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Disseminated intravascular coagulation complicating urothelial malignancy

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ABSTRACT Transitional cell carcinoma has rarely been reported to be associated with disseminated intravascular coagulation (DIC). We report a 55-year-old Chinese man who was diagnosed with transitional cell carcinoma with vertebral metastasis. He presented with severe anaemia and thrombocytopenia, and subsequent evaluation revealed features of DIC. Interestingly, he did not have fever, any localising symptoms or signs of infection. He was treated aggressively with transfusion of packed cells, platelets, intravenous vitamin K and fresh frozen plasma. Despite aggressive treatment, the coagulation abnormalities were resistant to correction. The patient continued to deteriorate and eventually died of cardiac arrest. This case illustrates that transitional cell carcinoma can also be associated with DIC, possibly due to the expression of certain unidentified procoagulant factors similar to the tissue factor responsible for DIC.

Keywords: disseminated intravascular coagulation, microangiopathic haemolytic anaemia, procoagulant factor, tissue factor, transitional cell carcinoma
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INTRODUCTION

Disseminated intravascular coagulation (DIC) has been reported to complicate up to 7% of malignancies. The commonest solid organ malignancies associated with DIC include adenocarcinomas of the pancreas, breast and prostate.[1] Transitional cell carcinoma has rarely been found to be associated with DIC.

CASE REPORT

We report a 55-year-old Chinese man who was diagnosed with transitional cell carcinoma of the ureter with vertebral metastasis four months before presentation. He presented to us with a history of poor appetite and vomiting for a few days, and was found to be unresponsive on the day of admission. On examination, he was drowsy and severely anaemic, with hypotension (86/56 mmHg) and hypoxia (SpO_2 86% on room air). He was also paraparetic, with an indwelling catheter *in situ* for urinary retention. The rest of the systemic examination was unremarkable. He had no bleeding manifestations (no bleeding per rectum and no haematuria).

Investigations revealed severe anaemia (Hb 2.6 g/dL) and thrombocytopenia (platelet count 33,000/mm^3), with a total white cell count of 4,900 cells/mm^3. Peripheral blood film showed features of haemolysis with fragmented red cells and polychromasia (Fig. 1). The patient also had severe coagulopathy (prothrombin time 43 seconds and activated partial thromboplastin time 74.3 seconds), along with low fibrinogen levels (< 0.3 mg/dL) and raised D-dimer levels (> 10), which were indicative of DIC. Interestingly, he had no fever or localising symptoms of infection, and investigations revealed normal white cell count, C-reactive protein (CRP) levels, urine microscopy and chest radiograph. Urine and blood cultures did not grow any organism, and dengue serology was negative. The patient was treated aggressively with blood transfusion, fresh frozen plasma (FFP) transfusion, vitamin K injection, omeprazole and was covered empirically with intravenous ceftriaxone. However, he continued to deteriorate and eventually died of cardiac arrest three days after admission.

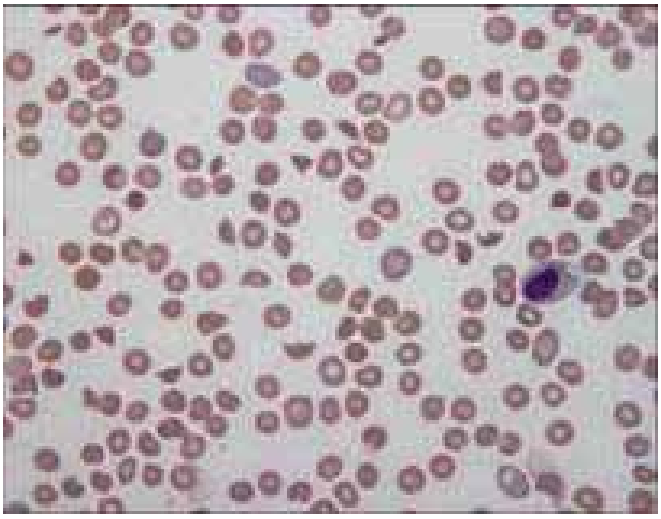

Fig. 1 Peripheral blood film shows fragmented red cells, polychromasia and severe thrombocytopenia.

DISCUSSION

DIC is a complex systemic thrombohaemorrhagic disorder seen in association with a variety of conditions, including malignancies. It is reported to complicate up to 7% of malignancies. The most common malignancies associated with DIC include haematological malignancies such as acute myeloid leukaemia and mucin-secreting solid organ

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Table I. International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC*.

Parameter	Score
Platelet count	
> 100	0
< 100	1
< 50	2
Elevated fibrin-degradation products	
No increase	0
Moderate increase	2
Strong increase	3
Prolonged prothrombin time (sec)	
< 3	0
3–6	1
> 6	2
Fibrinogen level (g/L)	
> 1	0
< 1	1

*Total score ≥ 5 is compatible with overt DIC.
DIC: disseminated intravascular coagulation

adenocarcinomas arising from the prostate, lung, breast and gastrointestinal tract.[2] However, urothelial malignancy is rarely reported to be associated with DIC.

The exact aetiology of DIC in malignancy is poorly understood. It is thought that the expression of procoagulant substances such as tissue factor (thromboplastin) by the circulating tumour cells is an essential step in the initiation of DIC. This tissue factor (TF) in turn activates the extrinsic pathway of coagulation. Excessive release of TF disturbs the normal control mechanisms, resulting in the generation of large amounts of thrombin, leading to fibrin formation and deposition in the microvasculature. Widespread microvascular thrombosis produces tissue ischaemia and organ damage. Blood flow through the thrombosed vessels causes mechanical shearing and haemolysis of red blood cells by the intravascular fibrin strands, resulting in a condition known as microangiopathic haemolytic anaemia. With continuing thrombosis, more platelets, fibrinogen, prothrombin and other clotting factors are consumed. When the rate of consumption of platelets and clotting factors exceeds the compensatory synthetic capacity of the body, thrombocytopenia and coagulopathy ensue, putting the patient at increased risk of bleeding. Finally, as a response to widespread intravascular thrombosis, excessive plasmin is secreted, which degrades both fibrinogen and fibrin into fibrin degradation products (FDPs). The resulting increased concentration of FDPs can be measured by a laboratory assay, which is essential for the diagnosis of DIC.[1]

Among solid organ tumours, mucin-secreting adenocarcinomas are supposedly rich in TF, whereas transitional cell carcinomas are usually not.[3] Therefore, the mechanism of DIC in our patient is speculative. He had all the features that satisfied the diagnostic criteria of DIC (Table I).[4] There were no other obvious causes of DIC, suggesting that the DIC in our patient was most likely secondary to the underlying metastatic ureteric malignancy. It is possible that malignant transitional cells express other substances such as cancer procoagulant or hepsin, which could have initiated the activation of coagulation.[5,6] The activated coagulation cascade process was unusually aggressive. Despite aggressive treatment with blood and FFP transfusion, the coagulation abnormalities were resistant to correction and the patient continued to deteriorate until he died of cardiac arrest.

In conclusion, this case illustrates that transitional cell carcinoma can also be associated with DIC. The onset of DIC complicating urothelial malignancies can be associated with a very poor prognosis, as it can be unusually aggressive and very resistant to correction. Physicians should be aware of this complication, and identify such cases early and treat aggressively before frank DIC develops.

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