Transfusion-related acute lung injury in a patient diagnosed with hypofibrinogenemia after a cesarean section – case report and review of the literature

Ostre potransfuzyjne uszkodzenie płuc u pacjentki po cięciu cesarskim z wrodzoną hipofibrynogenemią – opis przypadku i przegląd piśmiennictwa

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Abstract

Background: *Transfusion-related acute lung injury (TRALI) is a rare, but potentially fatal, complication of blood product transfusion, manifesting as acute respiratory distress syndrome. In most cases, TRALI is associated with massive transfusion of fresh frozen plasma and platelets.*

Case report: *A 38-year-old-woman at 40 weeks gestation was admitted to hospital with spontaneous labor contractions. A cesarean section was performed due to feto-pelvic disproportion and a male infant (Apgar 10) was delivered. After 37 hours low hemoglobin level and growing subfascial hematoma were detected. Urgent relaparotomy was carried out. The blood loss was over 1500 ml and a massive transfusion (6 units of red cell concentrate, 8 units of fresh frozen plasma and 6 units of cryoprecipitate) was necessary. The patient developed symptoms of acute respiratory distress 10 hours after relaparotomy. No pathological findings were shown in echocardiography and ECG. Chest CT revealed pulmonary edema. Low fibrinogen levels were observed in laboratory tests, decreasing in time after transfusion of the blood products to 1.0/L. Oxygen therapy with facial mask was initiated, furosemide was administered and continued for three days until symptom resolution. A series of hematological tests performed after the patient was discharged from hospital confirmed the diagnosis of TRALI and congenital hypofibrinogenemia.*

Conclusion: *Congenital hypofibrinogenemia may be responsible for the development of subfascial hematoma, a complication of cesarean section, necessitating relaparotomy. The following massive transfusion of blood products resulted in a potentially fatal complication in a form of TRALI.*

Key words: **acute respiratory distress syndrome / acute lung injury / blood transfusion / / post-transfusion complications / postpartum hemorrhage /**

Streszczenie

Ostre poprzetoczeniowe uszkodzenie płuc (transfusion related acute lung injury, TRALI) jest powikłaniem, które występuje po przetoczeniu preparatów krwiopochodnych i manifestuje się, jako zespół ostrej niewydolności oddechowej (acute respiratory distress syndrome, ARDS).W większości przypadków TRALI jest związany z masywnym przetoczeniem świeżo mrożonego osocza i płytek krwi.

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Opis przypadku: *U 38 letniej pacjentki w 40 tygodniu ciąży wykonano cięcie cesarskie w drugim okresie porodu z powodu niewspółmierności główkowo-miednicowej. Po 37 godzinach po cięciu cesarskim rozpoznano u pacjentki obecność krwiaka podpowięziowego. Z powodu znacznej anemizacji i objawów narastania krwiaka wykonano pilną relaparotomię. Ze względu na znaczną utratę krwi (ponad 1500 ml) przetoczono 6 jednostek masy erytrocytarnej, 8 jednostek osocza i 6 jednostek krioprecypitatu. 10 godzin po relaparotomii pacjentka rozwinęła objawy ostrej niewydolności oddechowej. Nie wykazano zmian patologicznych w echokardiografii i EKG. W tomografii komputerowej klatki piersiowej stwierdzono cechy obrzęku płuc. W badaniach laboratoryjnych zwracały uwagę niskie wartości fibrynogenu do wartości 1,0/L, obniżające się od momentu przetoczenia preparatów krwiopochodnych. Włączono tlenoterapię przy użyciu maski twarzowej oraz leki moczopędne. Przeprowadzono szereg testów hematologicznych, które potwierdziły rozpoznanie TRALI oraz wrodzoną hipofibrynogenemię.*

Wnioski: *Wrodzona hipofibrynogenemia może być odpowiedzialna za obserwowane powikłanie cięcia cesarskiego w postaci krwiaka podpowięziowego wymagającego relaparotomii. Następowe masywne przetoczenie preparatów krwi było związane z ciężkim powikłaniem w postaci zespołu TRALI.*

Słowa kluczowe: **ostra niewydolność oddechowa** / **ostre uszkodzenie płuc** / / **przetoczenie krwi** / **powikłania poprzetoczeniowe** / **krwotok poporodowy** /

Introduction

Transfusion-related acute lung injury (TRALI) is a complication of blood product transfusion that manifests as acute respiratory distress syndrome (ARDS). It is estimated to occur at 1:2000-5000 transfused blood units and in 1/625 of patients who undergo transfusion [1]. In most cases TRALI is associated with massive transfusion of fresh frozen plasma and platelets [2]. There are two forms of TRALI: immunological and non-immunological. In case of the former, the donor antibodies are directed against human leukocyte antigens (HLA) or against specific human granulocytic antigens. Alloantibodies react with recipient granulocytes, causing their agglutination, which in turn leads to granulocyte activation and production of adhesive particles. It is followed by migration of granulocytes to the interstitial space located between pulmonary alveoli and vascular endothelium. Granulocytes release inflammatory mediators which damage the vessels walls and increase their permeability, causing the development of non-cardiogenic pulmonary edema [3]. Immunological TRALI may develop also when recipient antibodies react against donor antigens. This form is more common and is associated with worse prognosis. Non-immunological TRALI is caused by simultaneous occurrence of two independent factors – the 'two-hit mechanism': presence of active mediators in donor blood and activation of the recipient immunological system due to infection, trauma or surgical procedure [4]. Lipids and cytokines activate granulocytes that release inflammatory mediators which in turn damage the endothelium of the capillaries in the lungs, resulting in transudate into the pulmonary alveoli and development of non-cardiogenic, non-inflammatory pulmonary edema [5, 6].

Sudden asphyxia remains to be the main symptom of TRALI. Saturation of the arterial blood drops to < 90%, crackling and wheezing appear over lung fields, often accompanied by tachycardia and hypo- or hypertension. Depending on symptom severity, high fever and central cyanosis may occur as well. Leucopenia is a typical but short-lasting symptom, that usually persists for a short time and can easily be overlooked [7]. Diagnostic criteria for TRALI, developed during the conference in Toronto, are as follows [8]: 1. acute lung injury (ALI): a) newly recognized respiratory distress without other respiratory distress risk factors, b) hypoxemia: PaO2/FiO2 ≤ 300 or SpO2 < 90% (without oxygen therapy), c) bilateral pulmonary edema on chest X-ray; 2. Lack of acute pulmonary trauma before transfusion; 3. First symptoms occurring up to 6 hours after transfusion.

TRALI treatment is symptomatic and is aimed at sustaining hemodynamic balance. Passive oxygen therapy is used in mild cases of TRALI, but in about 70% of patients intubation and mechanical ventilation are required. Patients with hypotension usually require vasopressor agents. There is not enough evidence to support the efficacy of glucocorticoids, non-steroid anti-inflammation medications, surfactant and diuretics [7]. Prognosis in TRALI is good, the syndrome rarely causes late consequences. Clinical condition of most patients improves within 48-96 hours after symptom onset. The complication usually resolves completely within 7 days. Currently, this syndrome is counted amongst the most common lethal post-transfusion complications: mortality rate is 5-10% [3, 9, 10], and even higher for immunological TRALI. Polish data on morbidity and mortality rate of TRALI is unavailable and only a few cases are described in the literature. We present a case of TRALI in a patient after caesarean delivery, complicated by subfascial hematoma, who was then diagnosed with congenital hypofibrinogenemia.

Case report

TRALI occurred in a 38-year-old woman following a transfusion of blood products after a caesarean section complicated by subfascial hematoma. The patient (height: 150 cm, weight before pregnancy: 43 kg), treated with laevorotatory thyroxin due to hypothyroidism, was in her second pregnancy, after a previous miscarriage. The course of pregnancy was uneventful until 39 weeks of gestation when the episodes of increased blood pressure without associated proteinuria occurred (once max. 190/100 mm Hg, then up to 160/95), but no pharmacological treatment was administered. The labor started spontaneously at 40 weeks of pregnancy. After admission to hospital, a feto-pelvic disproportion was diagnosed and a caesarean section was performed: a male infant with 2840 g birth weight was delivered with the Apgar score of 10. The course of the operation was

Table I. Test results: blood morphology.

	25h after cc	37h after cc decision of relaparotomy	9h after relaparotomy
WBC (G/l)	17.4	11.10	12.73
RBC (mln/µl)	3.09	2.49	3.28
HCT (l/l)	28.6	21.6	28.6
HBG (g/dl)	9.7	7.3	10.0
PLT (tys.)	186	107	113

Table II. Test results: blood gases.

	16h after relaparotomy	20h after relaparotomy	32h after relaparotomy
pH	7.46	7.5	7.47
pCO2 (mmHg)	35	37	38.8
pO2 (mmHg)	60	60	88.9
sO2 (%)	92	92.8	98.1
BE (mmol/l)	1.1	5.7	4.5
HCO3 (mmo/l)	25.8	29.1	28.5

Table III. Test results: coagulation system.

	0 day after relaparotomy (after 4j.FFP)	1 day after relaparotomy	7 days after relaparotomy	10 days after relaparotomy
D-dimer (ng/ml)	2162	-	33452	16381
Fibrinogen (g/l)	1.7	2.0	1.1	1.0
APTT (sec.)	34.59	33.47	32.6	
INR	1.1	1.0	1.1	
Thrombin time (sec.)	23.46	20.21	23.62	

uneventful, blood loss was estimated at 600 ml. After 37 hours, a relaparotomy was performed due to significant anemia (Table I) and the presence of an enlarging subfascial hematoma. The origin of the hematoma turned out to be only small blood vessels in the dissected pyramidal muscle, none of the major vessels was found to be responsible for bleeding. Over 1500 ml of liquid and clotted blood was evacuated. The following transfusion included 6 units of red cell concentrate, 8 units of fresh frozen plasma and 6 units of cryoprecipitate, additionally amoxicillin with clavulanic acid and 1.0 g of Exacyl were administered.

Clinical symptoms of respiratory insufficiency started to occur gradually, 10 hours after the relaparotomy: coughing, asphyxia and crackling heard bilaterally over the lungs. The arterial blood gas test confirmed laboratory features of respiratory insufficiency. The oxygen therapy with facial mask was initiated. The asphyxia regressed after furosemide was administered. Features of paralytic ileus were temporarily present for the next 24 hours. Chest X-ray showed a decrease in the transparency of the middle-lower field of the right lung and blurred right side of the diaphragm dome – parenchymal infiltrates and infiltrate in the upper field of the right lung. The imaging of the left lung was normal. The findings were interpreted by a radiologist as inflammation-related. Echocardiography showed no pathological findings, apart from slightly increased systolic pressure in the right ventricle. The ECG was normal.

Subsequent chest CT revealed pulmonary edema: presence of bilateral perihilar parenchymal infiltrates, peripherally thickened interlobular septa and fluid in both pleural cavities. Bronchial tree was patent, and lymph nodes of the mediastinum and pulmonary hilum were unchanged. CT scan of the abdomen showed edema of subcutaneous tissue and thickened left rectus abdominal muscle, but no fluid accumulation.

The treatment with oxygen and furosemide was continued due to poor diuresis. Disorders subsided 36 hours after relaparotomy. On the third day after relaparotomy signs of inflammations were observed in lab tests: CRP: 210 mg/l, PCT 9 mg/l, neutrophilia (white blood cells differential: neu 84.1%, lymphs 9%, monos 6.6% eos 0.1%, baso 0.2%). Body temperature remained normal. Antibiotic therapy was altered: doxycycline and ciprofloxacin were administered. The general condition of the patient improved on the following days. Since the third day after the caesarean section the patient was treated with alpha-methyldopa and enalapryl, with good effect, due to arterial hypertension. No abnormal bleeding was noted. Low fibrinogen levels that tended to decrease in time after transfusion (to a value of 1.0/L), were observed. Due to the suspected TRALI syndrome, hematological

tests were performed. Patient blood samples, taken before the first transfusion and on day 5 after the transfusion, lymphocytotoxic test revealed the presence of 10% PRA lymphocytotoxic antibodies (PRA: percentage of antibodies reacting with human leukocytes antigens). proBNP was determined – natriuretic peptide B-type in the serum: 227 pg/ml (normal<125). Fibrinogen concentration was 0.9g/l three weeks after the caesarean section. The patient was referred for further hematological diagnostic tests. Congenital hypofibrinogenemia was confirmed in a series of hematological tests and the patient was counseled about possible risk and the need of fibrinogen supplementation in cases of trauma, surgical procedure or more profound bleeding of any kind.

Disscussion

The clinical presentation of the presented case of TRALI was ambiguous, with the immunological reaction as the most probably suspected cause of acute respiratory distress. The diagnosis was supported by absence of disease in medical history, relatively good condition of the patient and the occurrence of respiratory distress symptoms after blood products transfusion. Nevertheless, septic and cardiologic causes of the respiratory distress were taken into consideration as well. Cardiogenic causes of respiratory distress were quickly excluded by additional tests. Septic causes of respiratory distress were supported by laboratory test results (CRP, PCT, neutrophilia in WBC), as well as by some clinical symptoms (paralytic ileus). Determining proBNP (serum level of the natriuretic peptide B-type) turned out to be very useful in differential diagnosis. Increased concentration of that peptide indicated activation of a compensating mechanism which preceded heart failure symptoms. Values of that peptide were above the normal limits in the presented case.

Treatment of TRALI usually includes oxygen therapy and mechanical ventilation. In the described case a symptomatic treatment in a form of oxygen therapy and diuretics was implemented but there was no need for mechanical ventilation. The treatment, applied in accordance with the international consensus, proved to be successful and the symptoms of ARDS subsided in the course of three days. According to the literature, the use of diuretics remains controversial. Most authors are of the opinion they should not be used, especially in cases when the patient can benefit from administration of fluids. In the presented case, the use of diuretics resulted in a prompt decrease of asphyxia and improvement in patient clinical condition.

Post-transfusion pulmonary trauma may occur at any age, with the same frequency for both, men and women. Risk factors for TRALI include serious clinical conditions prior to transfusion, especially severe hematological and cardiac diseases. In the described case, a severe anemia was observed, which undoubtedly contributed to the deterioration of patient condition. Moreover, congenital hypofibrinogenemia was confirmed in the patient. Transfusion-related acute lung injury usually develops in the course of transfusion or within 6 hours thereafter [1]. In most cases the symptoms occur during the first hours after the transfusion [11], although there are reports of atypical course of TRALI with symptoms occurring after 48 hours [5].

A shorter storage time of blood products [12], as well as introduction of leukofiltration which would remove antibodies from donor blood, have been suggested in order to prevent TRALI. It seems that introduction of an obligatory blood cell irrigation to remove biologically active lipids would be favorable as well [13]. Nevertheless, there is no large, randomized clinical research which would confirm usefulness of such procedures. Also, each of those procedures would considerably increase the costs of blood products treatment, thus none of them is currently recommended. Taking blood samples from female donors who gave birth to more than one child is avoided in many countries. Undoubtedly, it decreased the frequency of TRALI, but did not eliminate it altogether [14]. In cases when the presence of anti-leukocyte antibodies is detected in donor blood, a specific code of conduct is required. In the reported case, the PRBC (packed red blood cells) should be leukocyte low and the transferred BPC (blood platelets concentrate) should be prepared from blood of donors chosen according to the negative cross matching of a lymphocytotoxic test – LCT.

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