (electrocardiogram, SatO₂, blood pressure measurement every 30 min). In the meantime troponin I level was estimated (normal value in two assays). Electrocardiogram was also performed (heart rhythm 130/min, besides as at admission), echocardiography did not show any features indicating heart failure or ischemia (normal heart chambers' diameters, contractility not impaired, ejection fraction 65%). Oxygen and empirical therapy with dopamine at renal dose and furosemide in continuous infusion (80 mg/day initially) was introduced with a moderate improvement in blood pressure control (90–100/70–80 mm Hg) and without significant clinical amelioration.

On the next day, (the tenth day of hospitalization) the patient's general state was still severe: rest dyspnoea, tachypnoea, general weakening, tachycardia 120–140/min and tendency to hypotension persisted; body temperature was 37°C. Supposing pulmonary thromboembolism, low molecular weight heparin was introduced at a dose of 1 mg/kg subcutaneously and a computed tomography angiography of chest was performed immediately without presence of embolic material in pulmonary vessels and any pathology in chest organs. In laboratory tests, hypoalbuminemia was observed: total protein level 5.5 g/dL (normal: 6.0–8.0 g/dL), albumins 2.9 g/dL (3.5–5.5 g/dL), without progression of renal dysfunction: creatinine level 2.0 mg/dL, urea level 114 mg/dL, no liver dysfunction. Ongoing treatment was intensified: furosemide in continuous infusion (80 mg/day), dopamine and dobutamine initially at doses 2 µg/kg bw./min and 10 µg/kg bw./min, modified according to blood pressure.

The next day, due to the patient's persisting severe general state, significant rest dyspnoea and weakening, limiting activity to the bed area, impedance cardiography (ICG) was performed (five-minute rest examination) with use of Niccomo (Medis, Germany). It revealed a high level of thoracic fluid content (TFC), low cardiac index (CI), probably connected with very low stroke index (SI), compensated by a high heart rhythm and systemic vascular resistance. The value of cardioimpedance parameter describing heart inotropic function, Heather index (HI), was normal (Table 1). On the basis of ICG examination, the hypothesis of toxic lung injury and CLS was propounded. Methylprednisone therapy (Solu-Medrol) at high intravenous doses (initially 1.5 mg/kg bw./day) and a limitation of fluid supply to 2,000 mL/day was introduced. The next day a significant improvement in the patient's state was observed, dyspnoea gradually subsided (SatO₂ = 96%, without oxygen therapy), weakening diminished, breath sounds were normal, blood pressure 120/80 mm Hg, tachycardia persisted: 130/min. On the third day of methylprednisone therapy, in view of our patient's subsequent amelioration (without dyspnoea, better tolerance of exercise, discreet crural oedemas), therapy with dopamine, dobutamine and furosemide was aborted. On the following days of steroid therapy further improvement in the patient's general state was observed. On the sixteenth day of hospitalization, a control ICG examination was performed and revealed lower heart rhythm (101/min), CI and HI, still high TFC. On the twentieth day of hospitalization the

Table 1. Values of hemodynamic parameters in impedance cardiography examinations.

| Hemodynamic parameters | Impedance cardiography examinations | | | Unit |
|----------------------------------|---|--|--|---------------------------------------|
| | I 10 th day of hospitalization | II 6 th day after examination I | III 52 nd day after examination I | |
| Thoracic fluid content | 46.77 ± 0.57 | 50.93 ± 0.40 | 30.66 ± 0.18 | 1/kΩ |
| Cardiac index | 2.80 ± 0.63 | 2.09 ± 0.21 | 1.72 ± 0.33 | L/min/m ² |
| Stroke index | 21.59 ± 4.91 | 20.64 ± 2.03 | 22.75 ± 4.40 | mL/m ² |
| Heather index | 11.70 ± 2.68 | 7.08 ± 1.17 | 7.33 ± 1.24 | Ω/s ² |
| System vascular resistance index | 2460.74 ± 433.81 | 2927.95 ± 306.08 | 3456.08 ± 524.20 | dyn/s/cm ⁵ /m ² |
| Heart rhythm | 129.53 ± 4.33 | 101.21 ± 3.28 | 75.73 ± 2.26 | 1/min |
| Systolic blood pressure | 120.37 ± 3.50 | 103.54 ± 2.54 | 100.92 ± 3.07 | mm Hg |
| Diastolic blood pressure | 77.56 ± 1.50 | 72.79 ± 0.41 | 70.31 ± 0.73 | mm Hg |

patient was discharged from hospital with recommended oral pharmacotherapy (furosemide 80 mg/day, spironolactone 50 mg/day, ramipril 5 mg/day and prednisone 20 mg with gradual dose reduction). His next admission to the clinic was planned for one month hence in order to continue the treatment and perform control examinations (ICG and echocardiography).

On admission after one month, the patient was in a rather good general state, with complaints as at the first time (general weakening, decreased exercise tolerance). Physical examination showed regular heart rhythm 110/min, without other abnormalities. In echocardiography examination, hemodynamic function of heart muscle was the same as during the previous hospitalization. ICG revealed significant decrease of TFC, normal heart rhythm (about 75/min), moderately lower CI (Table 1). The patient underwent a chemotherapy cycle without anthracyclines (VMCP, vincristine, melphalan, cyclophosphamide and prednisone) and no serious adverse effects were observed in course or after therapy.

Discussion

Doxorubicin is an antibiotic from the group of anthracyclines of antineoplastic activity, connected with its ability to inhibit gene expression and cause apoptosis of neoplastic cells. The most common cause of ceasing therapy with doxorubicin is its cardiotoxicity. Anthracycline-induced cardiotoxicity can be manifested as acute or subacute (symptoms in course of therapy), chronic (in 12 months after the last dose) and delayed chronic (between one and five years after therapy). It is characterized by impaired heart contractility (ejection frac-

tion < 40–45%) with left ventricle and left atrium enlargement, rarely with the presence of pericardial fluid. In electrocardiogram, the following can be observed: sinus tachycardia, prolonged QTc interval, supraventricular and ventricular arrhythmias. Clinically the disease can manifest as acute or chronic heart failure, arrhythmias or even sudden cardiac death. It can also be mildly symptomatic or asymptomatic. The recognized risk factors of anthracyclines toxicity are: age (below 4 years and over 65 years), female sex, previous therapy with other cytostatic agents (i.e. anthracyclines, cyclophosphamide, fluorouracil), ischemic heart disease, hypertension, heart valve disease, diabetes mellitus, previous or present chest radiotherapy, high summary dose of drug (> 450–550 mg/m²), especially in a short time period, and simultaneous therapy with drugs such as cyclophosphamide, mitomycin and paclitaxel [3–5].

In the case we present, among the potential risk factors of anthracyclines-induced cardiomyopathy were: age > 65 years and previous therapy with doxorubicin (one VAD cycle one month before admission). On the basis of hemodynamic disregulations (tachycardia, hypotension, arrhythmia in the shape of supraventricular premature beats) and severe dyspnoea, on the second day after chemotherapy the diagnosis of acute heart failure induced by anthracyclines was propounded. In the examinations performed (electrocardiography, echocardiography, computer tomography angiography, troponin I test) there was no evidence of heart muscle dysfunction and pulmonary thromboembolism. Bearing in mind a possible noncardiogenic cause of dyspnoea, ICG examination was performed. It is a modern noninvasive tool of hemodynamic monitoring enabling the estimation of cardiac output (CO)

and many other hemodynamic parameters such as: heart rhythm, blood pressure, systemic vascular resistance and especially thoracic fluid content. It is used in monitoring patients in intensive care units, diagnosis and treatment of heart failure and hypertension [6]. In the case reported, ICG revealed high TFC in presence of very low SI and normal HI (Table 1). The results of this examination, performed during the severe clinical state, did not correspond with the typical hemodynamic profile of acute heart failure. Confrontation of ICG measurements with physical examination (normal breath sounds) and echocardiography (normal contractility) proved to be decisive. An analysis of these results led to the diagnosis of commencing noncardiogenic pulmonary interstitial oedema induced by toxic action of doxorubicin on alveolar-capillary barrier. High thoracic fluid content in presence of low stroke volume and preserved systolic function of heart muscle indicated interstitial fluid retention with decreased preload. Simultaneous progressive hypoalbuminemia of unknown etiology and increasing crural oedemas confirmed the diagnosis of CLS with dominating pulmonary manifestation.

It is a rare disease, characterized by sudden oedemas, hypotension and hypoalbuminemia connected with pathological capillary hyperpermeability. On the base of its pathophysiology, there is endothelial cells damage and activation of local inflammatory reaction. The disease is characterized by multifactor pathogenesis (i.e. bone marrow, liver, renal transplantation, chemotherapy) and varied clinical features (systemic, cutaneous and pulmonary form). There are reported clinical cases of CLS in patients with hematopoietic tumors, including multiple myeloma [7].

On the basis of available publications presenting effective treatment of similar clinical states [8], in our case methylprednisone therapy at high intravenous doses was introduced with rapid clinical amelioration. Effectiveness of the therapy confirmed toxic-inflammatory pathogenesis of the observed cardio-pulmonary disorders.

Results of the second ICG examination, performed at the time of general state stabilization, seemed surprising and disappointing at first glance: TFC persisted high, parameters of cardiac systolic function (CI, SI, HI) were lower than in the first examination, significant improvement was limited to heart rhythm control (Table 1). However, it is worth mentioning that the first ICG measurement was performed in a course of treatment with dopamine and dobutamine that might have affected

the values of contractility parameters. In an analysis of the cause of fluid retention, persisting hypoalbuminemia and prolonged regression of pathophysiological changes in lungs seemed to be important. To verify this hypothesis, a control ICG examination was performed after a month, revealing anticipated TFC normalization (Table 1). In view of the persisting features of low cardiac output control, electrocardiogram and echocardiography were performed that did not show any cardiotoxicity of doxorubicin.

Summary

Severe adverse effects connected with chemotherapy are a common clinical problem, requiring urgent and effective treatment. The use of impedance cardiography in the case reported proved important in the diagnosis of an uncommon syndrome demanding rapid and specific therapy. The presented case report convinces us that in cases of problematic and atypical patients, every diagnostic hint may be of crucial importance in the arduous diagnostic-therapeutic process.

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