CASE REPORT

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Deep vein thrombosis (DVT) in ovarian clear cell carcinoma with liver metastasis: a case report

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ABSTRACT

Introduction: Deep vein thrombosis (DVT) is a common complication found in malignancy patients. If not handled properly, this condition can be fatal. As many as 1-8% of cases developed into pulmonary embolism and cause death. Malignancy-associated thrombosis is the second leading cause of death in patients with malignancy. Ovarian clear cell carcinoma has the highest risk of thrombosis compared to other carcinomas, 5-16% of patients with ovarian malignancy. This condition is aggravated by liver metastasis.

Case: 36-year-old woman with left ovarian clear cell carcinoma stage IVB, get a series of Carboplatin and Paclitaxel chemotherapy, complained severe pain in the left leg that progressively increase with edema and erythema from the thigh to the calf. The patient was diagnosed as suspected DVT with Wells' scores 5 that supported by an increase in D-dimer and bilateral lower extremity venous doppler ultrasound showing DVT in the communal femoral, superficial femoral, and popliteal veins of the left leg. Abdominal CT-scan resulting in liver metastasis with massive ascites. The patient was treated with 2 x 40 mg furosemide, 5000 units of heparin bolus followed by 20000 units of heparin drip / 24 hours and 1 x 2 mg bridging Simarc. PT and APTT result show prolongation.

Conclusion: We reported a case of DVT in the left ovarian clear cell carcinoma stage IVB with liver metastasis. This case emphasizes coagulopathy manifestation in malignancy that can be caused by cancer management and the use of anticoagulants that are aggravated by liver metastasis.

Keywords: coagulopathy, ovarian cancer, liver metastasis.
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INTRODUCTION

Malignancy and its treatment have been identified as risk factors for venous thromboembolism (VTE), which is the second leading cause of death in patients with active malignancy.[1,2] Deep vein thrombosis (DVT) is a VTE manifestation that is often found in patients with malignancy, especially in ovarian cancer patients, 5-16% of cases. This condition is due to the length of time needed for intraabdominal surgery, immobilization during and after surgery, and blood vessels wall distortion due to the compression of the ovarian tumor itself.[3]

Based on several studies, ovarian carcinoma with clear cell histological feature has a high incidence among Asian women and has the highest risk of experiencing VTE compared to other carcinomas.[2-7] The study also suggested that there was an excessive expression of tissue factor (TF) in patients with ovarian clear cell carcinoma compared to other types of ovarian cancer.[7]

Increasing TF expression will trigger the extrinsic coagulation cascade by activating factor VII to factor VIIa and then it will activate factor X to factor Xa which activates prothrombin to thrombin. The formation of thrombin will trigger platelet activation and aggregation.[7,8] In addition to cause thrombosis, platelet activation also plays a role in the metastasis process by forming a thrombus cloak around the tumor. This thrombus cloak facilitate the migration of tumor cells along the vascular endothelium and also protect them from natural killer cells.[1,8,9]

Also, many studies suggest that the prognosis of ovarian clear cell carcinoma patients is aggravated by the presence of liver metastasis. Protein C and antithrombin (AT) are the most important natural anticoagulants that produced by the liver. Coagulation factors, besides factor VIII, are also produced by the liver.[8] Decreasing of anticoagulants and coagulation factors synthesis in malignancies with liver metastasis may worsen hypercoagulable conditions and can trigger disseminated intravascular coagulation (DIC). Hypercoagulable states in patients with malignancy often occur simultaneously with bleeding manifestations, such as DIC.[10] In this paper, we report a case of DVT with minor bleeding manifestation as a form of coagulopathy in malignancy, that is ovarian clear cell carcinoma, which aggravated with liver metastasis.

CASE-DESCRIPTION

A 36-year-old female came to the Cipto Mangukusumo National Central General Hospital (RSUPNCM) with progressive pain in the left leg since 1 week before hospital admission with edema and erythema from the thigh to the calf. There is no

history of DM, hypertension, drugs allergy, melena, hematemesis, vaginal bleeding, or asthma. There is a lump in the lower left abdomen accompanied by pain. Patients had a history of ovarian cancer with histopathological results was clear cell carcinoma stage IVB 1 year before hospital admission. The patient referred to RSUPNCM for chemotherapy, but she just went to the obstetrics and gynecology outpatient clinic at RSUPNCM 1 week before hospital admission. The chemotherapy plan then postponed until there is an improvement of the general condition.

At the time of admission, the patient was compos mentis, and her vital signs were within normal limits. She has a normal nutritional status (BMI 21.8 kg/m^2). On physical examination, pale conjunctiva is found, the sclera is not jaundiced, heart and lung within normal limits. Abdomen asymmetric, normal bowel movement, there are shifting dullness, and the suprapubic mass palpable with a diameter of 10 cm, irregular border, and surface, immobile, accompanied by tenderness (VAS 7-8). Left leg appears edema and erythema accompanied by pain at palpation (VAS 3-4), limited ROM, and positive Homan sign. Laboratory results suggest chronic anemia with / without iron deficiency and hypercoagulability et causa ovarian malignancy (Table 1).

Ultrasound color doppler of bilateral lower extremities veins shows DVT in the common

Table 1 Laboratory Results at Time of Hospital Admission

Test	Result	Unit	Reference Value	Interpretation
HEMATOLOGY				
Complete Blood Count				
Hemoglobin	10.7	g/dL	12.0 – 14.0	L
Hematocrit	35.6	%	37.0 – 43.0	L
Erythrocyte	5.09	10^6/µL	4.00 – 5.00	H
MCV	69.9	fL	82.0 – 92.0	L
MCH	21	pg	27.0 – 31.0	L
MCHC	30.1	g/dL	32.0 – 36.0	L
Platelet	612	10^3/µL	150 – 400	L
Leukocyte	19.23	10^3/µL	5.00 – 10.00	H
Differential Count				
Basophil	0.3	%	0 – 1	L
Eosinophil	0.5	%	1 – 3	L
Neutrophil	87	%	52.0 – 76	H
Lymphocyte	8.5	%	20 – 40	L
Monocyte	3.7	%	2 – 8	
RET-HE	26.6	pg	25.69 – 34.77	
ESR	25	mm	0 – 20	H
Reticulocyte Count				
Absolute	37,700	/µL	24,000 – 95,000	
Relative	0.74	%	0.50 – 2.00	
BLOOD CHEMISTRY				
FE(SI) – TIBC				
Serum Iron (Fe)	28	µg/dL	37 – 145	L
TIBC	221	µg/dL	228 – 428	L
Saturated Transferrin	13	%	15 – 45	L
Ferritin	923.6	ng/mL	13.0 – 150.0	H
Tumor Marker				
CA 125 (ovarium)	38	U/mL	0.0 – 35.0	H
Hemostasis				
D-dimer Quantitative	2300	µg/L	0 – 300	H
Fibrinogen	449.6	mg/dL	150 – 400	H

MCV, *mean corpuscular volume*; MCH, *mean corpuscular hemoglobin*; MCHC, *mean corpuscular hemoglobin concentration*; RET-HE, *reticulocyte hemoglobin equivalent;* ESR, *erythrocyte sedimentation rate; L: low; H: High*

Table 2 Laboratory results at a time prior to discharge

Test	Result	Unit	Reference Value	Interpretation
HEMOSTASIS				
PT + INR				
Patient	13.1	second	9.8 – 11.2	H
Control	11.1	second		
INR	1.27			
APTT				
Patient	140.5	second	31.0 – 47.0	H
Control	31.2	second		
URINALISA (URIN)				
Color	Yellow		Yellow	
Clarity	Clear		Clear	
Sediment				
– Leukocyte	0-2	/HPF	0 – 5	
– Erythrocyte	3-10	/HPF	0 – 2	H
– Cast	Negative		Negative	
– Epithelial cells	1+		Negative	
– Crystal	Negative		Negative	
– Bacteria	Negative		Negative	
Specific Gravity	1.020		1.005 - 1.030	
pH	7.0		4.5 - 8.0	
Albumin	Negative		Negative	
Glucose	Negative		Negative	
Keton	Negative		Negative	
Blood	***Trace***		Negative	
Bilirubin	Negative		Negative	P
Urobilinogen	3.2	µmol/L	3.2 - 16.0	
Nitrite	Negative		Negative	
Leukocyte Esterase	Negative		Negative	

PT, *prothrombin time*; INR, *International Normalized Ratio*; APTT, *activated partial thromboplastin time; L:low; H:High; P:Positive*

femoral vein, superficial femoral vein, and popliteal vein of the left leg. Abdominal CT scan showed a cystic mass in left adnexal that attached to the fallopian tube, hepatomegaly, multiple liver nodules, massive ascites, bilateral enlargement of paraaortic and inguinal lymph nodes.

During admission, the patient treated by Furosemide 2 x 40 mg, ketoprofen suppository if pain, Heparin bolus 5,000 units followed by Heparin drip 20,000 units / 24 hours. Bridging Simarc 1 x, 2 mg starts on the third day of care. Her DVT then has improved, marked by a decrease in calf circumference over 10 cm and a thigh over 6 cm. The clinician then starts one series of chemotherapy of Carboplatin and Paclitaxel. On the fifth day of admission, there were PT and APTT prolongation also there was microscopic hematuria in her urinalysis results (Table 2). The dose of Heparin drip is lowered, but the patient refuses to be treated and chooses to go home at his request. Patients were scheduled to control to the obstetrics and gynecology, hematology and oncology, and medical rehabilitation outpatient clinic a week later.

DISCUSSION

World Health Organization (WHO) described ovarian clear cell carcinoma as a solid tumor composed of clear cells with tubulocystic that usually appear as a 3-20 cm pelvic mass and most cases detected during a physical examination or from imaging. Ovarian clear cell carcinoma is known to have a higher risk of VTE than other carcinomas, which

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is 42% based on the Duska et al.[6] Hypercoagulable condition plays an essential role in the occurrence of these thromboembolic complications.

In this case, patient's hypercoagulability is characterized by increased of D-dimer and fibrinogen levels which show an increase in coagulation activity. Hypercoagulability in cancer patients can be caused due to the condition of stasis due to prolonged bed rest or because of direct compression of veins by the mass of the tumor.[3] In addition, cancer cells are known to have the ability to activate the coagulation system in the host's body, resulting in an imbalance between procoagulant and natural anticoagulants which ultimately induces a hypercoagulable state.[1]

In ovarian cancer patients with clear cell histology, there is an excessive expression of TF which will trigger the extrinsic coagulation cascade pathway.[7] Parenteral chemotherapy can also cause injury to blood vessels and increase TF expression by endothelial cells, which aggravates the hypercoagulable condition in this case.[11] The most obvious hypercoagulable manifestations in these patients are DVT, which is supported by the Well's score (Table 3) with a score of 5 that obtained from the anamnesis and physical examination which showing the possibility of high DVT and an increase in D-dimer and the color Doppler ultrasound that shows positive DVT in the left leg match the diagnosis algorithm (Figure 1).

The gold standard for DVT is venography. However, this examination is quite invasive and has a risk of causing allergies to the used radiocontrast material.[12] D-dimer level measurement is the first choice of alternative to establishing a diagnosis of DVT quickly and safely.[7,12] D-dimer has 80% sensitivity value and 100% negative predictive value.[7]

Hypercoagulable conditions in patients with malignancy often occur simultaneously with bleeding manifestations, such as DIC. DIC in malignancy tends to be chronic, so there is no decrease in platelet counts and fibrinogen levels as in this case. Coagulopathy result that can be found is usually only an increase in D-dimer.[8] However, thrombocytosis in these patients can be a form of reactive thrombocytosis due to inflammation, supported by the presence of neutrophilia, rapid erythrocyte sedimentation rate, and fibrinogen which is also an acute phase protein which can increase in inflammatory conditions, that make the possibility of acute DIC in this patients can not be excluded. Prolongation of PT and APTT associated with acute DIC can be found if the coagulation factors consumption occurs systemically because of patient's DVT condition. It is recommended to check AT activity that found to decrease in acute DIC and found to be normal in chronic DIC.[8,10]

Prolongation of PT and APTT in these patients can also be caused by the use of anticoagulant and thrombolytic drugs. It is known that patients get Simarc and Heparin therapy for her complaints. Simarc (warfarin) mechanism of action is inhibiting the synthesis of vitamin K in the liver which can affect coagulation factors II, VII, IX, and X so that prolongation of PT can be found in this patient. Because of the lack of standardization of PT, International Normalized Ratio (INR) is used to optimize doses and monitor the success of therapy while consuming warfarin. The INR value is specifically checked at least 4-5 times a week until it reaches therapeutic doses and the value of INR is stable. The desired INR value is usually 2–3.[8] This patient's INR is 1.27 which indicates that the received dose is not optimal yet and it is the cause of the ongoing coagulation activity.

In contrast to warfarin, heparin mechanism of action is increasing the effect of antithrombin III as a coagulation factor inhibitor and releasing tissue factor pathway inhibitors (TFPI) from the blood vessel walls. Heparin therapy is based on body weight and the dosage titrated based on APTT values, where the desired amount is 1.5-2.5 time control.[8] In this case, the APTT found to be exceeded the therapeutic target, which is 4.5-time control. This is also aggravated by the presence of liver metastases, so the risk of bleeding becomes higher which is characterized by the presence of microscopic hematuria in the patient's urinalysis. We recommend the use of low molecular-weight heparin (LMWH) compared to ordinary heparin for thrombosis therapy in malignancy. LMWH is safer and more effective in patients who have proven DVT and also have a protective effect on DVT suspect patients.[1]

CONCLUSION

We report a case of DVT as a complication of ovarian clear cell carcinoma stage IVB with a coagulopathy condition which may be caused by cancer management, anticoagulant, and antithrombotic drugs which are aggravated by liver metastasis. The possibility of DIC in patients cannot be excluded. It is recommended to check AT activity to make a definite diagnosis.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding manuscript

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AUTHOR'S CONTRIBUTION

The authors contribute equally to the content of the manuscript from data preparation until data analysis

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