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Case Report

Clear Cell Carcinoma of the Ovary with Disseminated Intravascular Coagulation and Haemoperitoneum with Tumour Rupture

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We report a 34-year-old woman with haemoperitoneum and acute disseminated intravascular coagulation (DIC) following the rupture of ovarian clear cell carcinoma (OCCC), the first documented case. Although DIC is known to be associated with ovarian cancer, acute DIC with bleeding in clear cell variants has not been reported. A patient with a right adnexal lesion was found to have anaemia with thrombocytopenia. Intra-abdominal bleeding with the rupture of a malignant ovarian cyst associated with DIC was found to be the cause. After surgery, DIC resolved, indicating that OCCC can be the aetiology for acute DIC and bleeding. Practitioners must be aware of this rare but potentially fatal association between OCCC and acute DIC.

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Introduction

Ovarian clear cell carcinoma (OCCC) is a rare subtype of ovarian epithelial carcinoma that can be associated with endometriosis, a known risk factor for OCCC [1]. OCCC has many common complications, and many are due to the hypercoagulable state, causing thromboembolic complications [2][3]. Disseminated intravascular coagulation (DIC), always a complication of another disease, such as malignancy, can manifest with thrombosis, thromboembolism, or bleeding [4]. Here, we report a woman presenting with a haemoperitoneum and DIC associated with ruptured clear cell carcinoma of the ovary.

Case Presentation

A 34-year-old woman reported dysmenorrhea four months before this presentation. Her abdominal ultrasound confirmed a right adnexal cystic lesion with thick and thin septae. A contrast-enhanced computed tomography (CT) scan showed a well-demarcated right adnexal cyst measuring 10 cm (anterior-posterior) x 9 cm (craniocaudal) x 8 cm (width) with a few thin and thick septae within the lesion, without pelvic or para-aortic lymphadenopathy.

Because of the elevated cancer antigen 125 (CA125) of 120 IU/ml (normal <35 IU/ml), she was admitted for surgical excision. On admission, she had mild shortness of breath for four days. Then, she developed a low-grade fever with a platelet count of $43x10^3$/uL (normal 150-400 $x10^3$/uL) and abdominal pain. Then, she developed worsening shortness of breath with mild intermenstrual bleeding. On examination, she was pale and dyspnoeic with a respiratory rate of 30 breaths per minute, a tachycardia of 124 beats per minute, and a blood pressure of 100/60 mmHg. The lower abdomen was tender with dullness on percussion, suspicious for ascites. However, the patient had no other apparent manifestation of bleeding except for mild inter-menstrual bleeding.

Her platelet count dropped rapidly from $43x10^3$/uL (normal 150-400 $x10^3$/uL) to $8x10^3$/uL, and her haemoglobin level decreased from 10.9 g/dl (normal 12-16 g/dl) to 8.2 g/dl. Her non-structural protein one antigen and dengue IgM antibody tests were negative, excluding dengue fever. Her first blood picture revealed anaemia with rouleaux formation and a low number of platelets with large forms but without evidence of DIC. However, the second blood picture demonstrated schistocytes with low

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haemoglobin, suggesting microangiopathic haemolytic anaemia. A rotational thromboelastometry (RoTEM) revealed clotting factor deficiency, low fibrinogen, and platelets, suggesting consumptive coagulopathy due to the DIC (Figure 1 and Table 1). Abdominal ultrasonography demonstrated predominantly solid areas in the right adnexal lesion, suggesting rupture of the tumour with free fluid in the abdomen, implying intraperitoneal bleeding. The rapid decrease in haemoglobin can be due to the intraperitoneal bleeding.

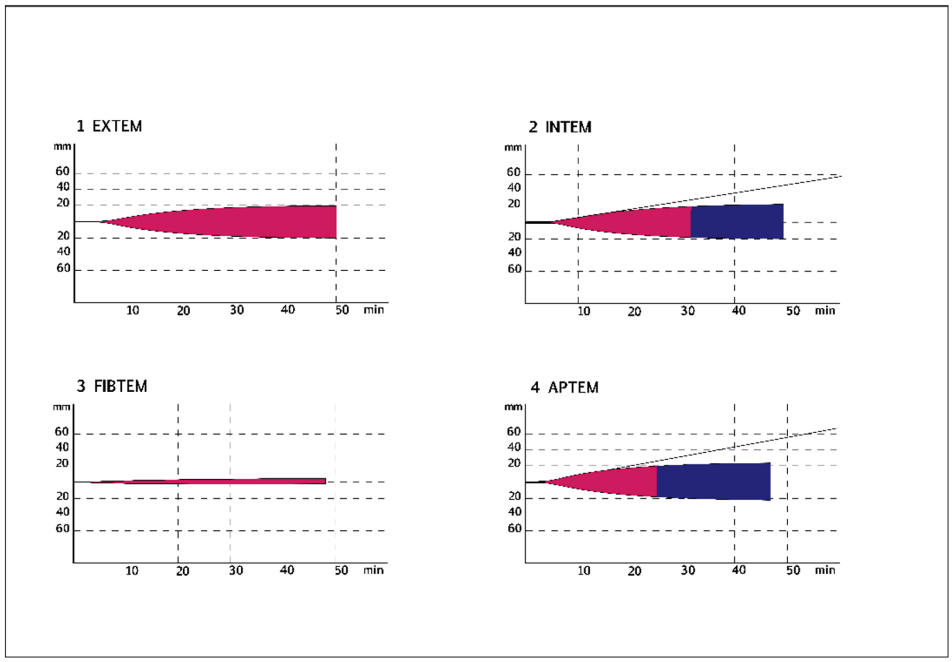

Figure 1. RoTEM study

RoTEM: Rotational thromboelastometry, EXTEM: extrinsically-activated test with tissue factor, INTEM: intrinsically-activated test using ellagic acid, FIBTEM: fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D, APTEM: a modified EXTEM assay incorporating aprotinin to stabilise the clot against hyperfibrinolysis, mm: millimetre, min: minute

	CT	CFT	α	A10	MCF
EXTEM	314 s (38-79)			11 mm (43-65)	20 mm (50-72)
INTEM	285 s (100-240)	1611 s (30-110)	14° (70-83)	12 mm (44-66)	22 mm (50-72)
FIBTEM	152 s			4 mm (7-23)	4 mm (9-25)
APTEM	237 s	1296 s	16°	13 mm	24 mm

Table 1. RoTEM study indicating clotting factor deficiency by prolonged CT and CFT and low fibrinogen by reduced α. Reduced clot strength due to low platelet, as low A10 and MCF indicate.

(RoTEM: Rotational thromboelastometry, CT: clotting time, CFT: clot formation time, α: alpha-angle, A10: amplitude at 10 minutes after clotting time, MCF: maximum clot firmness, EXTEM: extrinsically-activated test with tissue factor, INTEM: an intrinsically-activated test using ellagic acid, FIBTEM: fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor

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cytochalasin D, APTEM: a modified EXTEM assay incorporating aprotinin to stabilise the clot against hyperfibrinolysis)

An urgent laparotomy was planned, and two units of packed red blood cells, 30 ml/kg of fresh frozen plasma, 18 units of platelets, and 7 ml/kg of cryoprecipitate were transfused with the guidance of repeat RoTEM studies to stabilise the patient before the surgery. The surgery confirmed the presence of haemoperitoneum and bleeding from the right adnexal cyst. Bilateral salpingo-oophorectomy was performed due to the presence of bilateral ovarian cysts.

After the surgical resection, the platelet count increased, and the DIC resolved, indicating that the ovarian tumour triggered the DIC. Hence, other possibilities for low platelet counts were not considered. The summary of investigations is presented in Table 2.

Day	01	02					03			04	05	07	10	11
Time		01:20	09:48	13:30	17:30	19:30	05:00	19:50	21:10					
WBC 10^3/uL (4 -10)	15.1		15.07	12.7		11.52	8.74	15.71	11.14	10.97	14.41	12.47	18.7	
HB g/dL (12 – 16)	10.3		10.2	8.7		8.2	6.5	9.0	10.5	9.6	9.3	9.9	10.1	
PLT 10^3/uL (150 – 400)	43		15	14		8	48	115	108	81	114	121	241	
INR (<1.4)	1.55	1.39								1.24				1.19
aPTT seconds		33.2 (31 – 43)								27.8				28.4 (25.4-38.4)
AST U/L (10 – 35)				24	18									
ALT U/L (10 - 40)				10	10									
Total bilirubin umol/L (5 – 21)		31.11			18.03					29.8	13.81			
Direct bilirubin umol/L (<3.4)		6.06			3.34					12.5	4.7			
Indirect bilirubin umol/L (5.1 – 17)		25.1			14.7					17.3	9.1			
CRP mg/L (<5)					153					233	153			
ESR mm/1^{st} hour (< 22)		10												

Table 2. Summary of investigations

WBC: White blood cells, HB: Haemoglobin, PLT: Platelets, INR: International normalised ratio, aPTT: Activated partial thromboplastin time, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

The histopathology described right OCCC without lymphovascular or perineural invasion and endometriosis in the surrounding tissues (Figure 2 and Figure 3). Immunohistochemistry was positive for Napsin A and negative for Wilms tumour gene one and oestrogen receptor. Progesterone receptor expression showed scattered positivity in some cells. Tumour protein 53 showed a wild-type pattern, and the Ki67 index was 45%. According to the 8^{th} TNM classification, the stage was pT1c2, and the FIGO stage was IC_2. The left ovary showed only an endometriotic cyst without evidence of malignant tumour involvement.

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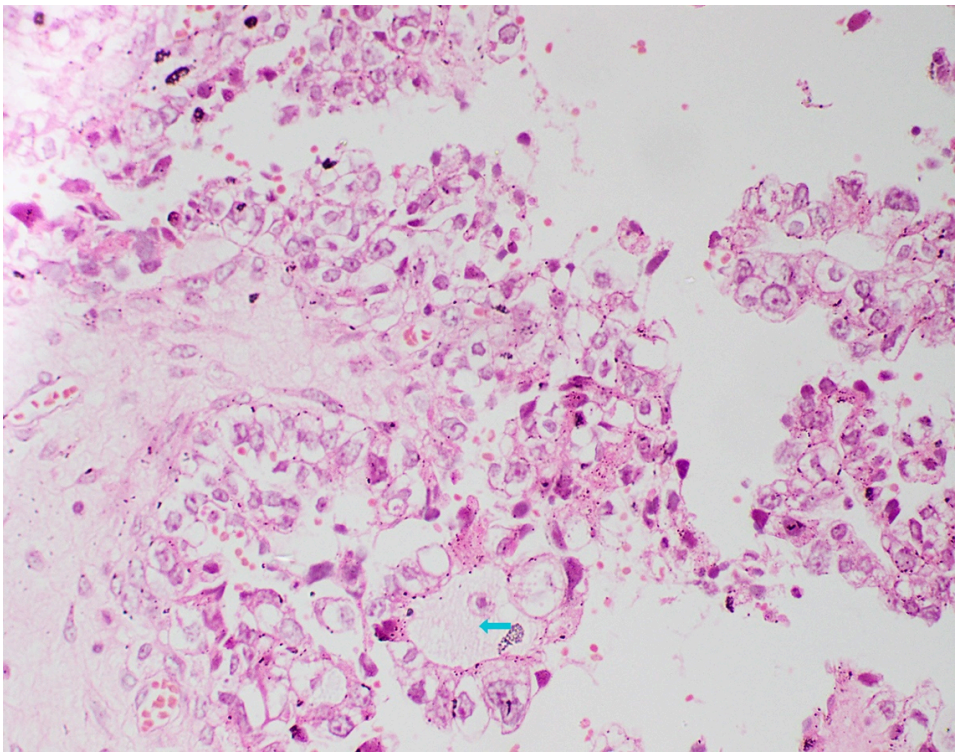

Figure 2. Histopathology of the tumour with haematoxylin and eosin stain showing a tubulocystic (light blue arrow) structure.

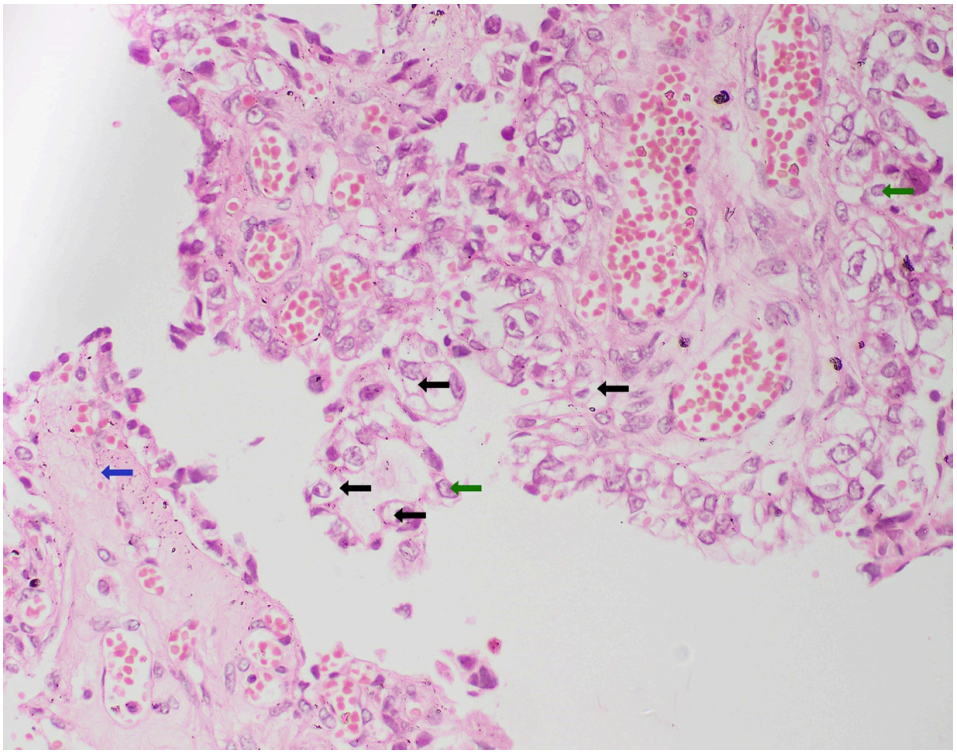

Figure 3. Histopathology of the tumour with haematoxylin and eosin stain showing papillary (blue arrow) structures lined by cells with clear cytoplasm (black arrows) and hobnail cells (green arrows).

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Before discharge, she developed shortness of breath again. She was diagnosed with pulmonary embolism involving the distal-most sub-segmental pulmonary arteries of both lower lobes, for which she received low molecular weight heparin. Then, after discharge from the hospital, she was started on intravenous chemotherapy with paclitaxel, carboplatin, and bevacizumab.

While on chemotherapy, seven months after the primary surgery, she underwent total abdominal hysterectomy and omentectomy. The uterus and omentum were free of tumour involvement. Then, her whole-body positron emission tomography with computed tomography (PET-CT), done after one year, revealed no metabolically active recurrence in the pelvic cavity or the peritoneum. There were no FDG avid metastases in the liver, lungs, or skeleton. Her CA-125 level gradually decreased to 8 ng/ml (normal <35 IU/ml) during the first year after surgery. The timeline of important events is presented in Table 3.

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Day and time	Events
Four months before admission	Developed dysmenorrhea.
Two months before admission	Radiological diagnosis of ovarian neoplasm with the aid of USS and CECT abdomen and pelvis.
Four days before admission	Developed mild shortness of breath.
Day of admission	
23:20	She was admitted with mild fever, with a haemoglobin of 10.3g/dL and a platelet count of 43 x 10^3/uL.
Day two	Gradual worsening of shortness of breath throughout.
09:30	There is no evidence of DIC in the blood picture.
13:30	Evidence of consumptive coagulopathy by RoTEM.
19:35	Haemoglobin decreased to 8.2 g/dL and platelet count to 8 x 10^3/uL.
Day three	
01:30	Five units of platelets, 15ml/kg of fresh frozen plasma, and a single unit of red cell concentrate were transfused.
10:30	Evidence of DIC from the blood picture.
10:45	Another five units of platelets transfused.
11:30	Another eight units of platelets, 15ml/kg of fresh frozen plasma, one unit of red cell concentrate, and 7ml/kg of cryoprecipitate were transfused.
15:20	An exploratory laparotomy was done.
19:00	Surgical ICU care was given.
21:00	Post-operative haemoglobin of 10.5g/dl and platelet count of 108 x 10^3u/L.
Day five	Histopathological diagnosis of right ovarian clear cell carcinoma.
Day 09	Haemoglobin increased to 10.1g/dl and platelet count to 241 x 10^3/uL.
Day 10	Development of shortness of breath again.
Day 11	Diagnosis of pulmonary embolism with CTPA.
Day 29	Discharged from the hospital with an oncology follow-up.
Two weeks after discharge	Intravenous chemotherapy was started.
Four months after discharge	CA 125 level – 30 IU/ml.
Six months	Repeat laparotomy for TAH and omentectomy.
Eleven months	CA 125 level – 14 IU/ml.
One year	Whole body PET - CT scan done. Chemotherapy completed.
One year and four months	CA – 125 level – 8 IU/ml.

Table 3. Timeline

USS: Ultrasound scan, DIC: Disseminated intravascular coagulation, CECT: Contrast-enhanced computed tomography, ICU: Intensive care unit, CTPA: CT pulmonary angiogram, CA – 125 normal range <35 IU/ml, TAH: Total abdominal hysterectomy, PET: Positron emission tomography.

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Discussion

The International Society on Thrombosis and Haemostasis developed an algorithm for DIC diagnosis. The scoring system includes platelet count, prothrombin time, D-dimer, and fibrinogen levels. However, RoTEM, a modified thromboelastography, can be utilised to diagnose DIC, as we have used in this patient. Because RoTEM can provide information about clot formation, strength, and lysis [4][5]. As it provides detailed information about deficient components, it is beneficial in an acute event to correct deficient components.

Here, this patient was admitted with four days of shortness of breath and low platelets. Her first blood picture revealed no evidence of DIC but showed thrombocytopenia with anaemia. Only the second blood picture demonstrated evidence of DIC. The exact cause of her initial platelet drop is questionable, as we could not identify the precise aetiology.

Solid organ and haematological malignancies are well-known causes of DIC. In contrast, a subacute or chronic DIC is associated with mucin-producing adenocarcinoma and haematological malignancies such as acute promyelocytic and monocytic leukaemia. Leukaemia is often associated with bleeding, and solid tumours are usually associated with thromboembolic phenomena or thrombosis [6]. Ovarian malignancies have a high risk of thrombosis. They can be associated with sub-clinical DIC, but acute DIC or bleeding is rare [6][7]. A hyperfibrinolytic type of DIC is associated with bleeding, as in this patient [8].

Ovarian endometriosis can be a precursor for developing OCCC. OCCC can be associated with a hypercoagulable state, manifesting with thrombosis and thromboembolism, and the risk is higher compared to other variants of ovarian carcinoma [1][3]. The pathogenesis of DIC in OCCC is poorly understood [3]. Expression of a procoagulant factor by malignant cells or the release of tissue factor by malignant cells can initiate the DIC [4][7]. DIC leads to unregulated coagulation pathway activation. When associated with malignancies, it is typically insidious with a more prolonged course than other etiologies [4]. D-dimer is frequently elevated with OCCC and is associated with a poor prognosis [3]. This intravascular coagulation pathway activation manifests as thrombotic obstruction of small vessels, leading to organ failure. This results in widespread bleeding due to the concurrent consumption of platelets and clotting factors with hyperfibrinolysis and other proteolytic effects [4].

Removal of the underlying pathology will resolve the DIC [8]. In this patient, the surgery was more lifesaving than curative, as it stopped bleeding into the peritoneum, and removing the tumour resolved the DIC. However, due to the possibility of tumour micro-embolism to the peritoneum, she required chemotherapy to achieve a complete cure, which was demonstrated by the whole-body PET-CT scan and improvement in CA125 levels.

Most (90%) ovarian tumours have an epithelial origin [9]. The lining of the ovaries and the fallopian tubes, the coelomic epithelium, is assumed to be the source of epithelial ovarian cancer. OCCC is a less common subtype that accounts for 6% of ovarian epithelial carcinoma [2][9]. Although there are reports of other types of ovarian carcinoma with DIC, this is the first case report of OCCC associated with acute DIC. Acute DIC with intra-tumoral bleeding into a mixed serous papillary and endometrioid well-differentiated adenocarcinoma of the ovary is reported [7]. A hypercoagulable state causing nonbacterial thrombotic endocarditis leading to thromboembolic manifestations with DIC in patients with OCCC in a Caucasian patient is described [2]. A patient with chronic DIC with recurrent cerebral thrombosis and OCCC and another with recurrent cerebral thrombosis with ovarian cancer were reported [10][11]. A case report of ovarian mucinous cystadenocarcinoma was associated with DIC complicating cerebral, peripheral, pulmonary, and coronary thrombotic events [12]. However, to our knowledge, no OCCC with acute DIC causing haemoperitoneum has been reported. Nevertheless, we are cautious in declaring a causal relationship.

We could not perform mutation analysis or check for microsatellite instability as they are not freely available. Immunophenotyping of HNF-1 beta could not be achieved either.

Conclusions

Though it is not essential for the diagnosis, RoTEM may help diagnose and manage acute DIC. In a patient with OCCC with low haemoglobin, bleeding due to DIC should be considered. Clear cell carcinoma, a subtype of ovarian epithelial carcinoma, can be associated with acute DIC, and acute DIC may be a complication of all ovarian cancers of epithelial origin.

Statements and Declarations

Ethics

The patient gave written informed consent to the publication of this case report and any accompanying images or data.

Data Availability

The data presented in this study are available within the article. Further inquiries can be directed to the corresponding author. Due to patient privacy regulations, raw clinical data cannot be made publicly available.

Author Contributions

Conceptualization: TR; Investigation: TR, LW, BJ, PW, SS; Resources: TR; Data Curation: TR, SS; Writing – Original Draft Preparation: TR; Writing – Review & Editing: TR, LW, PW, BJ, SS; Visualization: TR; Supervision: SS; Project Administration: SS. All authors contributed to the diagnosis and clinical management of the patient.

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Declarations

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