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Severe Disseminated Coagulopathy Caused by Adenocarcinoma with Bone Marrow Metastasis

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Keywords
Adenocarcinoma · Disseminated intravascular coagulation · Bone marrow metastasis · Thrombocytopenia

Summary
Background: Patients with mucin-producing adenocarcinoma have an increased risk for venous and arterial thrombosis. When these patients present with thrombocytopenia, disseminated intravascular coagulopathy (DIC) is often the underlying cause. **Case Report:** We report 2 patients who were admitted due to bleeding symptoms of unknown cause, in whom further workup revealed adenocarcinoma-induced DIC. **Conclusion:** In elderly patients presenting with signs of DIC, such as reduced fibrinogen levels, elevated prothrombin time, elevated D-dimer, and thrombocytopenia, without any obvious reason (e.g., sepsis), adenocarcinoma-associated coagulopathy should be considered as the underlying cause. Paradoxically, in these patients bleeding symptoms improve when the patient is sufficiently anticoagulated with low molecular weight heparin. Treatment of the underlying disease is of central importance in controlling acute or chronic DIC associated with malignant diseases and chemotherapy should be started as soon as possible.

Schlüsselwörter
Adenokarzinom · Disseminierte intravasale Gerinnung · Knochenmetastasen · Thrombozytopenie

Zusammenfassung
Hintergrund: Patienten mit einem muzinproduzierenden Adenokarzinom haben ein deutlich erhöhtes Risiko für venöse und arterielle Thrombosen. Wenn bei diesen Patienten eine Thrombozytopenie auftritt, ist die Ursache häufig eine disseminierte intravasale Gerinnung (DIC). **Kasuistik:** Wir berichten von 2 Patienten, die aufgrund einer unklaren Blutungsneigung stationär aufgenommen wurden. Die weitere Diagnostik sicherte bei beiden Patienten eine Adenokarzinom-induzierte DIC. **Schlussfolgerung:** Bei älteren Patienten, die mit Zeichen einer DIC wie erniedrigtem Fibrinogenspiegel, erhöhter Prothrombinzeit, erhöhtem D-Dimer-Wert und Thrombozytopenie ohne anderen ersichtlichen Grund (z.B. Sepsis) aufgenommen werden, sollte immer auch an eine Adenokarzinom-induzierte DIC gedacht werden. Paradoxerweise bessert sich die Blutungsneigung bei diesen Patienten durch eine effektive Antikoagulation mit einem niedermolekularen Heparin. Die Behandlung der Grunderkrankung ist von zentraler Bedeutung in der Therapie der akuten und chronischen DIC, sodass eine Chemotherapie so schnell wie möglich begonnen werden sollte.

Introduction

Patients with mucin-producing adenocarcinoma have an increased risk for venous and arterial thrombosis. When these patients present with thrombocytopenia, disseminated intravascular coagulopathy (DIC) is often the underlying cause. DIC is the most common coagulopathy associated with malignancy, accounting for approximately 7% of clinically evident cases [1]. However, acute overt DIC with major bleeding is rare, most often occurring in patients with acute promyelocytic leukemia. It can also complicate the course in patients with solid tumors and is associated with a high mortality [2–6], ranging from 30 to > 80% depending on the underlying disease, the severity of DIC, and the age of the patient.

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Significant risk factors for developing DIC include age > 60 years, male sex, breast cancer, tumor necrosis, advanced stage disease [1], and bone marrow metastasis [7]. The diagnosis is suggested by reduced fibrinogen levels (or prolonged thrombin time), elevated prothrombin time, and elevated D-dimer levels [8]. We report 2 patients who were admitted due to bleeding symptoms of unknown cause, in whom further workup revealed adenocarcinoma-induced DIC.

Case Reports

Case 1

A 68-year-old male patient was admitted with epistaxis and multiple hematomas. The patient had a history of locally advanced cancer of the rectum (adenocarcinoma), which had been diagnosed 12 months earlier, and treated by neoadjuvant radio-chemotherapy followed by anterior rectum resection with colostomy and adjuvant chemotherapy (FOLFOX: 5-fluoruracil, oxaliplatin, folinic acid). 2 months before admission re-staging by computed tomography (CT) showed complete remission. 2 weeks before admission, the patient developed severe thoracic pain treated by non-steroidal anti-inflammatory drugs without pain relief. On admission, based on a platelet count of 18 gigaparticles (Gpt)/l (male norm 150–362), fibrinogen 0.9 g/l (1.8–3.5), international normalized ratio (INR) 1.5 (1.0–1.2), thromboplastin time 45% (70–130), activated partial thromboplastin time (aPTT) 28 s (26–40), D-dimer > 35 mg/l (< 0.5), antithrombin 73% (80–120), and fragmented red cells, DIC was suspected. Detection of fibrin monomers were negative on admission, but became positive on day 3. Bleeding symptoms were treated by transfusion of red cell concentrates, platelets, antithrombin, fresh frozen plasma, prothrombin complex concentrates, and fibrinogen. While fibrinogen normalized, PTT and INR remained prolonged, and bleeding persisted. Because of highly elevated levels of the tumor marker carcinoembryonic antigen (CEA) and no evidence for other causes for DIC, progression of the malignant disease was suspected. While CT showed no tumor in the chest or abdomen, bone marrow biopsy revealed tumor cells (fig. 1), and blood smears showed fragmentocytes and leukoerythroblastic reaction (fig. 2). Diffuse bone metastasis was verified by scintigraphy. Palliative chemotherapy with irinotecan – recommended for symptom control – was refused by the patient who died within 1 week.

Case 2

A 73-year-old female patient was admitted for fatigue, loss of appetite, and spontaneous skin bruising. Based on a platelet count of 68 Gpt/l (female norm 150–400); fibrinogen 2.1 g/l (3.0–5.0); D-dimer 40.76 mg/l (< 0.15); thromboplastin time 55% (70–125); but normal aPTT, and INR, compensated DIC was suspected. Antithrombin and fibrin monomers were not measured in this case. Based on a history of malignant carcinoid of the small bowel with pulmonary and pleural metastasis 8 years previously, which, however, had remained in complete remission since initial treatment, tumor-associated DIC was suspected. Low molecular weight heparin (LMWH) was started in therapeutic dose. This resulted in a prompt increase in platelet counts to ~90 Gpt/l, but fibrinogen levels remained low and D-dimer stayed elevated. Like patient 1, this patient also developed severe back pain about 2 weeks before admission that was unresponsive to non-steroidal anti-inflammatory drugs. Endoscopy showed erosive gastritis complicated by gastric bleeding and biopsy revealed a low differentiated adenocarcinoma of the stomach not identical with the carcinoid diagnosed previously. Bone marrow biopsy revealed tumor cells, and scintigraphy showed diffuse bone metastasis. The tumor marker Ca 19-9 was massively elevated. For the planned palliative cisplatin-containing chemotherapy, a venous port system was implanted; postoperatively the patient developed a large hematoma of the chest. She was dismissed from hospital with a stable platelet count of 48 Gpt/l and fibrinogen of 2.4 g/l. Therapeutic anticoagulation with LMWH was continued at home. 2 weeks later, the patient was admitted to hospital with reduced general condition, severe headache, nausea, and hypertensive crisis. Platelet count was 21 Gpt/l; aPTT 40.5 s (23–40); fibrinogen 1.8 g/l; and D-dimer 20.14 mg/l. Cerebral CT showed extended intracerebral hemorrhage, and the patient died a few days later.

Discussion

These 2 cases indicate that in elderly patients presenting with signs of DIC, such as reduced fibrinogen levels, elevated prothrombin time, elevated D-dimer, and thrombocytopenia, without any obvious reason (e.g. sepsis), adenocarcinoma-associated coagulopathy should be considered as the underlying cause. Clinical manifestations of DIC are related to the imbalance of hemostasis, to the underlying disease, or to both.

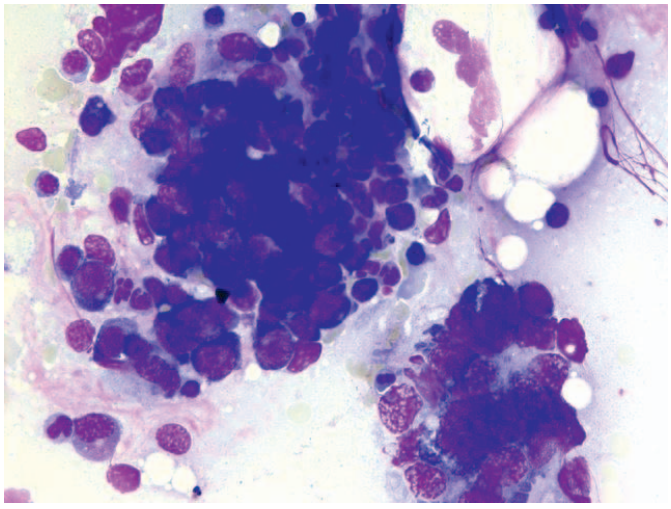

Fig. 1. Bone marrow smear of patient 1 showing carcinoma tumor cells in bone marrow.

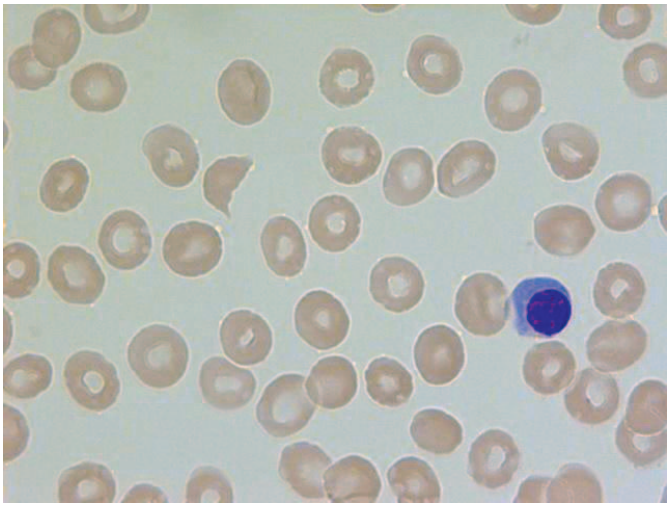

Fig. 2. Blood smear of patient 1 showing fragmentocytes and leukoerythroblastic reaction.

Mucin produced by adenocarcinomas may trigger coagulation by reacting with leukocyte and platelet selectins, resulting in the production of platelet-rich microthrombi. Other causes of DIC in malignancies include tumor cell procoagulants as tissue factor, and thrombotic microangiopathy [7].

The most common findings are bleeding ranging from oozing from venipuncture sites, petechiae, and ecchymoses to severe hemorrhage from the gastrointestinal tract or lung or into the central nervous system. Paradoxically, in these patients bleeding symptoms improve when the patient is sufficiently treated with anticoagulants, e.g. LMWH. The most likely reason for this is that anticoagulation measures enhances thrombin generation and consecutive consumption of platelets and clotting factors. However, therapeutic doses of anticoagulation bear the risk of inducing major, even fatal hemorrhage in case of severe thrombocytopenia or tumor-induced vessel erosion.

Transfusion of platelets and plasma into patients with DIC should not primarily be based on laboratory results, and should be in general be reserved for patients who present with bleeding. Administration of antithrombin cannot be recommended, because there is no prospective evidence from randomized controlled trials confirming a beneficial effect on clinically relevant endpoints in patients with DIC and not receiving heparin [9].

Adenocarcinoma provokes deep vein thrombosis more frequently than it causes decompensated DIC. In both situations, i.e. adenocarcinoma-induced DIC and adenocarcinoma-induced thrombosis (often associated with compensated DIC), it is important to avoid vitamin K antagonists (VKAs). VKAs often cause worsening of DIC, and are associated with a high risk for new or progressive thrombosis and especially venous limb gangrene. The reason for aggravation of DIC and/ or thrombosis is the rapid decrease of protein C caused by VKAs. A further decrease in platelet counts after the start of VKAs is a surrogate marker for this paradox procoagulatory effect in these patients and a supra-therapeutic INR represents a surrogate marker for severe acquired protein C deficiency [8]. The INR is altered by a rapid decrease in factor VII. Although protein C levels do not influence the INR, they parallel factor VII as both these vitamin K-dependent proteins have similarly short half-lives.

Treatment of the underlying disease is of central importance in controlling acute or chronic DIC [9] associated with malignant diseases, and chemotherapy should be started as soon as possible [2, 3]. In patients with bone marrow metastasis, we recommend dose adjustment to marrow insufficiency. A possible regimen is weekly application of chemotherapy under monitoring of blood cell count.

If chemotherapy is not feasible, for example due to reduced performance status, anticoagulation is the only symptomatic treatment of adenocarcinoma-induced DIC. However, this is not without risk, as shown by the second patient who died due to cerebral hemorrhage before treatment of the tumor could be started.

Disclosure Statement

There is no actual or potential conflict of interest in relation to this article.

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