REVIEW

Disseminated intravascular coagulation as clinical manifestation of colorectal cancer: a case report and review of the literature

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ABSTRACT

We describe the case of a 65-year-old woman, known with ulcerative colitis, who presented with progressive headaches, haematomas and rectal bleeding which turned out to be the initial manifestation of disseminated intravascular coagulation (DIC) associated with colorectal cancer. The presentation posed as a general medicine case but turned out to be a rare oncological complication. The patient revealed possible carcinocythaemia and bone marrow infiltration with signet ring-like cells, as indicators of advanced adenocarcinoma. Treatment of the underlying disease resolved the DIC and contributed to prolonged survival. Subsequently, we reviewed the English literature since 1990 on similar cases and demonstrated that this association is extremely rare and is associated with a poor prognosis. Prompt recognition and treatment of the underlying disease is confirmed to be of utmost importance to prolong (progression-free) survival.

KEYWORDS

Carcinocythaemia, colorectal neoplasm, disseminated intravascular coagulation

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a clinicopathological syndrome characterised by the occurrence of bleeding, thrombosis, or both, in patients with laboratory evidence of activation of the clotting and fibrinolytic systems.[1] Underlying diseases causing DIC include haematological malignancies, infection, sepsis, and trauma.[1] The relation with solid tumours is uncommon. We present the case of a patient who presented with a

coagulation disorder as a result of DIC accompanying metastasised colorectal cancer and review similar cases published since 1990.

CASE

A 65-year-old woman, known with ulcerative colitis, was admitted to the emergency department because of a sudden increase of headache, spontaneous haematomas, and rectal bleeding. One month before presentation she had experienced continuous headaches and an increased stool frequency accompanied by rectal bleeding, which she thought was an exacerbation of her inflammatory bowel disease. She also mentioned malaise and weight loss. Her ulcerative colitis was diagnosed in 2007 in another hospital, and she had withdrawn from follow-up, partly due to fear of having to undergo colonic endoscopies. At presentation her body temperature was 37.7 °C, blood pressure 165/90 mmHg, pulse 101 beats/min and respiratory rate 18/min. Physical examination revealed several haematomas of different sizes and age on the patient's legs. The lungs were clear, and the heart sounds were regular with no murmurs. The examination of the abdomen revealed an enlarged liver. There were no palpable lymph nodes and the rest of the physical and neurological examination was without abnormalities. Laboratory evaluation showed haemolytic anaemia with a haemoglobin concentration of 9.8 g/dl, haematocrit of 30%, mean corpuscular volume of 85 fl, reticulocyte count of 256 x 10³/ml, lactate dehydrogenase concentration of 891 U/l (normal range: 10-450 U/l), total bilirubin concentration of 0.9 mg/dl (normal range: 0.1-0.9 mg/dl), and haptoglobin concentration less than 10 mg/dl (normal range: 30-200 mg/dl). Furthermore, thrombocytopaenia of

136 x 10³/ml and leukocytosis of 14.1 x 10³/m were found. The prothrombin time was 19.2 seconds (normal range: 11-13 seconds), activated partial thromboplastin time was 29 seconds (normal range: 25-33 seconds), fibrinogen concentration of 50 mg/dl (normal range: 200-400 mg/dl), and D-dimer concentration of 14.45 µg/ml (normal range: 0-0.55 µg/ml), which indicated DIC. Examination of the peripheral blood smear excluded haematological malignancies but revealed limited leukoerythroblastosis, some fragmented erythrocytes and a sporadic atypical cell of unknown origin, resembling a seal ring (*figure 1*). An MRI of the cerebrum was performed and showed multiple cerebral infarctions. A bone marrow aspiration and biopsy demonstrated grouped mucin-forming atypical cells, positive for staining with CAM 5.2, an epithelial marker, indicating the possibility of an adenocarcinoma. Computed tomography (CT) of the thorax and abdomen revealed pathological thickening of the colon wall along more than 10 cm and pathological lymphadenopathy (mediastinal and para-aortic) (*figure 2*). The biopsy of the abnormality found by imaging, obtained through colonic endoscopy, confirmed the presence of a mucin-forming

Figure 1. *Peripheral blood smear demonstrating some fragmented erythrocytes and a sporadic atypical cell of unknown origin, resembling a seal ring*
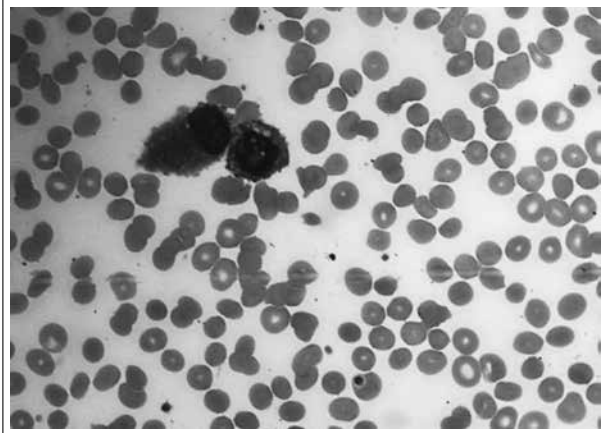

Figure 2. *Computed tomography of the abdomen revealing pathological thickening of the colon wall and pathological lymphadenopathy*

adenocarcinoma of the sigmoid. The patient started palliative chemotherapy three days after admission, consisting of XELOX: capecitabine 1000 mg/m² twice daily and oxaliplatin 130 mg/m² every three weeks, which she tolerated well despite of minor neuropathy after the second cycle. DIC was successfully suppressed after starting chemotherapy with clinically diminishing haematomas and resolution of her headache and with normalisation of platelet count, clotting times and rise in coagulation proteins after ten days. The patient was discharged 15 days after admission. The tumour marker carcinoembryonic antigen decreased after one month and CT scan after the third cycle of chemotherapy showed regression of the pathological lymph nodes. After eight cycles of chemotherapy disease progression occurred. Laboratory tests confirmed a new episode of DIC. The patient received a gift of FOLFIRI (folinic acid, fluorouracil and irinotecan), which did not improve her symptoms. She died eight months after the diagnosis of colorectal cancer due to disease progression. On autopsy, the colonic tumour invaded surrounding tissue and disseminated to the peritoneal cavity and bone marrow. Extended leptomeningeal carcinomatosis was found. There were no macrometastases in other visceral organs. An infarction of the spleen was present.

RESULTS AND DISCUSSION

The association of DIC and solid tumours is rare but has been known for decades. In 10-15% of patients with metastasised solid tumours there is evidence of DIC.[2] In a study by Sallah *et al.*[3] of 1117 patients with solid tumours, 6.8% were diagnosed with DIC. In a multivariate analysis, older age, male gender, advanced malignancy, breast cancer and the presence of necrosis in the tumour specimen emerged as independent factors significantly related to the occurrence of DIC. Patients diagnosed with DIC had a reduced survival, even when grouped by tumour stage, compared with patients without DIC. Nevertheless, the exact mechanism of DIC in patients with solid tumours remains unclear.[1] The initiation of widespread activation of the coagulation system could be based on the abnormal expression of procoagulant tissue factor on tumour cells and/or the vessel surface that leads to activation of the extrinsic coagulation pathway through a complex binding with factor VII.[2] For the treatment of DIC supportive measures, consisting of anticoagulants, platelets and plasma, coagulation inhibitors, or antifibrinolytic agents, may be necessary, although no consensus regarding optimal therapy exists at this time.[1] The widespread activation of coagulation can ultimately lead to thrombotic occlusion of small and middle sized vessels. At the same time, the use and subsequent depletion of platelets and

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coagulation proteins may induce severe bleeding. Bleeding can complicate decisions about anticoagulant treatment. Our patient demonstrated multiple cerebral infarctions, but without functional abnormalities. Next to that, blood loss in her stools was substantial and red blood cell transfusion was needed twice. Therefore, no anticoagulant therapy was administered.

This case demonstrates a rare presentation of advanced colorectal cancer. Reviewing the English literature published since 1990 on DIC and colorectal carcinoma revealed only five cases (*table 1*).[4-8] Including our case, patient age at diagnosis ranged from 50-79 years. Four out of six patients were male. DIC was the presenting symptom in all but two cases. In these two cases DIC occurred after initial surgery,[7] or chemotherapy.[4] The cases were associated with a pathological diagnosis of poorly/moderately differentiated or signet ring-like cell adenocarcinoma. Bone marrow invasion was described in four out of the six cases reviewed.[6-8] In five of the six cases the patients died with a survival, after the diagnosis of DIC, ranging from 12-210 days. In one case the patient died after 83 days of pneumonia, unrelated to DIC or tumour progression.[7] Supportive treatment for DIC was administered in four cases but did not really seem to affect outcome.[4,6-8] However, in the three cases where chemotherapy was initiated, the survival times were longest (83, >120, 210 vs. 12, 25, 30 days). Due to the limited number of cases statistical analyses could not be conducted. Overall, identification of the underlying disease and prompt treatment seemed essential for the effective management of DIC and (progression-free) survival. The underlying cause of our patient's coagulation disorder was diagnosed rapidly and chemotherapy was administered within three days after admission. She responded well with normalisation of several laboratory values after ten days, and eventually a decreasing tumour marker within one month. She had a progression-free survival of almost eight months, with good quality of life. However, after this period her disease progressed rapidly, leading to death within several weeks. At presentation, our patient had demonstrated an atypical cell in the peripheral blood smear. Carcinocythaemia, introduced by Carey *et al.*,[9] is known as a unique form of cancer metastasis in which the cancer cells can be detected in the peripheral blood, generally occurring in a far advanced stage of certain neoplasms, mostly breast cancer. Gallivan *et al.*[10] describe a mean time between detection of carcinocythaemia and death to be five weeks (median two weeks) reflecting the fact that it is generally a terminal event. The coincidence of DIC and carcinocythaemia is extremely rare and has been published only thrice to date.[6,10,11]

Table 1. *Cases of disseminated intravascular coagulation and colorectal carcinoma published since 1990*

Author	Year	Sex	Age (year)	Platelet count (x10³/ μl)	APTT (sec)	PTT (sec)	Fibrino-gen (mg/dl)	D-dimer (μg/ml)	Carcino-cythae mia	Marrow carcino-matosis	Histology	(Progres-sion-free) survival (days)	Therapy
Yoshioka et al.[8]	1992	M	62	71	44	13.3	142	x	x	Yes	Moderately differenti-ated adeno-carcinoma	12, died	Anti-DIC
Huang et al.[7]	2005	M	79	58	41	21.1	233.8	1.05	x	Yes	Moderately differenti-ated adeno-carcinoma	83, died*	Anti-DIC, 5-FU, leucoverin
Misawa et al.[6]	2008	M	51	129	x	x	95.2	0.615	Yes	Yes	Signet ring-like cell carcinoma	25, died	Anti-DIC
Kato et al.[5]	2010	F	72	23	29	36.6	381	0.063	x	x	Poorly dif-ferentiated adenocarci-noma	30, died	x
Mizota et al.[4]	2011	M	50	18	x	x	31.4	1.352	x	x	Poorly dif-ferentiated adenocarci-noma	>120	Anti-DIC, FOLFOX, bevacuz-imab
Van Bunderen et al. (present study)	2014	F	65	127	29	19.1	500	14.45	Yes	Yes	Signet ring-like cell carcinoma	210, died	XELOX, FOLFIRI

Sec=seconds; APTT=activated partial thromboplastin time; PTT=prothrombin time; M=male; x=not reported; anti-DIC=treatment for dissemi-nated intravascular coagulation; F=female; FOLFOX=folinic acid, fluorouracil, oxaliplatin; 5-FU=fluorouracol, XELOX=capecitabine, oxaliplatin; FOLFIRI=folinic acid, fluorouracil, irinotecan. *Patient died of pneumonia without signs of DIC or tumour progression.

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In conclusion, we report an unusual presentation of the association of DIC and colorectal cancer. This case, supported by a review of the literature, illustrates that DIC in advanced colorectal cancer is rare, but can be managed with prompt diagnosis and immediate chemotherapy, consequently prolonging survival.

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