Disseminated intravascular coagulation after cryoablation for metastatic pancreatic cancer: a case report

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Background: Pancreatic cancer is the fourth most common cause of cancer-related death in the United States. Despite advancements in surgery and chemoradiation therapies, pancreatic cancer has a 5-year survival rate of only 11% in the United States. Cryoablation is emerging as a new and effective therapy for locally advanced pancreatic cancer and symptom palliation in metastatic disease. To our knowledge, the occurrence of disseminated intravascular coagulation (DIC) after cryoablation is rare.

Case Description: A 47-year-old woman with no significant past medical history was diagnosed with pancreatic cancer and underwent a Whipple procedure followed by chemotherapy with gemcitabine and paclitaxel. Due to the abdominal lymph nodes, peritoneum, right femur, and surrounding soft tissue metastases, she received systemic palliative chemotherapy with gemcitabine and paclitaxel and underwent right femur tumor excision, open reduction, and internal fixation, followed by radiation therapy. She continued to have persistent pain and underwent palliative percutaneous cryoablation of the metastatic tumor under computed tomography (CT) and ultrasound guidance. Immediately post procedure, she developed slow but continuous blood oozing at the ablation site, which was difficult to control despite compression dressings, reinforcement sutures, and local thrombin powder. The patient was transferred to the intensive care unit where she was noted to be hypotensive and tachycardic, with petechiae in both lower extremities. Laboratory studies were consistent with DIC and peripheral blood smear revealed multiple schistocytes. CT angiogram of the right lower extremity did not show any bleeding vessel amenable to embolization. She was transfused red blood cells, platelets, fresh frozen plasma, and cryoprecipitate. Despite multiple daily transfusions, she continued to have pain and remained persistently thrombocytopenic and coagulopathic. After discussion with the patient and her family, she chose to transition to comfort care measures and died.

Conclusions: DIC is an unusual but life-threatening complication of advanced pancreatic cancer.

Keywords: Cryoablation; pancreatic cancer (PC); bone metastasis; disseminated intravascular coagulation (DIC); case report

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Introduction

Pancreatic cancer (PC) is the fourth most common cause of cancer-related death in the United States. Despite advancements in surgery and chemoradiation therapies, PC has a 5-year survival rate of only 11% in the United States (1). Pain is a major problem due to cancer invasion and compression of nerves locally and at distant sites due to metastasis. In recent years, tumor embolization and ablation modalities including microwave, radiofrequency, high-intensity focused ultrasound, ethanol and cryoablation have been used more commonly as palliative therapeutic options (2-11).

Cryoablation is minimally invasive, safe, and has been shown to increase survival and palliate pain for various solid malignancies (2-8). Cryoablation utilizes argon or nitrogen gas to generate repeated freeze-thaw cycles in the tissue, reaching temperatures as low as –190 ℃ (7). It can be performed via open surgical, laparoscopic, or percutaneous approaches.

Cellular death from cryoablation occurs by direct and indirect mechanisms (9,10). Direct injury to the cells is due to physical damage of cellular membranes by formation of intracellular ice crystals at temperatures below –20 ℃. Indirect injury is produced by local vascular stasis and thrombosis, and by activation of the immune response resulting from cellular necrosis with systemic release of cellular content, including DNA, RNA, heat shock proteins and damage-associated molecular patterns (DAMPs) that act as tumor-specific antigens. This cryoimmunologic effect, known as the abscopal effect, can affect cancer cells outside and distanced from the ablated tissue for antitumoral response (2,7,9). A few studies have reported safe and successful palliative use of cryoablation in patients with locally advanced and unresectable PC with no adverse reactions (4,5,11).

Patients with advanced or metastatic PC are prone to develop thromboembolic events and disseminated intravascular coagulation (DIC), with reported incidence between 17–57% (12). The pathogenesis of DIC in cancer involves the expression of tissue factor and thrombin by the malignant cells followed by platelet activation as part of angiogenesis and tumor metastasis (13). Treatment is generally supportive, and the condition is associated with a poor prognosis. To our knowledge, the occurrence of DIC after cryoablation is rare. Our objective is to describe a case of severe DIC after palliative bone tumor cryoablation in a patient with metastatic PC. We present this case in accordance with the CARE reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-13/rc).

Highlight box

Key Findings

- Our case describes an episode of life-threatening disseminated intravascular coagulopathy (DIC) complicated by consumptive coagulopathy and severe bleeding after palliative cryoablation.

What is known and what is new?

- Cryoablation is emerging as a new and effective therapy for locally advanced solid tumors and symptom palliation in metastatic disease.
- Cryoablation utilizes argon or nitrogen gas to generate repeated freeze-thaw cycles in the tissue, reaching temperatures as low as –190 ℃.
- To our knowledge, the occurrence of DIC after cryoablation is rare.

What is the implication, and what should change now?

- DIC is an unusual but life-threatening complication of advanced pancreatic cancer.
- Patients undergoing cryoablation should be evaluated for subclinical procoagulant DIC and risk-assessed for the likelihood of thrombosis and bleeding before the procedure.

Case description

A 47-year-old woman with no significant past medical history was diagnosed with PC and underwent an uncomplicated Whipple procedure with curative intent. A year later, she developed deep venous thrombosis and was treated with rivaroxaban 20 mg daily. Computed tomography (CT) revealed metastases to the abdominal lymph nodes, peritoneum, right femur, and surrounding soft tissue. She received systemic palliative chemotherapy with weekly gemcitabine [900 mg/m^2 (1,500 mg)] and paclitaxel [100 mg/m^2 (160 mg)] for 5 months and underwent right femur tumor excision, open reduction, and internal fixation, followed by radiation therapy. Shortly after she developed local femoral bone recurrence associated with disabling right leg pain, requiring high doses of opioids which affected her quality of life. She underwent an uneventful palliative cryoablation procedure of the proximal femoral lesion; however, the pain was not controlled, requiring a nerve block along with high doses of narcotics.

Two months later, the decision was made to proceed with a second palliative cryoablation of the two 5 cm large femur osseous metastases. Four days before the procedure, the rivaroxaban was stopped and the patient had a hemoglobin

Table 1 Laboratory findings pre-procedure, on procedure day, and over the next 72 hours

Laboratory Parameters	Pre-procedural (4 days earlier)	Procedure day	At 24 h	At 48 h	At 72 h
Hgb (g/dL)	7.4	5.1	5.5	5.2	6.6
Platelets (/μL)	70	28	45	48	44
Fibrinogen (mg/dL)	NA	36	87	137	164
Haptoglobin (mg/dL)	NA	Undetectable	Undetectable	Undetectable	Undetectable
PT (s)	19	25	19	18	18
PTT (s)	24.9	47	37	35	35
INR	1.61	2.29	1.59	1.54	1.42
LDH (U/L)	NA	1,823	1,564	1,565	2,967
Bilirubin (mg/dL)	NA	1.6	1.9	2.8	2.4
ALT (U/L)	NA	13	14	11	13
AST (U/L)	NA	45	40	43	83
Absolute reticulocyte count, k/mcL	NA	435	NA	284	303
ESR	NA	3	NA	NA	NA

Hgb, hemoglobin; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; LDH, lactic dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; ESR, erythrocyte sedimentation rate; NA, not available.

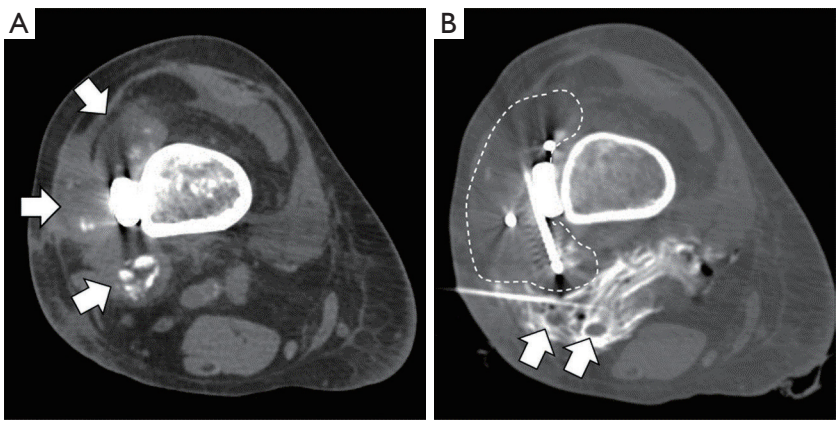

Figure 1 Computed tomography images of the distal femur tumor recurrence and CT-guided cryoablation. (A) CT without contrast showing the large distal femur tumor recurrence, partially calcified, and infiltrating soft tissues (arrows). (B) CT without contrast showing the cryoablation "iceball" covering the lesion (dashed lines), as well as the hydrodissection by saline and contrast performed to avoid sciatic nerve injury (arrows). CT, computed tomography.

of 7.4 g/dL, platelets of 70,000/μL, and an international normalized ratio (INR) of 1.61 (*Table 1*). Her moderate anemia and thrombocytopenia were attributed to her progressive and metastatic PC and/or chemotherapy.

Figure 1A shows the large tumor recurrence in the distal femur, partially calcified, and infiltrating the soft tissues. Image-guided cryoablation was performed under CT and ultrasound guidance with the ablation applicator(s) advanced and positioned within the target(s) (*Figure 1B*). For each target lesion, the applicators were placed and repositioned as necessary to achieve the desired ablation zone. The ablation applicators were then removed, and

sterile bandages were applied. Immediately post procedure, she developed slow but continuous blood oozing at the ablation site, which was difficult to control despite compression dressings, reinforcement sutures, and local thrombin powder. Her hemoglobin and platelets fell to 5.1 g/dL and 28,000 µL, respectively with an elevated INR of 2.29 and markedly low fibrinogen level of 36 mg/dL (range, 200–400 mg/dL), consistent with DIC (14) (*Table 1*). The patient was transferred to the intensive care unit (ICU) where she was noted to be hypotensive and tachycardic, with petechiae in both lower extremities. Peripheral blood smear revealed multiple schistocytes. CT angiogram of the right lower extremity did not show any bleeding vessel amenable to embolization. Laboratory studies over the next 3 days after the procedure are shown in *Table 1*. She was transfused multiple units of red blood cells, platelets, fresh frozen plasma, and cryoprecipitate.

Despite multiple daily transfusions, she continued to have pain and remained persistently thrombocytopenic and coagulopathic. The local wound bleeding was eventually controlled with extra enforced sutures, compression dressings, and local thrombin powder. Workup for sepsis, liver failure secondary to metastases, other microangiopathic syndromes, and antiphospholipid syndrome was negative. After discussion with the patient and her family, she chose to transition to comfort care measures and died during inpatient hospice.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was unable to be obtained from the patient for publication of this case report and accompanying images due to her being deceased prior to the compilation of this manuscript. Efforts were taken by all of the authors to not include any identifiable information regarding the patient within this manuscript.

Discussion

To our knowledge, the occurrence of severe DIC after percutaneous bone tumor cryoablation for metastatic PC has not been previously reported. Our case describes an episode of life-threatening DIC complicated by consumptive coagulopathy and severe bleeding after palliative cryoablation of two 5-cm large metastatic pancreatic tumors.

PC is among the most common solid malignancies associated with thromboembolic events, with a rate up to 36% in patients with advanced cancer. The spectrum of presentation varies widely from subacute and chronic abnormal coagulation tests, migratory superficial thrombophlebitis, deep venous thrombosis, marantic endocarditis, thrombotic microangiopathy, arterial thrombosis, and DIC (15).

The pathogenesis of cancer-associated DIC is multifactorial and complex (12). Procoagulant molecules like tissue factor positive microparticles are produced by tumor cells, released in circulation, and can initiate the coagulation cascade. Tumor cells ectopically expressing FVII and/or FX exhibit a prothrombotic effect by inducing platelet aggregation, activation and a dysregulatory effect on the fibrinolytic system.

Cryoablation is mostly used for palliation in metastatic PC. It is monitored intra-procedurally with CT or ultrasound, as there is clear visualization of the entire ice ball. Use of multiple cryoprobes allows for control of the size and shape of the ice ball to prevent the involvement of adjacent critical structures. Cellular injury can be influenced by variation in cooling and thawing rates, target, and time at target temperature (7). Limitations of cryoablation include incomplete killing of tumor cells around the margins of the ice ball and potential risk of freezing healthy tissues in cases where tumor is not readily visible by imaging (7).

Our patient suffered DIC with the repeated treatment of multiple and large tumors. We attribute the occurrence of DIC as a result of the necrotic malignant tissue that remains *in situ* after cryoablation that can stimulate immunologic responses and/or to the massive release of tissue factor in the circulation during cell death.

Since thrombocytopenia can be observed in patients with PC, patients undergoing cryoablation should be evaluated for subclinical procoagulant DIC and risk-assessed for the likelihood of thrombosis and bleeding before the procedure (16). Serial platelet count measurements should be obtained after the procedure particularly when a large volume tumor ablation is performed.

Conclusions

DIC is a life-threatening complication of advanced PC and can be exacerbated by large volume cryoablation. More studies are needed to understand the mechanism by which

cryoablation enhances anti-tumor immunity and to risk stratify patients at risk of life threatening DIC.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-23-13/rc

Peer Review File: Available at https://amj.amegroups.com/article/view/10.21037/amj-23-13/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-23-13/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was unable to be obtained from the patient for publication of this case report and accompanying images due to her being deceased prior to the compilation of this manuscript. Efforts were taken by all of the authors to not include any identifiable information regarding the patient within this manuscript.

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