Journal of Cancer Research and Practice

journal homepage: https://journals.lww.com/jcrp

Case Report

Pancreatic Cancer Presenting with Thrombotic Thrombocytopenic Purpura: A Case Report and Review of Literature

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare form of thrombotic microangiopathy (TMA). Cancer-related TMA typically arises from microvascular metastasis and bone marrow involvement. ADAMTS13 is a plasma protease that regulates von Willebrand factor and prevents platelet aggregation and microvascular thrombosis, with clinical value in diagnosing TTP. While cancer-related TMA typically presents with normal ADAMTS13 levels, some patients have severely reduced ADAMTS13 levels, consistent with cancer-related TTP. Potential mechanisms include immunomediated ADAMTS13 deficiency, endothelial damage from bone marrow metastasis, and paraneoplastic processes. Differentiating cancer-related TTP from other types of TMA is challenging due to overlapping clinical features; however, severely decreased ADAMTS13 activity (<10%) and high PLASMIC score, a predictor of severe ADAMTS13 deficiency, can help to identify TTP. Timely initiation of plasma exchange is critical for TTP management, while cancer-related TMA generally does not benefit from plasma exchange. Here, we report a case of metastatic pancreatic cancer presenting with TTP in whom the rapid initiation of plasma exchange and systemic chemotherapy led to the resolution of TTP. The patient continues to receive systemic chemotherapy with regular follow-up, highlighting the importance of early diagnosis and tailored treatment in improving outcomes.

Keywords: Pancreatic cancer, PLASMIC score, thrombotic microangiopathy, thrombotic thrombocytopenic purpura

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy (TMA). It is characterized by the severe deficiency of ADAMTS13, a von Willebrand factor (vWF)-cleaving protease that prevents platelet aggregation and microvascular thrombosis.[1] The differential diagnosis of disseminated malignancy presenting

Submitted: 30-Dec-2024 **Revised:** 07-Jan-2025
Accepted: 16-Jan-2025 **Published:** 21-May-2025

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jcrp

DOI: 10.4103/ejcrp.eJCRP-D-24-00042

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How to cite this article: Wang YC, Chan YC, Wang HP, Chen PY. Pancreatic cancer presenting with thrombotic thrombocytopenic purpura: A case report and review of literature. J Cancer Res Pract 2025;12:49-52.

with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia includes cancer and chemotherapy-related TMA. However, some patients with cancer-related TMA may have cancer-related TTP, requiring the urgent initiation of plasma exchange therapy.[2] Accurately diagnosing cancer-related TTP requires testing beyond ADAMTS13 activity alone. The PLASMIC score, originally derived from 214 patients in the Harvard TMA Research Collaborative Registry, is a seven-component clinical prediction tool including history of active cancer or organ transplant, hemolysis profile, platelet count, mean corpuscular volume (MCV) of red blood cells, prothrombin time/international normalized ratio (PT/INR), and creatinine level. The PLASMIC score can be used to stratify patients into those at low (score 0–4), intermediate (score 5), and high risk (score 6–7) of severe ADAMTS13 deficiency.[3] A precise diagnosis of TTP can be achieved through the integration of clinical history, ADAMTS13 activity levels, and PLASMIC score.[4]

Gemcitabine is a commonly used chemotherapy drug for metastatic pancreatic cancer, and it has been well-documented in case series to cause TMA. TMA has been reported to develop on average 161 days after the initiation of gemcitabine, with an incidence rate of <1%.[5]

Herein, we report a case of pancreatic adenocarcinoma with liver and peritoneal metastases presenting with TTP. Hematologic manifestations in mucin-producing pancreatic adenocarcinomas can include TMA, which arises from tumor invasion causing endothelial damage and disruption of the microcirculation.[6,7] To our knowledge, this is the first reported case of TTP associated with untreated disseminated pancreatic cancer.

Case Report

A 70-year-old male with underlying hypertension and hyperlipidemia presented with decreased appetite and weight loss of 10 kg in 2 months. Yellowish skin, clay-colored stool, and tea-colored urine were also noted. Initial laboratory data at our outpatient clinic showed direct hyperbilirubinemia with cholestatic hepatitis. A computed tomography scan showed dilatation of the intrahepatic duct to the common bile duct and a pancreatic head tumor with liver and peritoneal metastasis [Figure 1]. Endoscopic retrograde cholangiopancreatography was performed for biliary drainage, and endoscopic ultrasound-guided fine needle biopsy was performed for the pancreatic head tumor. The pathology revealed poorly formed glands with hyperchromatic nucleoli infiltrating the stroma, compatible with adenocarcinoma. The diagnosis of pancreatic adenocarcinoma, clinically staged as T4N2M1 (Stage IV) with liver and peritoneal metastases, was made according to the American Joint Committee on Cancer 8th edition.

On admission, the patient presented with intermittent fever without subjective discomfort and positive culture results. One episode of high fever, followed by a generalized tonic–clonic seizure and hypoxic respiratory failure, occurred 4 days later.

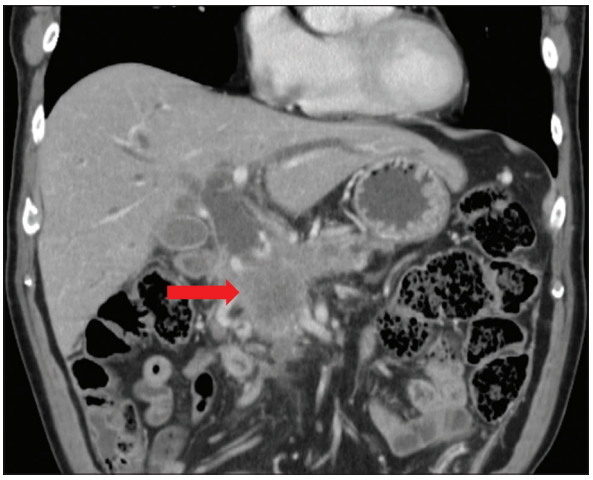

Figure 1: Pancreatic head tumor (red arrow) with common bile duct and dilatation of bilateral intrahepatic ducts

Laboratory data revealed an abrupt decrease in platelet count from 2,18,000 to 28,000 per microliter, normocytic anemia, low haptoglobin (<29.2 mg/dL), normal PT (11.6 s), activated partial thromboplastin time (aPTT, 28.8 s), low procalcitonin level, and elevated lactate dehydrogenase and reticulocyte count. Indirect hyperbilirubinemia was not observed but may have been confounded by obstructive jaundice despite adequate drainage (total bilirubin decreased from 14 to 5 mg/dL during that period). Brain and chest computed tomography revealed no evidence of brain metastasis; however, bilateral diffuse consolidation in the lungs was noted in the dependent regions along with ground-glass opacities [Figure 2]. Platelet and red blood cell transfusions were administered, but bicytopenia persisted. A peripheral blood smear showed schistocytes and thrombocytopenia [Figure 3]. A high PLASMIC score of 6 (including low platelet count, hemolysis, no history of organ transplantation, MCV <90 fL, INR <1.5, and creatinine <2.0 mg/dL) indicated a high clinical risk of TTP, and therefore, emergent plasma exchange and methylprednisolone 40 mg every 8 h were administered. The result of an ADAMTS13 activity test was 4.6 IU/dL (normal range: 60–130 IU/dL), indicating severely decreased ADAMTS13 activity. After four courses of plasma exchange, the patient's platelet count recovered significantly [Figure 4]. In addition, his vital signs including fever, tachycardia, and tachypnea with hypoxemia returned to baseline. Other possible etiologies of TTP such as autoimmune disease or medications were excluded based on his history and laboratory results. The final diagnosis was pancreatic cancer complicated with TTP, and first-line systemic chemotherapy including gemcitabine, oxaliplatin, and TS-1/Folina (SLOG) was started after plasma exchange. He has now been followed up and treated at our outpatient clinic for 4 months, with no signs of TTP recurrence.

Discussion

TTP is defined as a severe deficiency of the vWF-cleaving protease, ADAMTS13,[1] and it is a rare form of TMA.

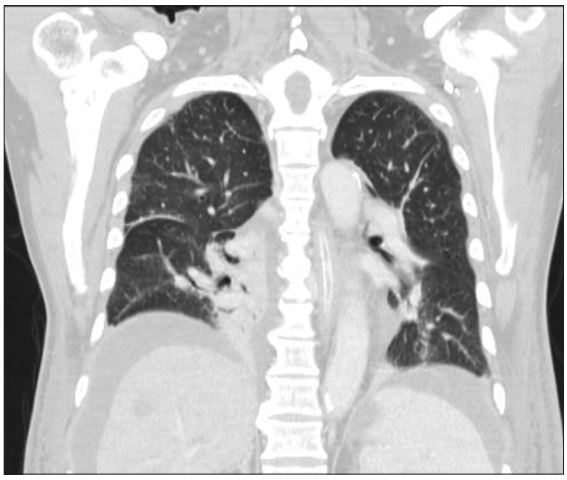

Figure 2: Noncontrast chest computed tomography showed diffuse ground-glass opacities over bilateral lungs

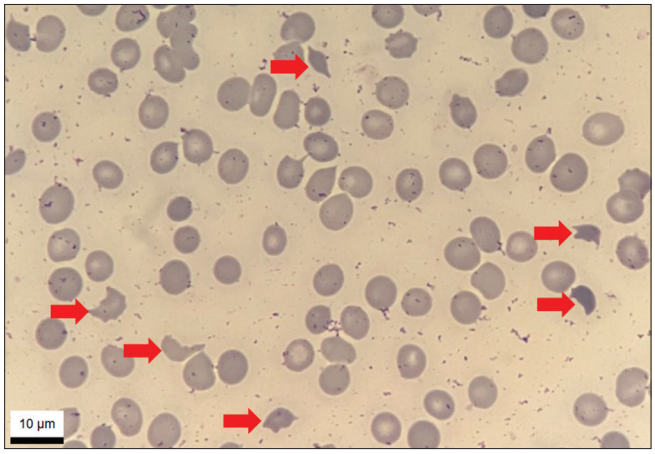

Figure 3: Peripheral blood smear showed schistocytes (red arrow), indicating microangiopathic hemolytic anemia

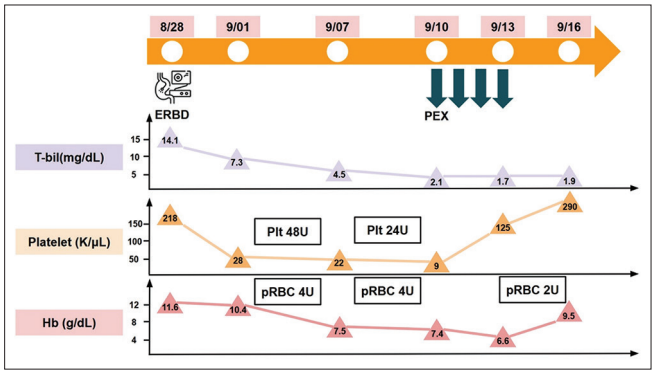

Figure 4: Serial changes in total bilirubin level, platelet count, and hemoglobin before and after plasma exchange (dark green arrow, one arrow indicates one session of plasma exchange). ERBD: Endoscopic retrograde biliary drainage, Hb: Hemoglobin, Plt: Platelet, PEX: Plasma exchange, pRBC: Packed red blood cell, T-bil: Total bilirubin

TTP commonly manifests with a classic pentad of MAHA, thrombocytopenia, fever, acute kidney injury, and neurological abnormalities.[8] In our patient, another possible differential diagnosis that needed to be considered was severe acute cholangitis presenting with Reynolds pentad (including fever, jaundice, right upper quadrant abdominal pain, altered mental status, and hypotension). However, due to adequate biliary drainage [Figure 4], no signs of abdominal pain and low procalcitonin level, active infection was deemed an unlikely diagnosis.

In previous studies, cancer patients presenting with MAHA and thrombocytopenia have been considered to have cancer-related TMA due to widespread microvascular metastases and bone marrow involvement with normal or moderately reduced ADAMTS13 activity.[2] However, a small subset of cancer-related TMA patients present with low ADAMTS13 activity and TTP. A previous study reported that three of 17 patients with cancer-related TMA had undetectable ADAMTS13 activity and that two of them had normalized platelet and hemoglobin levels after plasma exchange and rituximab infusion.[9] Although the pathophysiology of cancer-related TTP is not completely understood, possible mechanisms based on existing studies include: (1) decreased production or immune reactions leading to a low level of ADAMTS13; (2) bone marrow metastasis with secondary myelofibrosis resulting in damage to endothelial cells of the marrow and consequently the release of ultra-large vWF multimers; (3) hematogenous cancer cells directly causing endothelial dysfunction, and (4) paraneoplastic syndrome with protease inhibition resulting in ADAMTS13 deficiency.[10-12] However, these hypotheses require further experimental validation.

The challenge in diagnosing cancer-related TTP lies in its similarity to cancer-related TMA; however, previous studies have reported subtle differences in their clinical presentations. Morton *et al*.[2] reported that cancer-related TMA typically manifests with a more gradual onset of symptoms over weeks to months, whereas TTP presents acutely, often within a few days. In addition, cancer-related TMA is more commonly associated with symptoms such as weight loss, respiratory issues, or bone pain, which are rarely observed in TTP. With regard to laboratory findings, severely decreased ADAMTS13 activity (<10%) may only be seen in TTP. In contrast, patients with cancer-related TMA may have normal or mildly decreased ADAMTS13 activity (>20%).[2] However, due to the long turnaround time for ADAMTS13 results, the PLASMIC score (composite of history of active cancer or organ transplant, hemolysis profile, platelet count, MCV, PT INR, and creatinine level) can be used as an alternative tool to assess the likelihood of low ADAMTS13 activity. A PLASMIC score of 6 or 7 indicates a high probability of TTP, warrants the immediate initiation of plasma exchange, and is a contraindication for plasma transfusion.[2,3]

The prognosis of cancer-related TTP is extremely poor, with a median survival of around 12 days after the diagnosis.[4] In addition, cancer-related TTP has a significantly poorer prognosis compared to idiopathic TTP, with a previous study reporting only 2 survivors of 13 patients, in contrast to 118 survivors of 148 patients without cancer.[13]

Conclusion

We report a case of metastatic pancreatic cancer presenting with TTP. Uncontrolled disseminated malignancy and high PLASMIC score led to the urgent initiation of plasma exchange, high-dose steroids, and systemic chemotherapy. TTP was successfully resolved, and the patient is currently under regular follow-up and receiving systemic chemotherapy at our outpatient clinic.

Ethical approval

This study was performed in accordance with and conforming to the Declaration of Helsinki, it was approved by the IRB of National Taiwan University Hospital (IRB approval number: 202412136W; Approval date: January 16, 2025). The patient's consent was waived by the IRB.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Acknowledgment

We appreciate the multidisciplinary team at our hospital for their delicate care.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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