[Case Report] Clear Cell Carcinoma of the Ovary with Disseminated Intravascular Coagulation and Haemoperitoneum with Tumour Rupture

Thilina Rathnasekara¹, Lanka Wijekoon², Prasanna Weerawansa², Bhagya Jayasiri, Sisira Siribaddana²

¹ University of Colombo
² Rajarata University of Sri Lanka

Funding: No specific funding was received for this work.
Potential competing interests: No potential competing interests to declare.

Abstract

We report a 34-year-old woman with haemoperitoneum and acute disseminated intravascular coagulation (DIC) following 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 is not 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 OCCC can be the aetiology for acute DIC and bleeding. Practitioners must know this rare but potentially fatal association between OCCC and acute DIC.

Rathnasekara T¹, Wijekoon L², Weerawansa P², Jayasiri B³, Siribaddana SH²

¹ Postgraduate Institute of Medicine, University of Colombo
² Department of Medicine, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka
³ Department of Gynaecology and Obstetrics, Teaching Hospital Anuradhapura
Introduction

Ovarian clear cell carcinoma (OCCC) is a rare subtype of ovarian epithelial carcinoma which 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. 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 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, 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 haemoglobin to suggest 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.
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

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.

<table>
<thead>
<tr>
<th>Test</th>
<th>CT</th>
<th>CFT</th>
<th>α</th>
<th>A10</th>
<th>MCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTEM</td>
<td>314 s</td>
<td>(38-79)</td>
<td>11 mm</td>
<td>(43-65)</td>
<td>20 mm</td>
</tr>
<tr>
<td>INTEM</td>
<td>285 s</td>
<td>(100-240)</td>
<td>1611 s</td>
<td>(30-110)</td>
<td>14°</td>
</tr>
<tr>
<td>FIBTEM</td>
<td>152 s</td>
<td></td>
<td>4 mm</td>
<td>(7-23)</td>
<td>4 mm</td>
</tr>
<tr>
<td>APTEM</td>
<td>237 s</td>
<td>1296 s</td>
<td>16°</td>
<td>13 mm</td>
<td>24 mm</td>
</tr>
</tbody>
</table>

(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 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.

<table>
<thead>
<tr>
<th>Table 2. Summary of investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
</tr>
<tr>
<td><strong>Time</strong></td>
</tr>
<tr>
<td>(4 -10)</td>
</tr>
<tr>
<td><strong>HB g/dL</strong></td>
</tr>
<tr>
<td>(12 – 16)</td>
</tr>
<tr>
<td><strong>PLT 10^3/uL</strong></td>
</tr>
<tr>
<td>(150 – 400)</td>
</tr>
<tr>
<td><strong>INR (&lt;1.4)</strong></td>
</tr>
<tr>
<td><strong>aPTT seconds</strong></td>
</tr>
<tr>
<td><strong>AST U/L</strong></td>
</tr>
<tr>
<td>(10 – 35)</td>
</tr>
<tr>
<td><strong>ALT U/L</strong></td>
</tr>
<tr>
<td>(10 - 40)</td>
</tr>
<tr>
<td><strong>Total bilirubin umol/L</strong></td>
</tr>
<tr>
<td>(5 – 21)</td>
</tr>
<tr>
<td><strong>Direct bilirubin umol/L</strong></td>
</tr>
<tr>
<td>(&lt;3.4)</td>
</tr>
<tr>
<td><strong>Indirect bilirubin umol/L</strong></td>
</tr>
<tr>
<td>(5.1 – 17)</td>
</tr>
<tr>
<td><strong>CRP mg/L</strong></td>
</tr>
<tr>
<td>(&lt;5)</td>
</tr>
<tr>
<td><strong>ESR mm/1st hour</strong></td>
</tr>
<tr>
<td>(&lt; 22)</td>
</tr>
</tbody>
</table>

**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 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 8th TNM classification, the stage was pT1c2, and the FIGO stage was IC2. The left ovary showed only an endometriotic cyst without evidence of malignant tumour involvement.

Figure 2. Histopathology of the tumour with haematoxylin and eosin stain showing a tubulocystic (light blue arrow) structure.
Before discharge, she developed shortness of breath again. She was diagnosed with pulmonary embolism involving 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.

**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).
**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 haemoglobin of 10.3g/dL and platelet count of 43 x 10^3/uL.  

**Day two**  
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 6 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 platelet transfused.  
11:30 | Another eight units of platelets, 15ml/kg of fresh frozen plasma, one unit of red cell concentrate, and 7ml/kg 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 10^3/uL.  

**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.  

---  

**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.  

---  

**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 \cite{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 with low platelets. Her first blood picture revealed no evidence of DIC but thrombocytopenia with anaemia. Only the second blood picture demonstrated evidence of DIC. The exact cause for 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 \cite{6}. Ovarian malignancies have a high risk of thrombosis. They can be associated with sub-clinical DIC, but acute DIC or bleeding is rare \cite{6,7}. Hyperfibrinolytic type of DIC is associated with bleeding, as in this patient \cite{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 \cite{1,3}. The pathogenesis of DIC in OCCC is poorly understood \cite{3}. Expression of procoagulant factor by malignant cells or release of tissue factor by malignant cells can initiate the DIC \cite{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 \cite{4}. D-dimer is frequently elevated with OCCC and is associated with poor prognosis \cite{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 \cite{4}.

Removal of underlying pathology will resolve the DIC \cite{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 have 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 \cite{9}. The lining of ovaries and the fallopian tubes, the coelomic epithelium, is assumed to be the source of epithelial ovarian cancer. OCCC is a less common subtype which accounts for 6\% of ovarian epithelial carcinoma \cite{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 \cite{7}. A hypercoagulable state causing nonbacterial thrombotic endocarditis leading to thromboembolic manifestations with DIC in patients with OCCC in a Caucasian patient is described \cite{2}. A patient with chronic DIC with recurrent cerebral thrombosis and OCCC and another with recurrent cerebral thrombosis with ovarian cancer were reported \cite{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 from the epithelial origin.

Statements and Declarations

Patient consent

Informed written consent was obtained.

References


