Expression and Release of Tumor Cell Tissue Factor Triggers Recurrent Thromboembolism in a Patient with Endometrial Cancer

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Abstract

Although cancer-associated thrombosis (CAT) is a frequent complication in patients with malignancies, its treatment remains a challenge in daily practice. Here, we report the clinical course of a 51-year-old woman presenting with a highly thrombogenic paraneoplastic coagulopathy. Despite therapeutic anticoagulation with various agents, including rivaroxaban, fondaparinux, and low-molecular-weight heparin, the patient suffered from recurrent venous and arterial thromboembolism. Locally advanced endometrial cancer was identified. Tumor cells showed strong expression of tissue factor (TF), and significant concentrations of TF-bearing microvesicles were detected in patient plasma. Coagulopathy was controlled only by continuous intravenous anticoagulation with the direct thrombin inhibitor, argatroban. Multimodal antineoplastic treatment, including neoadjuvant chemotherapy followed by surgery and postoperative radiotherapy, resulted in clinical cancer remission, which was paralleled by normalization of tumor markers, CA125 and CA19–9, D-dimer levels, and TF-bearing microvesicles. In summary, continuous anticoagulation with argatroban and multimodal anticancer treatment may be necessary to control TF-driven coagulation activation with recurrent CAT in endometrial cancer.

Keywords

- cancer-associated thrombosis
- paraneoplastic coagulopathy
- tissue factor
- endometrial cancer
- microvesicle

Zusammenfassung

Obwohl die tumorassoziierte Thrombose (CAT) eine häufige Komplikation bei Patienten mit malignen Erkrankungen darstellt, bleibt ihre Behandlung in der täglichen Praxis eine Herausforderung. Wir berichten über den klinischen Fall einer 51-jährigen Patientin, die sich mit einer hochgradig thrombogenen paraneoplastischen Gerinnungsstörung vorstellte. Trotz therapeutischer Antikoagulation mit verschiedenen Präparaten, unter anderem Rivaroxaban, Fondaparinux und niedermolekulares Heparin, entwickelte die Patientin rezidivierende venöse und arterielle Thromboembolien. Es konnte ein lokal fortgeschrittenes Endometriumkarzinom nachgewiesen werden mit starker Expression von Gewebefaktor (Tissue-Faktor, TF) auf den Tumorzellen. Es fanden sich zudem signifikant erhöhte Konzentrationen von TF-tragenden

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Schlüsselwörter
- Krebs-assoziierte Thrombose
- paraneoplastische Koagulopathie
- Gewebefaktor
- Endometrium-karzinom
- Mikrovesikel

Mikrovesikeln im Plasma der Patientin. Die Koagulopathie konnte nur durch eine kontinuierliche intravenöse Antikoagulation mit dem direkten Thrombininhibitor Argatroban kontrolliert werden. Eine multimodale antineoplastische Behandlung, einschließlich einer neoadjuvanten Chemotherapie mit anschließender Operation und postoperativer Strahlentherapie, führte zu einer klinischen Remission des Tumors, welche mit einer Normalisierung der Tumormarker CA125 und CA19–9, der D-Dimere und der TF-exprimierenden Mikrovesikel einherging. Somit könnte die Kombination aus kontinuierlicher Antikoagulation mit Argatroban und multimodaler Krebstherapie erforderlich sein, um eine TF-vermittelte paraneoplastische Koagulopathie mit rezidivierender CAT bei Patientinnen mit Endometriumkarzinom zu kontrollieren.

Introduction

Cancer-associated thrombosis (CAT) is a frequent complication in patients with solid tumors or hematological malignancies.[1] CAT significantly reduces quality of life and indicates an unfavorable clinical outcome of the underlying malignancy.[1–3] Furthermore, CAT directly contributes to mortality in hematology and oncology patients.[3,4]

In general, the risk of venous thromboembolism (VTE) is increased four- to ninefold in patients with cancer.[1,5] However, the risk is highly heterogeneous among individual cancer entities, with highest VTE incidence rates reported in tumors of pancreatic, gastric, brain, or genitourinary (excluding prostate) origin.[6] Moreover, in up to 11% of spontaneous VTE cases, an underlying malignancy is identified.[7] Finally, prevention and treatment of CAT are challenging since cancer patients are at particularly high risk for both, recurrent thrombosis and bleeding, during anticoagulant therapy.[3,8]

Here, we present the case of a 51-year-old woman who developed recurrent VTE and arterial thromboembolism (ATE) despite standard therapeutic anticoagulation as the initial manifestation of advanced endometrial cancer.

Case Presentation

A 51-year-old woman (175 cm, 70 kg) was transferred to our institution in August three years ago for suspected paraneoplastic coagulopathy due to cancer of unknown primary (CUP) with peritoneal and lymphatic metastases. The patient had no history of symptomatic COVID-19. In addition, twice weekly PCR testing for SARS-CoV-2 remained negative during hospitalization.

Three months earlier, the patient had developed deep vein thrombosis (DVT) of the right lower extremity (►Fig. 1). Anticoagulation with rivaroxaban was initiated, but despite reliably good adherence the patient experienced an acute episode of amaurosis fugax, abdominal pain, tachycardia, and shortness of breath 4 weeks later requiring hospital admission. Computed tomography scanning of the chest and abdomen revealed right-sided pulmonary embolism (PE), embolic infarction of the right upper kidney, and a suspicious lymph node located in perisigmoid fat tissue with no evidence for a primary cancer. In addition, a thrombus in the right atrium was revealed by echocardiography. There was no sign for an atrial shunt or atrial fibrillation. Investigations for primary tumor site, including gastroscopy, colonoscopy,

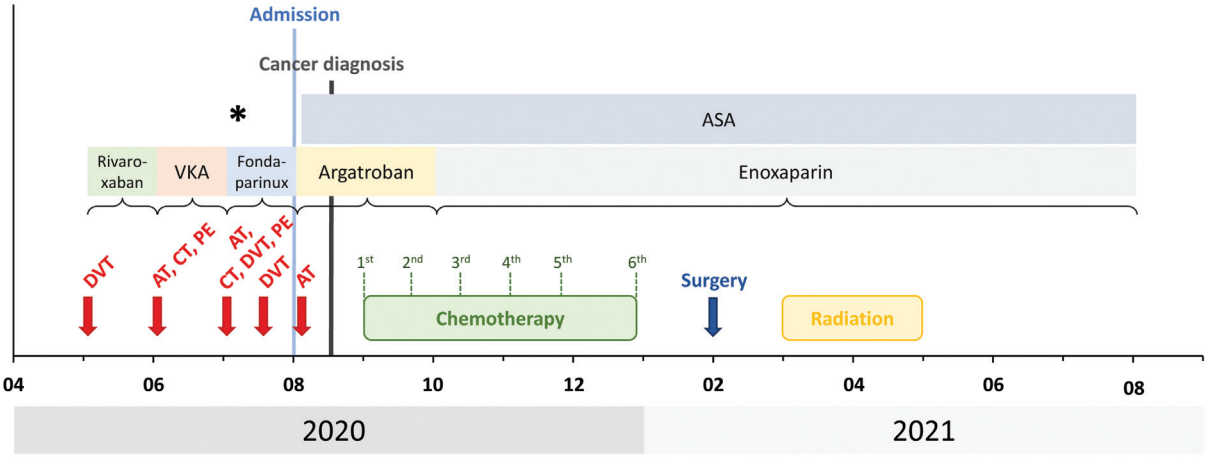

Fig. 1 Clinical course of the patient. ASA, acetylsalicylic acid; AT, arterial thrombosis; CT, cardiac thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist. Asterisk indicates time point of laboratory workup (►Table 1).

and gynecological examination, remained unremarkable. Thus, anticoagulation was continued with the vitamin K antagonist, phenprocoumon, at dosages titrated to maintain the international normalized ratio between 3 and 4, and the patient was discharged home from hospital. Several days later, painful swelling of the left leg occurred, and DVT of the upper and lower extremity was confirmed by ultrasound (►Fig. 1). Moreover, progressive PE and cerebral infarctions in addition to new thrombotic deposits on mitral valve leaflets were observed. Anticoagulation was continued with fondaparinux at 7.5 mg once daily (OD), and extensive laboratory workup ruled out antithrombin deficiency, overt disseminated intravascular coagulation, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and autoimmune (or spontaneous) heparin-induced thrombocytopenia (►Table 1). In addition, molecular testing for $JAK2^{V617F}$, prothrombin G20210A, and factor V gene mutation Leiden was negative. Tumor markers CA125, CA15–3, CA19–9, and CEA were elevated. Follow-up computed tomography and magnetic resonance imaging studies of abdomen and pelvis revealed progressive tumor manifestations with multiple pelvic lymphatic and peritoneal lesions. Moreover, suspicious endometrial alterations were suggestive of a gynecological cancer. Because of clinically progressive coagulopathy, anticoagulation with fondaparinux was intensified to 7.5 mg three times daily, and the patient was transferred to our institution for further diagnostic workup.

Anticoagulation was switched to the direct thrombin inhibitor, argatroban (►Fig. 1). Compared with healthy controls, significantly elevated concentrations of microvesicle-associated tissue factor procoagulant activity (MV TF PCA) were detected in patient plasma (►Fig. 2A), as assessed by a previously described chromogenic Xa generation endpoint assay.[9] High dosages of argatroban were required to maintain the activated partial thromboplastin time within the upper therapeutic target range (►Fig. 2B). With the exception of an additional transient ischemic attack at the beginning of argatroban therapy, which prompted initiation of antiplatelet therapy with acetylsalicyclic acid (ASA) 100 mg OD, no further thrombotic events occurred (►Fig. 1). Positron emission tomography scanning confirmed a tumorous process located in the uterus with cervical, rectal, and bowel infiltrations and multiple lymphatic and peritoneal metastases. While initial endometrial and cervical biopsy specimens were nondiagnostic, a percutaneous core biopsy of a peritoneal tumor manifestation revealed a highly estrogen and progesterone receptor positive endometrial adenocarcinoma, thus confirming the paraneoplastic etiopathogenesis of coagulopathy.

The endometrial cancer was classified as stage FIGO IVB, and the patient received neoadjuvant chemotherapy with carboplatin and paclitaxel. Inhibition of tumor angiogenesis with the monoclonal vascular endothelial growth factor antibody, bevacizumab, was waived because of recurrent thromboembolic events. The patient showed a good clinical response with decreasing tumor markers (►Fig. 2C). Consistently, release of MV TF PCA (►Fig. 2D) and D-dimer levels (►Fig. 2E) steadily declined during chemotherapy. In addition, MV TF PCA (►Fig. 2F), CA125 (►Fig. 2G), and CA19–9 (►Fig. 2H) strongly correlated with plasma D-dimers. Since tumor response was accompanied by an improvement in coagulopathy, anticoagulation was continued with the low-molecular-weight heparin (LMWH), enoxaparin, at supratherapeutic dosages (1.25 mg/kg twice daily [BID]). After completion of all six chemotherapy cycles, the enoxaparin dosage was reduced to 1 mg/kg BID. Cancer therapy was continued with debulking surgery, resulting in complete resection of gross tumor lesions, followed by adjuvant percutaneous and local radiotherapy. Immunohistochemical staining of the resected mass confirmed endometrial cancer with tumor cells showing abundant TF expression (►Fig. 3). At 15 months of follow-up, the patient is still in complete remission. No further thrombotic events have occurred.

Discussion

In the patient discussed in this study, recurrent thromboembolism was triggered by advanced endometrial cancer. Endometrial cancer is the 7th leading type of cancer in women worldwide with even higher prevalence in developed countries of the western hemisphere.[10] In the majority of cases, endometrial cancer is diagnosed at localized stages, since abnormal uterine bleeding typically occurs early in affected women.[10,11] Bleeding, however, was absent in our patient, and thrombotic coagulopathy was the first manifestation of the hitherto occult malignancy. VTE rates of up to 11.5% have been reported in endometrial cancer, with highest risks observed in patients with advanced tumors.[12–15] In addition, endometrial cancer was the third leading tumor entity identified in women with VTE and occult cancer.[16] Also, VTE occurrence is associated with an adverse outcome in this patient population.[13]

The pathogenesis of cancer-associated coagulopathy is complex and involves a plethora of cellular and molecular mechanisms. These include aberrant expression and activation of coagulation factors, release of procoagulant MVs, and activation of platelets and leukocytes (i.e., monocytes and neutrophils) in the proinflammatory tumor microenvironment.[6,17,18] In particular, aberrant expression of TF, the physiologic initiator of the extrinsic coagulation protease cascade, on cancer cells and release of TF-bearing MVs have been associated with highly prothrombotic tumor entities and overt tumor cell-induced coagulation activation.[17–19] In addition, some tumor entities may also produce other coagulation factors, including coagulation factor VII (FVII) or cancer procoagulant,[20,21] or initiate coagulation by activation of the contact-dependent intrinsic pathway.[22] In our patient, we identified strong tumor cell TF expression in tissue sections obtained from debulking surgery (►Fig. 3C, D), a finding consistent with previous (pre-)clinical studies.[23,24] Moreover, dramatically increased levels of MV TF PCA, presumably released by TF-expressing tumor cells, were measured in patient plasma at initial presentation to our institution, which steadily decreased during effective anticancer therapy (►Fig. 2A, D) and strongly correlated with

Table 1 Laboratory workup of the patient in July

	Value	Reference range
Blood counts		
Hemoglobin, g/dL	12.4	14.0–17.5
Leukocytes, 10^9/L	10.5	3.8–11.0
Platelets, 10^9/L	159	150–350
Clinical chemistry		
Creatinine, mg/dL	0.5	0.6–1.3
LDH, U/L	292	87–241
Coagulation parameters		
Prothrombin time, %	88	80–130
INR	1.0	0.85–1.15
aPTT, s	21	25–38
Thrombin time, s	16	16–22
Fibrinogen, g/L	3.7	1.8–4.0
D-dimer, mg/L	> 20	< 0.5
Antithrombin, %	103	83–118
PC activity, %	59	70–140
Free PS antigen, %	52	60–114
Ratio APC resistance	1.1	> 0.7
Factor VIII:C, %	129	70–150
Factor XIII:C, %	123	70–140
Plasminogen, %	110	75–140
Plasmin inhibitor, %	117	80–120
Tumor markers		
CA125, kU/L	1,378	< 35
CA15–3, kU/L	92.4	< 25
CA19–9, kU/L	4,271	< 37
CEA, µg/L	47.3	< 3.8
Autoantibodies		
IgM–aCL, U/mL	2.3	< 10
IgG–aCL, U/mL	2.7	< 10
IgM–anti-β_2GPI, U/mL	< 0.9	< 7
IgG–anti-β_2GPI, U/mL	0.8	< 7
LA	Negative	Negative
Genetic analysis		
JAK2, pV617F	Negative	Negative
F5 mutation, Leiden	Negative	Negative
Prothrombin G20210A mutation	Negative	Negative

Abbreviations: aCL, anticardiolipin; anti-β_2GPI, anti-β_2-glycoprotein-I; APC, activated protein C; aPTT, activated partial thromboplastin time; CA, cancer antigen; CEA, carcinoembryonic antigen; *F5*, gene for coagulation factor V; INR, international normalized ratio; JAK2, Janus kinase 2; LDH, lactate dehydrogenase; LA, lupus anticoagulant; PC, protein C; PS, protein S.
Notes: EDTA-anticoagulated whole blood was used for genetic analysis and blood counts. Clinical chemistry parameters were measured in lithium heparin-anticoagulated plasma and coagulation parameters were measured in platelet-poor plasma obtained by centrifugation of sodium citrate-anticoagulated whole blood for 15 minutes at 2,755 × *g* and 15 °C. Serum was used to quantify tumor markers and antiphospholipid antibodies.

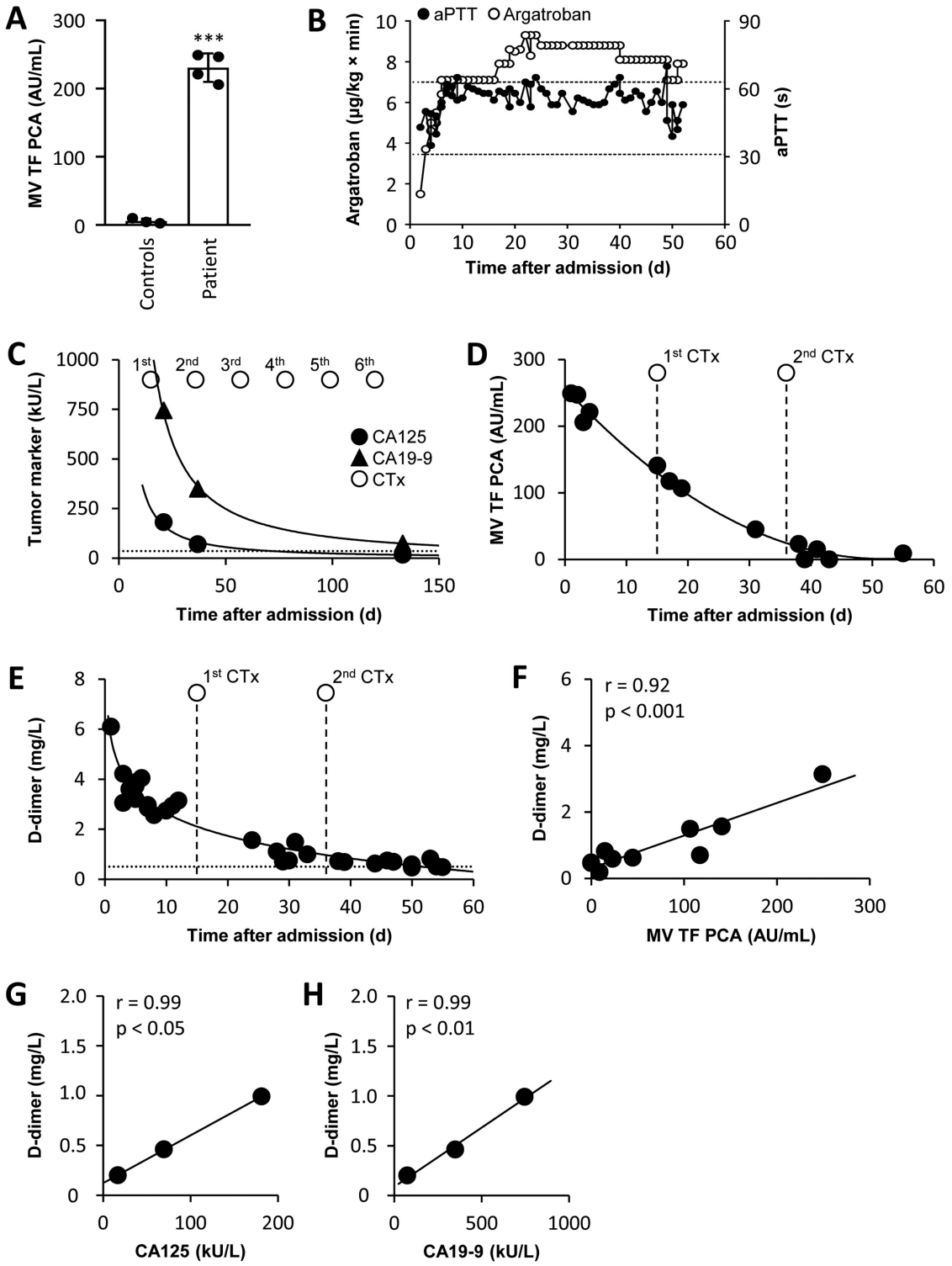

Fig. 2 Characterization of paraneoplastic coagulation disorder. (**A**) Tissue factor–dependent procoagulant activity of plasma microvesicles (MV TF PCA) was assessed by a chromogenic factor Xa generation assay. MVs were isolated from patient plasma on four distinct occasions during early anticoagulation with argatroban. Plasma MVs obtained from three sex-matched healthy individuals served as controls. For MV isolation, sodium citrate-anticoagulated whole blood was centrifuged within 1 hour after collection twice at 2,050 × *g* and 4 °C for 10 minutes to obtain platelet-poor plasma (PPP). Subsequently, MVs were isolated from PPP by double high-speed centrifugation at 16,100 × *g* and 4 °C for 30 minutes. (**B**) Time course of activated partial thromboplastin time (aPTT) and argatroban dosages. Target range is defined as 1.5- to 3.0-fold prolongation of the patient's baseline aPTT and highlighted by horizontal dashed lines. (**C**) Time course of tumor markers CA125 and CA19–9. Application of each cycle of neoadjuvant chemotherapy (CTx) and upper limit of the reference range of tumor markers (dashed lines) are indicated. Time course of patient MV TF PCA (**D**) and D-dimer levels (**E**) are shown. In panel (**E**), the upper limit of the D-dimer reference range is indicated by a dotted line. Correlations of D-dimer with MV TF PCA (**F**) and tumor markers CA125 (**G**) and CA19–9 (**H**). All data were normally distributed using the Shapiro–Wilk test. *p*-Values are according to two-sample *t*-test (***, $p < 0.001$) in panel (**A**). Correlation coefficients (*r*) and *p*-values are according to the method of Pearson in panels **F–H**.

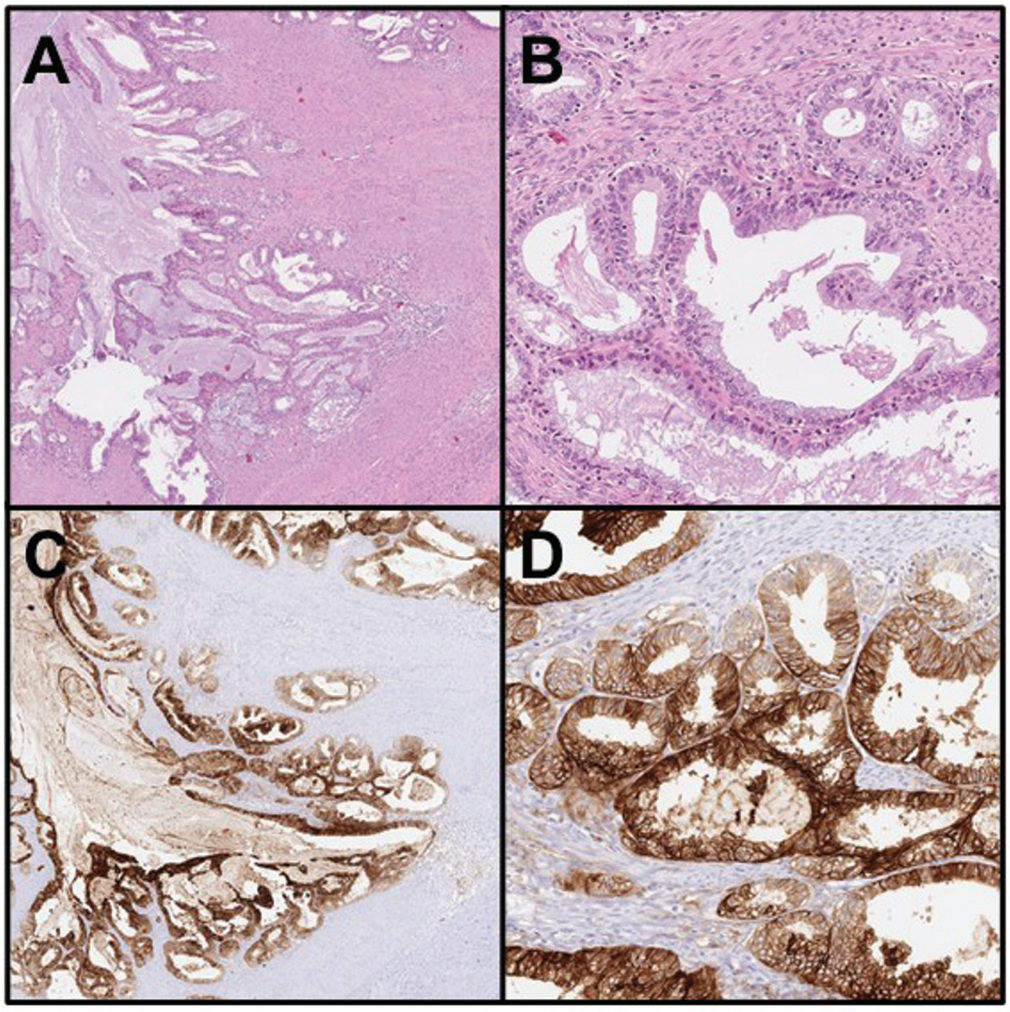

Fig. 3 Histopathological analysis of resected tumor. (**A, B**) Histopathological analysis of tissue specimens obtained from debulking surgery revealed an endometrioid adenocarcinoma. (**C, D**) Immunohistochemical staining of tumor cells for TF using a specific rabbit monoclonal IgG antibody (clone, EPR22548–240; Abcam, Cambridge, UK). Images were captured with ×2 magnification in panels (**A**) and (**C**), and ×10 magnification in panels (**B**) and (**D**).

plasma D-dimers (►**Fig. 2F**). Despite a limited number of data points, tumor markers CA125 and CA19–9 showed a strikingly close correlation with plasma D-dimer levels (►**Fig. 2G, H**). It is thus tempting to speculate that TF expressed by tumor cells and cancer cell-derived MVs was the main driver of paraneoplastic coagulation activation. Similarly, high dosages of argatroban were required to control the hypercoagulable state (►**Fig. 2B**), which is in line with significant TF-driven thrombin generation.

Interestingly, MV TF PCA had markedly decreased during anticoagulation with argatroban (►**Fig. 2D**), suggesting that thrombin contributed to CAT pathogenesis by mechanisms additional to fibrin formation. Several previous (pre-)clinical studies have indicated that thrombin participates in primary tumor growth, cell proliferation and survival, metastasis, angiogenesis, inflammation, and oncogenesis, particularly via cleavage activation of protease-activated receptors (PARs).[25–28] In the proinflammatory tumor microenvironment, thrombin also promotes leukocyte trafficking and activation of platelets and endothelial cells.[25–27] Moreover, thrombin inhibitors such as dabigatran or ximelagatran may reduce cancer growth and metastasis in mice, but effects are highly variable between individual tumor models and direct oral anticoagulant (DOAC) treatment schedules.[29] Similarly, rivaroxaban prevented FXa-mediated PAR2 activation on murine tumor-associated monocytes/macrophages, which has been implicated in immune evasion of cancer cells.[30] Thus, it is tempting to speculate that thrombin-directed anticoagulants may inhibit cancer progression, thereby enhancing their antithrombotic potency in CAT therapy. However, convincing data from prospective clinical trials are currently not available.[26]

Despite significant insights into the molecular basis of paraneoplastic coagulopathies over the past decades, prevention and treatment of CAT remain challenging. Consistent with our case report (►**Fig. 1**), cancer patients are at increased risk of recurrent thrombosis, with risks correlating with tumor stage and entity.[1,6] Thus, extended anticoagulation beyond 6 months is recommended, especially in patients whose cancer is still active and who carry a high

thromboembolic risk.[31–35] In this population, current treatment guidelines recommend anticoagulation with LMWH or direct oral FXa inhibitors (i.e., apixaban, edoxaban, and rivaroxaban).[31–34] In addition, effective treatment of the underlying malignancy is of utmost importance as it addresses the primary cause of the coagulopathy.

Another challenge is VTE recurrence despite therapeutic anticoagulation. Following exclusion of treatment nonadherence, switching the anticoagulant class (e.g., from LMWH to DOAC or vice versa) can be considered.[32] Alternatively, the dose of LMWH may be increased by 20 to 25%.[32]

In addition to VTE, cancer patients are at increased risk of ATE, including myocardial infarction, stroke, and peripheral arterial occlusions.[36,37] Similar to VTE, the highest risks were observed in patients with brain, stomach, or pancreatic cancer.[36]

Our patient, however, developed recurrent ATE and VTE despite therapeutic anticoagulation with various agents (►Fig. 1). While arterial embolic events were most probably caused by cardiac thrombotic manifestations, TF-driven coagulation activation by tumor cells and released MVs was likely the main pathway leading to venous thrombosis (►Fig. 2A, D, F). Only continuous anticoagulation with argatroban in combination with antiplatelet therapy with ASA was sufficient to attenuate initial coagulation activation, while effective anticancer treatment was required for long-term control of the coagulopathy.

In conclusion, in patients with catastrophic paraneoplastic coagulation activation, synergistic effects of therapeutic anticoagulation and effective anticancer therapy may be required to control the thrombotic storm.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1 Lee AYY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation 2003;107(23, Suppl 1):I17–I21
2 Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343(25):1846–1850
3 Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. a population-based cohort study. Thromb Haemost 2017;117(01):57–65
4 Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5 (03):632–634
5 Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood 2021;137(14):1959–1969
6 Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: burden, mechanisms, and management. Thromb Haemost 2017;117(02):219–230
7 Sørensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med 1998;338 (17):1169–1173
8 Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100(10):3484–3488
9 Beckmann L, Rolling CC, Voigtländer M, et al. Bacitracin and rutin regulate tissue factor production in inflammatory monocytes and acute myeloid leukemia blasts. Cancers (Basel) 2021;13 (16):3941
10 Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet 2005;366(9484):491–505
11 Lu KH, Broaddus RR. Endometrial cancer. N Engl J Med 2020;383 (21):2053–2064
12 Rodriguez AO, Gonik AM, Zhou H, Leiserowitz GS, White RH. Venous thromboembolism in uterine cancer. Int J Gynecol Cancer 2011;21(05):870–876
13 Pin S, Mateshaytis J, Ghosh S, Batuyong E, Easaw JC. Risk factors for venous thromboembolism in endometrial cancer. Curr Oncol 2020;27(04):198–203
14 Tasaka N, Minaguchi T, Hosokawa Y, et al. Prevalence of venous thromboembolism at pretreatment screening and associated risk factors in 2086 patients with gynecological cancer. J Obstet Gynaecol Res 2020;46(05):765–773
15 Habu Y, Mitsuhashi A, Hanawa S, et al. High prevalence of pulmonary embolism prior to cancer therapies in patients with ovarian and endometrial cancers detected by contrast-enhanced CT using D-dimer as an index. J Surg Oncol 2021;124(01): 106–114
16 Jara-Palomares L, Otero R, Jiménez D, et al. Sex differences in patients with occult cancer after venous thromboembolism. Clin Appl Thromb Hemost 2018;24(03):489–495
17 Kasthuri RS, Taubman MB, Mackman N. Role of tissue factor in cancer. J Clin Oncol 2009;27(29):4834–4838
18 Hell L, Däullary T, Burghart V, et al. Extracellular vesicle-associated tissue factor activity in prostate cancer patients with disseminated intravascular coagulation. Cancers (Basel) 2021;13(07): 1487
19 Zwicker JI, Liebman HA, Bauer KA, et al. Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study). Br J Haematol 2013;160(04):530–537
20 Falanga A, Alessio MG, Donati MB, Barbui T. A new procoagulant in acute leukemia. Blood 1988;71(04):870–875
21 Yokota N, Koizume S, Miyagi E, et al. Self-production of tissue factor-coagulation factor VII complex by ovarian cancer cells. Br J Cancer 2009;101(12):2023–2029
22 Nickel KF, Ronquist G, Langer F, et al. The polyphosphate-factor XII pathway drives coagulation in prostate cancer-associated thrombosis. Blood 2015;126(11):1379–1389
23 Fadare O, Renshaw IL, Liang SX. Expression of tissue factor and heparanase in endometrial clear cell carcinoma: possible role for tissue factor in thromboembolic events. Int J Gynecol Pathol 2011; 30(03):252–261
24 Kato S, Pinto M, Carvajal A, et al. Tissue factor is regulated by epidermal growth factor in normal and malignant human endometrial epithelial cells. Thromb Haemost 2005;94(02): 444–453
25 Reddel CJ, Tan CW, Chen VM. Thrombin generation and cancer: contributors and consequences. Cancers (Basel) 2019;11(01):100
26 Franchini M, Mannucci PM. Thrombin and cancer: from molecular basis to therapeutic implications. Semin Thromb Hemost 2012;38 (01):95–101
27 Kaplan ZS, Zarpellon A, Alwis I, et al. Thrombin-dependent intravascular leukocyte trafficking regulated by fibrin and the platelet receptors GPIb and PAR4. Nat Commun 2015;6: 7835
28 Metelli A, Wu BX, Riesenberg B, et al. Thrombin contributes to cancer immune evasion via proteolysis of platelet-bound GARP to activate LTGF-β. Sci Transl Med 2020;12(525): eaay4860

29 Najidh S, Versteeg HH, Buijs JT. A systematic review on the effects of direct oral anticoagulants on cancer growth and metastasis in animal models. Thromb Res 2020;187:18–27
30 Graf C, Wilgenbus P, Pagel S, et al. Myeloid cell-synthesized coagulation factor X dampens antitumor immunity. Sci Immunol 2019;4(39):eaaw8405
31 Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16(09):1891–1894
32 Farge D, Frere C, Connors JM, et al; International Initiative on Thrombosis and Cancer (ITAC) advisory panel. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2019;20(10):e566–e581
33 Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2020;38(05):496–520
34 Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021;5(04):927–974
35 Marin-Romero S, Jara-Palomares L. Extended treatment of cancer-associated thrombosis. Thromb Res 2019;181:1–9
36 Mulder FI, Horváth-Puhó E, van Es N, et al. Arterial thromboembolism in cancer patients: a Danish population-based cohort study. JACC CardioOncol 2021;3(02):205–218
37 Grilz E, Posch F, Nopp S, et al. Relative risk of arterial and venous thromboembolism in persons with cancer vs. persons without cancer-a nationwide analysis. Eur Heart J 2021;42(23):2299–2307