

## UNEXPECTED POSITIVE EFFECT OF FRESH FROZEN PLASMA ON STANDARD ANTICOAGULATION IN THE CASE OF PULMONARY EMBOLISM ACCOMPANIED BY SEPSIS – A CASE REPORT

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### ABSTRACT

**Introduction.** In recent years there have been significant advances in the diagnosis and management of venous thromboembolism. This has resulted in the establishment of detailed diagnostic and therapeutic guidelines. Despite the benefits coming from their implementations, a clinical outcome of thromboembolic complications in particular patients poses a number of diagnostic difficulties. Treatment results and prognosis, despite following commonly recognized therapeutic standards, are difficult to predict.

**Aim.** This paper aimed at presenting an atypical course of high-risk pulmonary embolism (PE) and the remote outcome of its treatment in a surgical patient with an initial low risk of thrombotic complications.

**Case study.** The patient was a 58-year old female with a history of primary arterial hypertension who was electively operated on for euthyretic polynodular goiter. On the 2<sup>nd</sup> postoperative day, she had to be resuscitated due to PE accompanied by sepsis with disseminated intravascular coagulation and shock. As shock symptoms did not subside despite the administration of typical treatment (Dextran, intravenous infusion fluids, dopamine, heparin, broad-spectrum antibiotics), and because of gastrointestinal bleeding suspicion, the patient was also administered fresh frozen plasma. Following resuscitation, lasting 2.5 hours, long-term improvement in hemodynamic parameters occurred. After respiratory therapy, lasting several hours, a gradual improvement of the patient's general condition was observed. She regained consciousness, dyspnea subsided, and features of acute right ventricular overload gradually subsided in electrocardiogram.

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**Results and discussion.** On the one hand, the effectiveness of a combined treatment employing heparin and fresh frozen plasma could have resulted from its effect on improving tissue hypoperfusion secondary to the shock; and, on the other hand, because of the coexisting intravascular coagulation process. Fresh frozen plasma, apart from its commonly known procoagulative effect, may also enhance fibrinolytic processes. The potential influence of endogenous anticoagulants contained in plasma with respect to the course of PE has been discussed. It may have contributed to the regression of PE symptoms, despite the fact that in the acute phase the patient was on heparin only.

**Conclusions.** Fresh frozen plasma, due to its endogenous anticoagulation activity, may positively influence the course of high-risk PE.

**Key words:** pulmonary embolism (PE), surgical procedure, heparin, fresh frozen plasma

## INTRODUCTION

The clinical likelihood of venous thromboembolism (VTE) is assessed individually for each patient on the basis of the presence of known risk factors [1]. Risk factors, which are most dangerous, include: age, obesity, congenital and acquired thrombophilia, neoplastic diseases, acute and chronic inflammatory diseases, paroxysmal nocturnal hemoglobinuria, long-term immobilization with venostasis, injuries, cardiac or respiratory failure, and hormonal therapy [1]. A specific risk group involves patients treated at surgical departments. It is estimated that thromboembolic complications in this population who have undergone surgical procedures account for 65% of all such complications observed in hospitalized patients [9]. It is believed that major operations, especially those involving lower extremities, pelvis and abdominal cavity, predispose one to more frequent thromboembolic complications [1, 13]. A significant advancement with respect to antithrombotic therapy has been noted within the last 30 years. A number of detailed guidelines concerning treatment have been established, and benefits stemming from implementation of particular therapeutic procedures have also been recognized. Nevertheless, a clinical course of thromboembolic complications in individual cases poses numerous diagnostic difficulties, and treatment results and prognosis despite following commonly recognized standards are difficult to assess.

## AIM

This paper aims at presenting an atypical course of high-risk pulmonary embolism (PE) and the remote outcome in a surgical patient who initially presented a low risk of thrombotic complications.

## CASE STUDY

A 58-year old female (General Hospital Register No 5428/1991), with primary arterial hypertension lasting for several years, was admitted for elective strumectomy due to euthyretic multinodular goiter. On admission, her general condition was stable. On physical examination her temperature was 36.4°C, pulse 72/min, BP 150/85 mmHg. Body type was normostenic (BMI 23.8). The thyroid gland was bilaterally markedly enlarged; lungs, heart and other organs and systems did not show any abnormalities. On November 12, 1991, a subtotal strumectomy was performed, removing a thyroid lump of a male fist size. On November 13, 1991, at about 9:00 in the morning, the patient fainted. Hypotonia of 60/30 mmHg was recorded. Despite the intravascular infusion of 200 mg of hydrocortisone, circulatory arrest occurred. Resuscitation procedures were undertaken, resulting in regaining cardiac function. The patient was then transferred to the Cardiac Intensive Care Unit. The patient was conscious and reported strong resting dyspnea. Tachypnoe 30–35/min, BP 70/30 mmHg, regular cardiac rhythm accelerated to 110/min were observed. The patient was pale with signs of central and peripheral cyanosis. On auscultation vesicular sounds were heard above the lungs, along with a prolonged expiratory phase, as well as single wheezes on the right side. On the left side, vesicular sound was diminished. Before the resuscitation, the electrocardiogram (ECG) showed normal axis and regular sinus rhythm of 86/min. Following the resuscitation right axis deviation, accelerated sinus rhythm to 110/min, complete right bundle branch block were detected. Blood gases analysis revealed metabolic acidosis (pH 7.11) and hypoxemia (pO<sub>2</sub> 51.4 mmHg) with hypocapnia (pCO<sub>2</sub> 21.4 mmHg). Heparin was administered as two consecutive boluses of 5000 units intravenously (IV) within 5 minutes, and then as an IV infusion adjusted to activated partial thromboplastin time (APTT). IV infusion of dopamine and Dextran 40 000 of 500 mL were also given. Dyspnea progressed, respiratory disturbances appeared. The patient was intubated and hooked up to a respirator. An ECG monitor recorded a diminishing frequency of cardiac rhythm (30–40/min). She was given: 0.5 mg of atropine, 1 mg of adrenaline, 100 mL of Natrium bicarbonate, followed by 500 mg of hydrocortisone and 1 mg of atropine. At about 9:10 atrial fibrillation occurred, with heart rhythm about 140/min, arterial pressure on radial artery was undetectable. 0.4 mg of Lanatosid C IV and 500 mg of hydrocortisone IV were administered, and 1200 ml of fresh frozen plasma was transfused. Heart rhythm decreased to 100/min, the BP was 70/50 mmHg. Laboratory tests revealed: K 3.3 mEq/L, Na 131 mEq/L. An IV infusion of 500 mL of 0.9% NaCl with 3.0 g of KCl was given. At 11:30, the sinus rhythm of 80–100/min appeared and a BP reading was 110/70 mm Hg. Blood tests obtained in the morning revealed anemia. The hemoglobin level decreased from 14.4 g% to 9.6 g%, and the erythrocyte count decreased from  $4.96 \times 10^6/\text{mL}$  to  $3.47 \times 10^6/\text{mL}$ . At 13:00, the white blood cell count increased from  $5.1 \times 10^3/\text{mL}$  to  $12.6 \times 10^3/\text{mL}$ , showing a decreased maturation of granulocytes and shift in their image to the left

(6 rod neutrophils and 85 segments). The thrombocyte count was  $7.7 \times 10^3/\text{mL}$ . Since 11:30, low intensity bleeding from the postoperative wound was observed. APTT was immeasurable, prothrombin index – 69%. An infusion of heparin was stopped, 840 ml of erythrocyte concentrate and 700 ml of fresh frozen plasma were transfused. Laboratory tests revealed a gradual shortening of APTT to 60 sec. (at 20:30). Heparin infusion was reintroduced. At about 22:00, bleeding from the postoperative wound stopped. Transaminase values ALAt and AspAt were within a normal range. When the cardiovascular system was stabilized, the patient was still unconscious, her pupils were dilated with pupilloplegia; Babinski sign was positive bilaterally. Dexametasonone and a wide-spectrum antibiotic therapy were administered. Since blood culture test was positive (*Acinetobacter anitratum*), consistently with the obtained antibiogram, Cefotaxim was administered in a dose of 2 g/ 24 hours. On the 2<sup>nd</sup> day the patient regained consciousness and logical contact was established. The respirator was switched off and the intubation tube was removed as well. Central cyanosis persisted, the values of pulse and BP were 86/min and 140/90 mmHg, respectively. Blood gases analysis: pH 7.42, pCO<sub>2</sub> 30.9 mmHg, pO<sub>2</sub> 92.3 mmHg. The ECG showed a disappearance of a right axis deviation alongside with signs of complete right bundle bunch block. It also showed negative T waves in leads V1–V4, which gradually normalized within the following 7 days. Chest X-ray (November 14, 1991) revealed an enlarged cardiac silhouette and features of congestion in pulmonary circulation. A neurological examination did not show neck stiffness or focal symptoms. Histopathological examination revealed *struma nodosa cum signis hyperfunctionis*. Thyroid-stimulating hormone (TSH) value was 3.2 mIU/L, and free Thyroxin (FT4) was 1.1 ng/dL – both values were within the normal limits. In the course of further antibiotic therapy the fever subsided and leukocytosis was normalized. The patient was discharged in a good general condition, with full logical contact, mobilized, and advised to follow long-term therapy with an oral anticoagulant, which she was receiving beginning with the 4<sup>th</sup> day following resuscitation. The patient discontinued use of medication 2 months following her discharge. Diagnosis: Case of surgical treatment of benign nodular goiter, complicated on the 1<sup>st</sup> day with high-risk PE and sepsis. Primary arterial hypertension.

The patient is still alive. She was hospitalized 6 times between 1994–2011. Hospitalizations were caused by: chronic gastritis, cholecystectomy due to acute gangrenous cholecystitis, and upper respiratory tract infections. Three years following the episode of PE, her chest X-ray revealed no abnormalities, the ECG was also normal. Echocardiography (ECHO) performed on June 23, 2000 showed normal morphology of cardiac valves, normal sizes of cardiac cavities and normal left ventricular systolic function, ejection fraction – 65%. The examination was repeated during 2002 and detected fibrosis on the leaflet of the mitral valve and on the cusps of the aortic valve, mitral regurgitation (+), minimal tricuspid regurgitation, normal sizes of cardiac cavities and normal thickness and contractility of both ventricular walls.

## RESULTS AND DISCUSSION

It is believed that the postoperative risk of PE is highest within the first 2 weeks following the operation [13]. Embolism is more frequently found in patients who, in the perioperative period, are not administered with preventive antithrombotic therapy and is particularly dangerous when it co-occurs with asymptomatic thrombosis [2, 3]. Schizas et al., despite the implementation of heparin prophylaxis, observed that 50% of PE cases occurred up till the 3<sup>rd</sup> day following the operation [7].

In the herein described case, one of the reasons for the early occurrence of PE and its acute course may have been the lack of antithrombotic prophylaxis. Other risk factors for thromboembolism which were observed in this patient were her age and immobilization connected with the surgical procedure. Although strumectomy is not recognized as a high-risk procedure with respect to thromboembolic complications, it is, nevertheless, like the majority of surgical procedures, connected with a decreased activity of antithrombin, C protein, and plasminogen [5, 10, 11]. No recurrence of thromboembolism within a 19-year long observation period, and experiencing a surgical procedure with a higher-risk of thromboembolism, exclude hereditary thrombophilia. Another reason for PE may have been an infection, also leading to hypercoagulability. Features of infection, in the form of hyperleukocytosis and changes in blood smear, were detected during the 4<sup>th</sup> hour following the beginning of resuscitation. They do not belong to the clinical manifestations of PE. The diagnosis of PE was made on the basis of a characteristic clinical course, hypoxemia with hypocapnia, and typical ECG changes. We did not perform examinations showing the right ventricular overload due to the lack of possibility to carry out such an examination. A form of high-risk PE was suggested by the symptoms of the co-occurring shock and an enlarged cardiac silhouette seen in the chest X-ray, which later on normalized. A major and/or multiple embolism may lead to a sudden increase in the pulmonary vascular resistance to a level which the right ventricle cannot overcome [13]. Consequently, hypoperfusion may occur, accompanied with a shock, circulatory arrest and, as observed in this patient, progressive metabolic acidosis, which may have been also caused by the co-occurring sepsis. This is what we associate a decreased level of the prothrombin index and a low platelets count with. These features indicate that both these factors were used up in the course of the co-occurring disseminated intravascular coagulation syndrome. These conditions, however, do not explain changes observed in the ECG, typical of PE: right bundle branch block, which regressed on the 2<sup>nd</sup> day following resuscitation, and negative T waves in leads V1–V4, lasting for 7 days. Such ECG changes in the course of PE have been frequently reported earlier [6, 8, 12]. Also, dominant clinical symptoms, such as dyspnea, tachypnoe, hypotonia, tachycardia, detected in the patient in the early postoperative period, were typical of PE. The chest X-ray eliminated diagnosis of pneumonia and pneumothorax. In the differentiating diagnosis, myocardial in-

farction was also considered. ECG examinations did not indicate, however, changes typical of acute myocardial ischemia. Additionally, long-term asymptomatic observation, and a lack of disturbances concerning the contractility of both ventricular walls in ECHO performed later, contribute to the fact that myocardial infarction in the acute phase of the disease was unlikely. Since symptoms of shock did not subside despite the administration of typical treatment, and because of suspicious bleedings, the patient was administered with fresh frozen plasma. Further observation did not confirm bleeding from the gastrointestinal tract, and the observed anemia may have resulted from the loss of blood during the operation.

The presence of known risk factors for PE is important in evaluating a clinical likelihood of PE. The risk increases together with the increase of their number, however, in about 30% of cases there are no predisposing factors (such as unprovoked or idiopathic PE) [13]. In order to stratify the likelihood of PE, commonly known scales are employed, such as the Wells score and modified Geneva score [13]. In the case of the patient described therein, the clinical probability of PE was moderate, respectively 6 points (range of 2–6), 7 and 8 points (range of 4–10). The patient met the criteria qualifying for the application of fibrinolytic therapy in high-risk PE, with a short-term mortality risk exceeding 15% [13], and such treatment should be currently considered. On the other hand, the implementation of this treatment before the first 24 hours following the surgical procedure is associated with a high-risk of hemorrhage complications, which is a relative contraindication for administering fibrinolytic agents [13]. Although fibrinolytic therapy was not administered, after a 2.5-hour long resuscitation, bleeding from the postoperative wound was observed. Simultaneously, long-term improvement in hemodynamic parameters occurred. It appears that these two entities should be associated with endogenous fibrinolysis, which could have been caused by the administration of fresh frozen plasma, since heparin does not produce such effects. Procoagulative activity of fresh frozen plasma was inhibited by the concurrent administration of heparin, which was documented by the prolonged APTT, and anticoagulants contained within plasma may have had a positive influence on the further course of PE. This was evidenced by an improvement in the hemodynamic status, the quick regression of dyspnea, as well as a typical evolution of ECG changes.

In the subject literature, we have not found any reports describing an anticoagulation treatment combined with administering fresh frozen plasma. Recently there have appeared reports which modify opinions concerning fibrinolysis in the course of PE. It has been reported that decreasing a standard dose of a fibrinolytic agent by 50%, or prolonging its infusion time, in comparison with current therapeutic guidelines, does not have any effect on the final outcome [14, 15]. A large study material, involving more than 2000 patients, of Polish Registry of Pulmonary Embolism (ZATPOL), indicated an association of applied fibrinolytic therapy with

increased mortality in the course of PE [4]. These data may suggest that fibrinolytic therapy alone does not always eliminate the substrate for PE, which may have an impact upon its effectiveness. In a preliminary analysis carried out during the perioperative period and involving a small group of patients with colorectal cancer, who were administered with prophylactic doses of low molecular weight heparin, and did not manifest thrombosis, coagulation times were prolonged, and the thrombocytes count decreased along with a simultaneous decrease in the levels of endogenous anticoagulants [11]. It appears that when thromboembolism develops, it results from a shift of balance towards procoagulation, which results from a simultaneous decrease in the activity of endogenous anticoagulants.

Thus far it has been believed that the major factors contributing to the ineffectiveness of managing PE are hypercoagulability or an inadequate dose of the fibrinolytic agent. Available data and everyday practice indicate that a relatively small dose of heparin controls hypercoagulability effectively, and administering fibrinolytic therapy is not always effective. Thus, a question arises as to whether endogenous fibrinolytic agents or direct substrates for a fibrinolytic agent may contribute to improving the effectiveness of PE management. It should be considered whether fresh frozen plasma, via providing endogenous anticoagulants, which apart from being a simple substrate for a fibrinolytic agent may also provide anticoagulation substances acting through a different mechanism, can contribute to improving the effectiveness of treatment.

## CONCLUSIONS

Fresh frozen plasma, due to its endogenous anticoagulation activity, may positively influence the course of high-risk PE.

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