CASE REPORT
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Postpartum DIC in the course of septic shock due to urinary tract infection – case report and review of literature

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Abstract

Disseminated intravascular coagulation (DIC) in the course of septic shock is a very serious clinical event that requires immediate specialist medical care. Often, DIC occurs in people with a severe inflammatory response. As a rule, the prognosis is poor. The activation of the coagulation cascade leads to the occlusion of small blood vessels, which results in organ failure. In addition, secondary fibrinolysis leads to an increased risk of bleeding and is problematic in the selection of appropriate pharmacological therapy. In our paper, we will present the case of a patient with postpartum DIC in the course of septic shock in the course of urinary tract infection. *Anestezjologia i Ratownictwo 2023; 17: 210-217. doi:10.53139/AIR.20231727*

Keywords: DIC, septic shock

Introduction

Disseminated intravascular coagulation (DIC) belongs to the syndrome of hemostatic disorders, sometimes also called consumption coagulopathy or defibrillation syndrome [1-3]. It is characterized by intravascular activation of the coagulation process and secondary fibrinolysis (the physiological process of decomposition of a clot) [1,2]. If both systems are activated simultaneously, it results in the consumption of coagulation factors (mainly fibrinogen, factors V and VIII) and platelets and causes plasma–platelet hemorrhagic diathesis [4]. This syndrome typically develops in the course of disease processes in which large amounts of tissue thromboplastin are released and the clotting process is activated, for example, obstetric complications, tissue injuries, or neoplastic processes [5,6]. The vascular endothelium is damaged, most often as a result of bacterial or viral infections. This then activates the clotting process through the released proteolytic enzymes [7].

DIC should be differentiated from many other diseases, such as, for example, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, thrombotic microangiopathies, e.g. in pregnancy, primary hyperfibrinogenolysis, coagulation disorders in liver diseases, heparin-induced immune thrombocytopenia and catastrophic antiphospholipid syndrome. The symptoms of DIC includerecurrent nosebleeds, peripheral cyanosis, periodic blood in the urine or stools, petechiae on the skin, and recurrent bleeding of the gums [8]. The clinical picture of DIC consists of a hemorrhagic diathesis and fibrin deposition in the capillaries [9]. Hemorrhagic diathesis generally manifests as subcutaneous and submucosal hemorrhages. In acute DIC, there is an over-activation of fibrinolysis, exacerbation of hemorrhagic symptoms, excess release of plasma kinins, and reduction in blood pressure, which may cause shock [10]. Broadly speaking, shock

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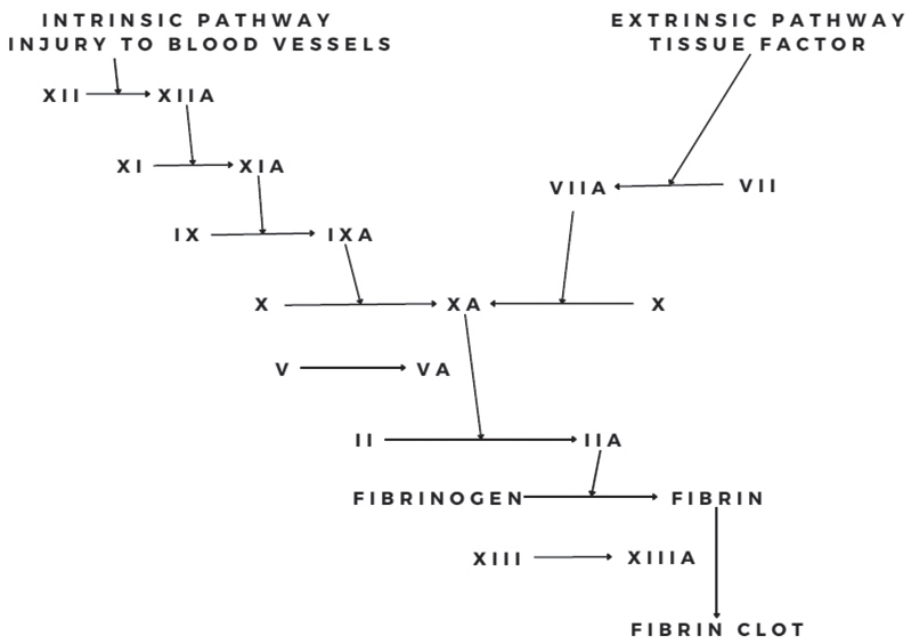


Figure 1. Coagulation cascade (own source)

is a critical impairment of microcirculation that leads to hypoxia and metabolic tissue disturbances in [11]. Septic shock, the most serious and fatal complication of sepsis, is the result of the paralysis of the vascular muscle by bacterial toxins[11]. It is usually caused by sepsis and classically associated with Gram-negative bacterial infections, but it can also be associated with Gram-positive bacteria, mycoses, and viruses. Shock may also be caused by a urinary tract infection (UTI). The vast majority of UTIs are uncomplicated infections in young women. For the most part, an extensive evaluation is not required, and UTIs can be safely treated on an outpatient basis with oral antibiotics. However, due to the physiological changes that occur, pregnancy mayincrease the susceptibility to UTIs [12-14]. The most common complications during pregnancy are asymptomatic bacteriuria (5-10% of healthy pregnant women) and symptomatic UTIs (2-4% of pregnant women), which in most cases (70-80%) are preceded by asymptomatic bacteriuria [15]. UTIsdevelop in the second half of pregnancy (secondand thirdtrimester) and are associated with obstructed outflow of urine and changes in the urinary tract (fever, chills, pain in the lumbar region and abdominal pain, nausea, vomiting, headaches).Pain in the lumbar region in response due to UTIs in pregnant women should always be treated as complicated [16-18].Treatment is required, as a number of complications may arise: in the mother, anemia and pre-eclampsia, and in the fetus, miscarriage, prematurity, low birth weight, and increased perinatal mortality [15,18].UTI treatment, which should usually be initiated in a hospital, generally does not differ from that in non-pregnant women. However, fluoroquinolones and co-trimoxazole should be avoided in the first trimester [16]. A diagnosis of DIC may be elusive during pregnancy and requires vigilance and knowledge of the physiological changes that occur during pregnancy [16,19]. This can be facilitated by using a DIC score with three elements: 1) fibrinogen concentration, 2) PT difference, and 3) platelet count. With a cut-off of ≥ 26 points, the pregnancy-specific DIC score has a sensitivity of 88%, a specificity of 96%, a positive likelihood ratio (LR) of 22, and a negative LR of 0.125 [12]. DIC during pregnancy is one of the main causes of maternal mortality worldwide, with percentages ranging from 0.03% to 0.35% [12], [20]. This complication is often secondary to the underlying maternal and/or fetal complications, including placental detachment, postpartum hemorrhage, amniotic fluid embolism, acute fatty liver during pregnancy, pre-eclampsia and hemolysis, elevated liver enzymes, HELLP syndrome (this abbreviation is derived from the main symp-

toms of this syndrome:Hypertension, Elevated Liver enzymes, Low Platelets), and preserved stillbirth. Asymptomatic infection may occur inabout 2–12% of women [15]. Escherichia coli is by far the most common uropathogen, accounting for>80% of all UTI cases [21]. Other serious clinical problems associated with UTIs include asymptomatic bacteriuria and a complicated form of theinfection [21-23]. Complicated UTIs are a heterogeneous group associated with conditions that increase the risk of infection or treatment failure [14]. In our case, we present a course of DIC in a pregnant patient with a UTI. We also reviewed the literature to identify the causes and potential treatment modalities of this syndrome.

Case report

A 37-year-old patient was admitted to the intensive care unit (ICU)of the University Hospital. The reason for admission was postpartum coagulation

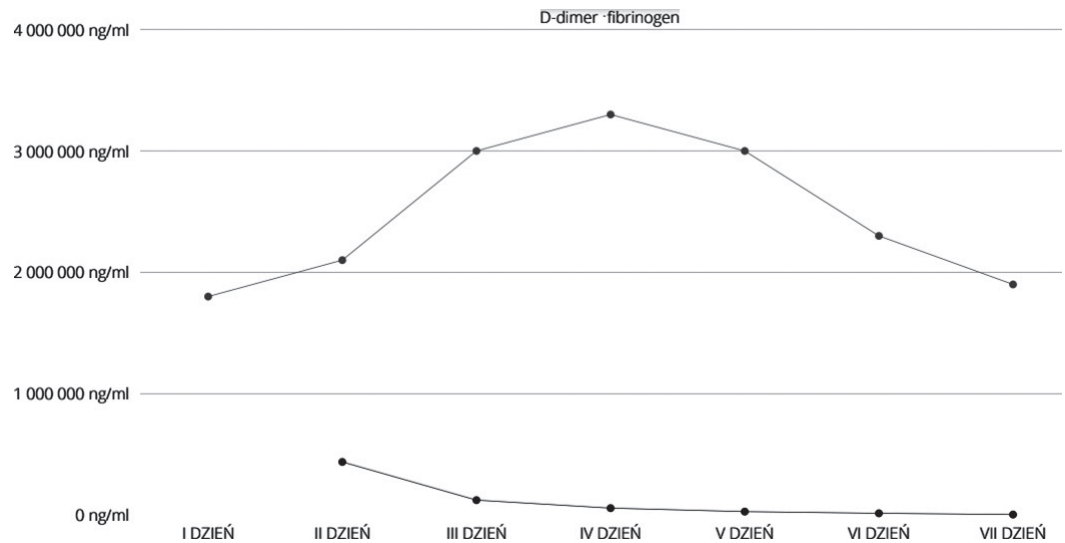
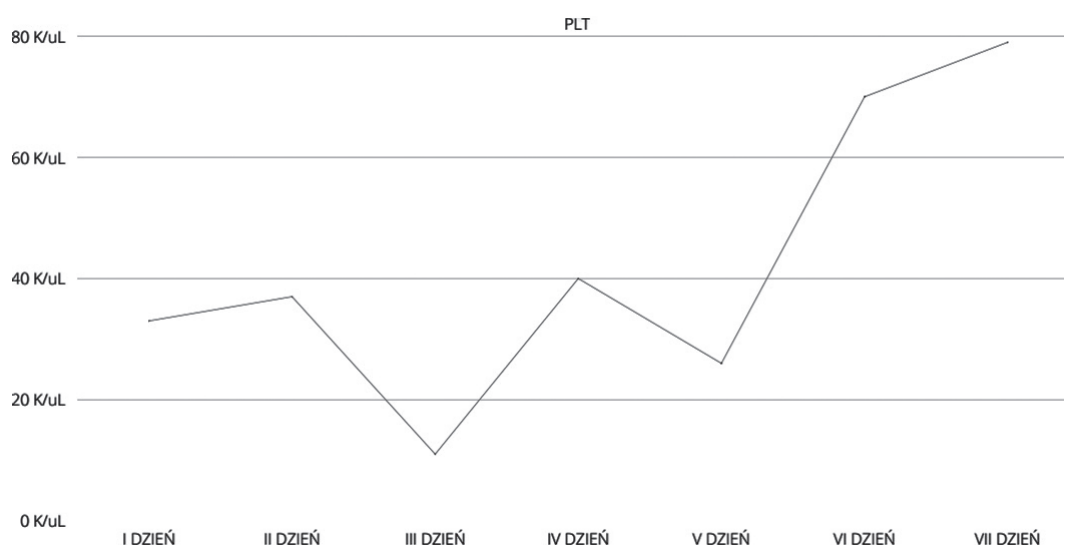


Figure 2. Concentration of D-dimers and fibrinogen over time (own source)



PLT: platelets

Figure 3. Platelet count over time (own source)

disorders (miscarriage in the 20th week of pregnancy). The patient was admitted to the regional ICU due to an attack of renal colic. Imaging studies showed congestion in the right kidney, and a double J (JJ) catheter was inserted into the right kidney. On admission, the patient was in a mediocre general condition, conscious and in logical contact. She was breathing spontaneously with passive oxygen therapy. Due to decreased vascular resistance and systemic hypotension, the patient required an infusion of noradrenaline. On physical examination, the abdomen was tender in the epigastric region and the right subcostal area. There was a discolored rash and petechiae on the skin of the face and limbs. Meropenem and levofloxacin antibiotic therapy was initiated. Fluid deficiencies were constantly replenished, and electrolyte disturbances were corrected. Blood was collected for laboratory tests, and material was collected for microbiological tests. Fiveunits of cryoprecipitate, two units of red blood cell concentrate, and 3 grams of fibrinogen were administered. The results of the microbiological tests were negative. Serum sodium concentration was 138 mmol/L, potassium was 4.18 mmol/L, and creatinine was 0.970 mg/dL. The hematocrit was 29.8%. The leukocyte count was 19.90 K/uL. On the second day after admission, DIC was diagnosed in the course of UTI-induced septic shock. On that day, a gynecological consultation revealed hardness of the uterus in the middle of the distance between the symphysis pubis and the navel. The patient had soft breasts, and the droppings were bloody and fairly profuse. The patient was treated with bromocriptini mesylas and continued treatment as usual.

Table I. Specialized hemostasis results (own source)

Anti-Xa (factor Xa inhibitors)	0.23 IU/ml
Protein C	29.0 %
Free protein S-antigen	9.4 %
Factor IX (Christmasfactor)	54.4 %
Factor V (proaccelerin)	27.4 %
Factor VII (proconvertin)	55.5 %
Factor VIII (antihemophilicfactor)	52.9 %
Factor XII (Hagemanfactor)	116.8 %

On the third day, two units of concentrated red blood cells, fourunits of fresh frozen plasma, and threeliters of crystalloids were transfused. Antithrombotic prophylaxis was restored with the return of fibrinogen to approximately 2 g/L. On the fourth day, the patient reported slight dyspnea and became tired eating quickly. Spontaneous diuresis was present. On the fifth day, swelling was noted on the backs of the patient's feet. On the sixth day, an ultrasound was performed, which showed fluid in the left pleural cavity. Edema around the ankles of the lower extremities persisted, while petechiae on limbs and face diminished. Accordingly,

Table II. Applied pharmacotherapy and its effects (own source)

Norepinephrine	Restoration of normal blood pressure
Oxycodone	A painkiller from the group of opioids
Hydroxyzine	Sedative, anxiolytic, hypnotic, antihistamine effect
Estazolam	Anticonvulsant, sedative, anxiolytic, hypnotic, and muscle-relaxing effect
Ondansetron	Antiemeticdrug
Metoclopramide	It increases the tone of smooth muscles and the strength of propulsive movements in the digestive tract
Metamizole	Analgesic and antipyreticeffect
Drotaverine	It has a relaxing effect on smooth muscles
Fibrinogenhuman	It reduces the risk of bleeding
Omeprazole	It inhibits the secretion of hydrochloric acid in the gastric juice
Oxytocin	It causes muscle contractions by increasing the intracellular concentration of Ca^{2+} ions
Lactulose	It causes acidification of the content of the large intestine, thus accelerating the reaction of converting ammonia to ammonium ions and reducing the absorption of ammonia into the blood; this leads to a reduction in blood ammonia levels
Simeticone	Facilitates the removal of gases from the digestive tract
Bromocriptinimesylas	It inhibits the secretion of prolactin
Nadroparin	It inhibits the blood clotting process

one packet of platelet cell concentrate was transfused. On the seventh day of hospitalization, a puncture of the left pleural cavity was performed, and 700 ml of clear fluid outflow was obtained. There was a slight pasty swelling of the patient's lower limbs. On the eighth day, the patient was transferred to the regional ICU for further treatment. The patient was in average general condition, in full verbal-logical contact, breathing spontaneously with passive oxygen therapy through the mustache 3l/min. and circulatory efficient.

Discussion

It is hard to say unequivocally what caused the miscarriage and DIC. It is probably thatboth postpartum disorders and the UTI contributed to some extent. Likely, the pregnancy led to a UTI, which in turn led to a miscarriage and DIC.In patients with sepsis, DIC is common and may worsen the prognosis [24]. There are a number of anticoagulants that have been proposed as potential treatments to resolve DIC and improve conditions in patients with septic DIC [24].

Critically ill patients have an increased risk of developing venous thromboembolism (VTE), as reflected in the fact that almost 10% of ICUpatients experienced VTE during hospitalization despite thromboembolism prophylaxis with unfractionated heparin [25]. For this reason, in critically ill patients anticoagulant prophylaxis is used with unfractionated heparin or low molecular weight heparin, regardless of the presence of DIC [25], [26]. Studies have shownthe effect of heparins, especially unfractionated heparin, in patients with sepsis [27]. The results summarized in ameta-analysis showed reduced mortality within 28 days but an increased risk of bleeding [25,28]. Pharmacological thromboprophylaxis should be discontinued in patients with DIC who have major bleeding, in patients at high risk of bleeding, or when the patient's platelet count drops below 20×10^9/l [25]. As obstetric DIC mainly manifests as bleeding, the role of unfractionated heparin or low molecular weight heparin is unclear, and it should be reserved for patients with thrombosis [25,29]. Some sources have indicated that direct thrombin inhibitors may reduce hypercoagulability in patients with DIC, but this has not been studied under controlled clinical conditions [25]. In Japan, studies have been conducted on the efficacy of anti-Xa sodium danaparoid and synthetic protease inhibitors in the treatment of DIC. Both are recommended by the Japanese Society for Thrombosis and Haemostasis in the anticoagulation treatment of DIC [25]. During the course of DIC, the level of antithrombin decreases as a result of ingestion by thrombin, and in septic DIC, antithrombin is inactivated due to degradation by neutrophilic elastase and the bacterial enzyme thermolysin [25]. Some clinical trials have showna relationship between a decreased level of antithrombin and poor clinical results [30]. Thus, it be concluded that antithrombin substitution may be beneficial in patients with DIC. The KyberSept study, a large-scale multi-site randomized controlled trial (RCT), investigated the effect of high-dose antithrombin substances on mortality in 2,314 patients with severe sepsis [31]. The resultsdid not show an improvement in survival in the intervention group, but there wasan increased frequency of bleeding in patients receiving antithrombin concentrate and heparin at the same time [31]. However, a posthoc analysis showed that patients with sepsis and DIC who did not receive concomitant heparin during treatment with antithrombin concentrate had prolonged survival, with an absolute 28-day reduction in mortality of 14.6% compared to placebo [25]. Thrombomodulin forms a complex with thrombin and then inhibits its activity in addition to amplifying the formation of activated protein C [25]. Several studies from Japan have demonstrated the beneficial clinical properties of recombinant human-soluble thrombomodulin in patients suffering from DIC due to hematological malignancy or infection [25]. As the first natural anticoagulant, recombinant activated protein C (rAPC) was approved for the treatment of sepsis after its beneficial effect was demonstratedin a large-scale RCT involving patients with severe sepsis. Moreover, protein C has shown a beneficial effect on the survival of patients with overt DIC [25,32]. However, rAPC was later withdrawn from the market and is no longer available for clinical use due to a subsequentRCTthat found no beneficial effects of rAPC but an increased risk of bleeding [25]. Tissue factor pathway inhibitor directly inhibits factor Xa [25]. Therefore, it can be concluded that it would be an appropriate choice for DIC therapy to inhibit the uncontrolled activation of the coagulation system [25]. However, studies havenot shown an improvement in survival in patients with severe sepsis receiving a recombinant inhibitor of the tissue factor pathway compared to placebo [33]. The supportive treatment of bleeding complications

may include substitution with plaques or coagulation factors. Platelet concentrate should be administered in patients with DIC with serious bleeding or in patients whose bleeding risk is significantly increased [25]. In patients with obstetric DIC, it is particularly important to maintain the level above 50×10^9/l [25]. Meanwhile, in patients with little or no bleeding as well as in cancer patients, the threshold is 20×10^9/l [25]. Substitution with clotting factors is recommended forpatients with major bleeding and a partial thromboplastin time (APTT) and/or a prothrombin time (PT) greater than 1.5 times the normal value. As a rule, the first choice for treatment is frozen plasma, with aninitial dose of 15–30 ml / kg [34,35]. Occasionally, large volumes of fresh frozen plasma may be needed to restore equilibrium, implying a risk of volume overload. Most prothrombin complex concentrates contain vitamin K-dependent coagulation factors II, VII, IX, and X and may also be rich in natural anticoagulants, protein S, protein C, and antithrombin [36,37]. However, they lack important clotting factors, such as factor V, and there is no well-defined dosing strategy [25]. Vitamin K is a useful alternative for the correction of clotting factors that are dependent on vitamin K, but it doesnot havea significant effect forsixhours [25]. In the absence of a specific fibrinogen, administration of fibrinogen may be essential in the form of fibrinogen concentrate or cryoprecipitate [25]. In bleeding patients, it is important to maintain a level of fibrinogen above 0.0015kg/l, which is approximately 4.4 µmol/l, while in women with postpartum hemorrhage, a dose exceeding 0.002kg/l is recommended [25]. An increase in the level of fibrinogen by 0.001 kg/l, approximately 2.9 µmol/l, results from the administration of 3×10^{-5} kg of fibrinogen concentrate per kilogram of body weight [25]. In the case of cryoprecipitate, it is recommended that two pools be administeredto increase the level of fibrinogen [25]. Due to the fact that inhibition of endogenous fibrinolysis is the most common change of fibrinolysis in DIC caused by sepsis, the use of antifibrinolytic drugs in these patients is not recommended [25]. Hyperfibrinolysis secondary to DIC has been reported in some cancer patients, especially in thosewith acute promyelocytic leukemia and adenocarcinoma-induced DIC. In such cases, we can use anti-fibrinolytic drugs, such as tranexamic acid. However, such therapy should be reserved for patients with refractory bleeding who have a clear picture of hyperfibrinolysis. While tranexamic acid can be used forpostpartum hemorrhage, caution is advised in obstetric DIC where inhibited fibrinolysis may be present, caution is advised.

Table III. DIC treatment (own source)

LOW MOLECULAR WEIGHT HEPARIN		
	Treatmentdose	**Prophylacticdose**
Dalteparin	100 IU/kg every 12 h or 200 IU/kg every 24 h	100 IU every 24 h
Enoxaparin	1 mg/kg every 12 h or 1.5 mg/kg every 24 h	1 mg/kg every 24 h
Nadroparin	85 IU/kg every 12 h or 170 IU every 24 h	85 IU/kg every 24 h
DIRECT TROMBINE INHIBITORS		
	Treatmentdose	**Prophylacticdose**
Rivaroxaban	15 mg every 12 h	20 mg every 24 h
Apixaban	5 mg every 12 h	2.5 mg every 12 h
Dabigatran	220 mg every 24 h	150 mg every 12 h
ANTITHROMBINE		
Treatmentdose	**Prophylacticdose**	
35–50 IU/kg	It is replenished depending on the level of antithrombin in the body	
PROTEIN C		
Treatmentdose	**Prophylacticdose**	
60–80 IU/kg every 12 h	It replenishes depending on the level of protein C in the body	

Conclusions

Despite numerous attempts to understand the pathogenesis of DIC, the prognosis for DIC patients remains bleak. While there are diagnostic scoring systems that can aid diagnosis, DIC is difficult to diagnose in the early stages prior to the onset of organ failure. Treatment of DIC should be tailored to the individual, depending on the cause, clinical symptoms, and biochemical abnormalities. Since most RCTs related to life threatening coagulation abnormalities have been conducted on sepsis patients, which also included patients without DIC, the implementation of biomarkers of microclotting and hyperfibrinolysis would improve the quality of future RCTs and allow for more personalized DIC treatment.

Konflikt interesów / Conflict of interest
Brak/None

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