MEGA JOURNAL OF CASE REPORTS

Case Presentation

Compiled Date: December 12, 2022

Primary Hyperfibrinolysis as the Presenting Sign of Metastatic Pancreatic Cancer: A Case Report and Literature Review

Heng Cao[1#] and Xiangke Xin[2#*]

[1]Department of General Surgery, Xinyang Central Hospital, China

[2]Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China

[#]Heng Cao and Xiangke Xin have contributed equally to this work and shared the first authorship.

[*]**Corresponding author:** Xiangke Xin, Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hubei, China, Tel: 17637641184; E-mail: d202182055@hust.edu.cn

Abstract

Background: Primary hyperfibrinolysis indicates an excessive fibrinolytic activity generated without connection with a hypercoagulable or prothrombotic state. Metastatic pancreatic cancer might rarely occur with intractable bleeding secondary to hyperfibrinolysis. The laboratory diagnosis of primary hyperfibrinolysis is not specific, such as the increase of biomarkers like plasminogen; fibrinogen split products, and euglobulin lysis test. We reported the case of a patient with metastatic pancreatic cancer complicated by refractory bleeding due to primary hyperfibrinolysis as the main clinical symptom.

Case report: We described a case of a 62-year-old male patient with mild subcutaneous hemorrhage and gingival bleeding which developed two days before hospitalization. He was diagnosed with pancreatic head cancer three months ago. Initial coagulation testing: prothrombin time, activated partial thromboplastin time, and thromboplastin time was mildly extended (16.9 s, 52.6 s, and 26.3s respectively) as well as D-dimer 1.0 mg/L, while fibrinogen level was very low (0.74 g/L) and the fibrinogen degradation product was extremely high 66.51 ug/mL. The antithrombin III was within normal limits. No schistocytes were found in the peripheral blood smear. All these laboratory examinations displayed primary fibrinolysis. After the combined administration of antifibrinolytic agents, plasma, and cryoprecipitate, the fibrinogen level was normalized within three days (2.1 g/L). No new subcutaneous hemorrhage was developed.

Conclusion: The distinction from other causes of bleeding, especially disseminated intravascular coagulopathy is difficult due to differences in treatment of the two conditions. Our case highlights the rarity of our case, the challenging differential diagnosis, and the importance of successful treatment.

Keywords: Primary hyperfibrinolysis; Bleeding; Disseminated intravascular coagulopathy; Pancreatic cancer

Abbreviations: t-PA: Tissue Plasminogen Activator; u-PA: Urokinase Plasminogen Activator; TAFI: Thrombin-Activatable Fibrinolysis Inhibitor; PAI-1: Plasminogen Activator Inhibitor 1; a2-AP: α2-Antiplasmin; FDP: Fibrinogen Degradation Products; ELT: Euglobulin Lysis Test; NV: Normal Value; CEA: Carcinoembryonic Antigen; CA199: Carbohydrate Antigen 199; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; TXA: Tranexamic Acid; EACA: Aminocaproic Acid; DIC: Disseminated Intravascular Coagulopathy

Introduction

Hemostasis is a finely tuned, complex system that depends on the intricate balance among pro coagulant, anticoagulant, and fibrinolytic proteins **[1].** Reduced clotting factors, thrombocytopenia, increased anticoagulant, and hyperfibrinolysis can cause bleeding. We rarely think of hyperfibrinolysis if initial laboratory testing in a bleeding patient does not reveal severe thrombocytopenia and coagulopathy. Fibrinolysis, referring to fibrin degradation, regulate the conversion of plasminogen to plasmin through two opposing drivers **[2,3].** The Tissue Plasminogen Activator (t-PA) and the Urokinase Plasminogen Activator (u-PA) are the profibrinolytic enzymes. The antifibrinolytic moieties contain the plasminogen Activator Inhibitor 1 (PAI-1), Thrombin-Activatable Fibrinolysis Inhibitor (TAFI), and the α2-Antiplasmin (α2-AP) **[4,5].** Any imbalance in the fibrinolysis pathway may lead to hypofibrinolysis or hyperfibrinolysis **[1].** Primary hyperfibrinolysis refers to in the pathophysiological process of certain primary diseases, the increase of Plasminogen Activator (t-PA, u-PA), kallikrein, and activator 12 or the decrease of fibrinolytic system inhibitors (PAl, a2-AP, TAFI), resulting in hyper fibrinolytic activity **[6].** The name itself is fallacious because it is secondary to genetic-based diseases or several disorders such as severe trauma, shock, surgical procedures, chronic liver failure, liver transplantation, acute promyelocytic leukemia, or malignancies **[6-8].** Laboratory diagnosis of hyperfibrinolysis is on the basis of the increase of biomarkers like Fibrinogen Degradation Products (FDP), Euglobulin Lysis Test (ELT), and plasminogen **[9].** However, none of these tests are specific to primary hyperfibrinolysis **[10].** We presented a rare case of intractable bleeding caused by primary hyperfibrinolysis, emphasizing the importance of establishing the correct diagnosis of a hemorrhagic syndrome and leading to the selection of effective treatment.

Case Presentation

A 62-year-old male was admitted to our hospital with a mild subcutaneous hemorrhage and gingival bleeding which developed two days before hospitalization. The patient's past medical history showed the diagnosis of a gastric signet ring cell carcinoma five years ago and right lung squamous cell carcinoma two years ago. He was treated by giving oxaliplatin and 5-fluorocytosine for five cycles of systemic chemotherapy five years ago. Three months ago, due to abdominal pain and bloating he made an abdominal enhancement CT which showed pancreatic head cancer and abdominal cavity metastasis **(Figure 1).** At the time coagulation test illustrated a slightly low level of fibrinogen **(Table 1).** Partial tumor markers are elevated **(Table 2).** He had received 3 courses of oxaliplatin combined with tegafur, the chemotherapy process went smoothly. He had not experienced any physical trauma and was not receiving antiplatelet agents or anticoagulants. Performed laboratory analyses showed mild normocytic anemia of chronic disease hemoglobin 116 g/L (Normal Value (NV), 135–175 g/L), mean corpuscular hemoglobin 96.4fL (NV 80–90 fL), red blood cell 3.68×10^{12}/L (NV $4.3–5.8\times10^{12}$/L),

hematocrit 35.5% (NV 40–50.0%), platelet 96×10^9/L (NV 125–350×10^9/L), white blood cell 6.38 ×10^9/L (NV 3.5–9.5×10^9/L), neutrophils 67.9% (NV40–75%). Renal and liver function tests were within normal limits. Viral tests were negative (HBs Ag, anti-HCV, and anti-HIV). Other tumor markers tests were performed, which showed a significantly increased level of CEA and CA199 **(Table 3).**To assess tumor lesions, another abdominal enhancement CT was performed to assess tumor size **(Figure 2).** Comparing the CT result to three months ago, the tumor size did not change, but the thoracolumbar vertebral body metastasis increased significantly. Bone scans displayed extensive bone metastasis of pancreatic head cancer **(Figure 3).**

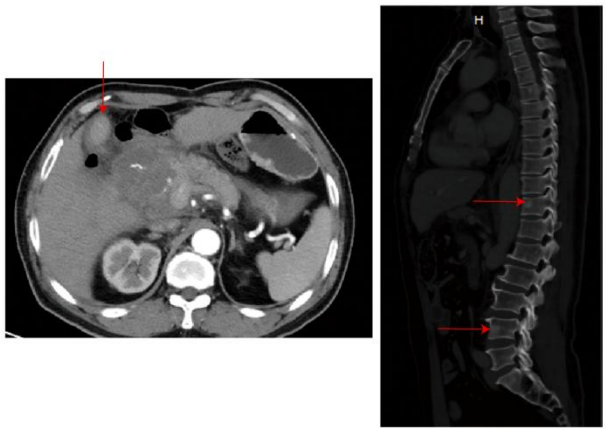

Figure 1: Abdominal enhanced CT scan revealing pancreatic head cancer metastasized to the abdominal cavity and thoracolumbar vertebral body three months ago.

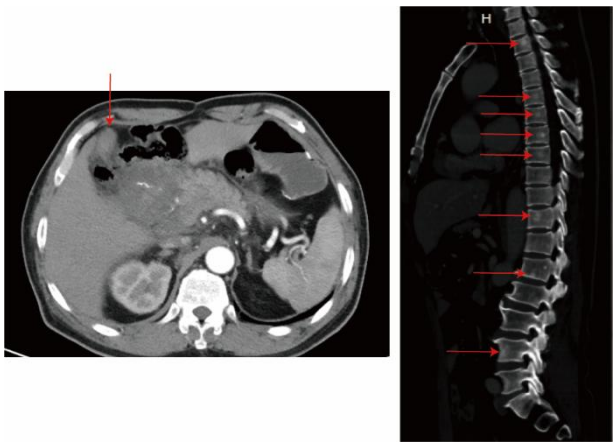

Figure 2: Abdominal enhanced CT scan revealing pancreatic head cancer size did not change, while metastasized to the thoracolumbar vertebral body increased significantly.

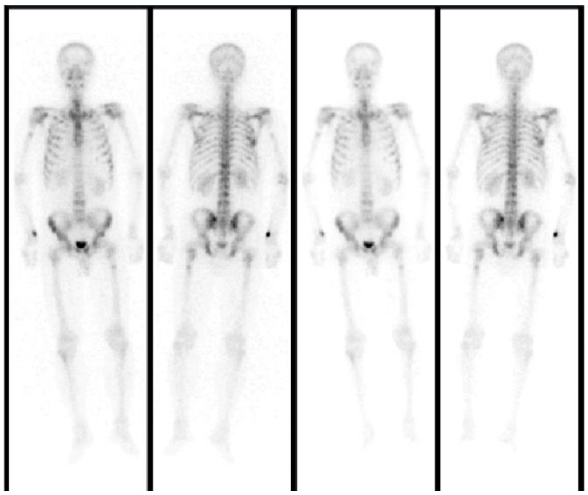

Figure 3: Bone scan showed extensive bone metastasis of pancreatic head cancer. Multiple spines, ribs, sternum, bilateral clavicle, upper right humerus, pelvis, bilateral upper femur, scattered, point-like abnormal nuclide concentration.

Table 1: Results of coagulation test (Three months ago).

Coagulation test	Values	Normal ranges
PT (s)	15.1	11-15
APTT (s)	41.4	23-43.5
TT (s)	18.8	14-21
Fibrinogen (g/L)	1.71	2-4
INR	1.21	0.8-1.25

PT – Prothrombin time; APTT – Activated Partial Thromboplastin Time; TT – Thrombin Time; INR – International Standardization Ratio

Table 2: Results of tumor markers test (Three months ago).

Tumor markers	Values	Normal ranges
CEA (ng/ml)	340.2	0-4.3
CA125 (U/ml)	30.3	0-35
CA153 (U/ml)	17.51	0-25
CA199 (U/ml)	17370	0-27
NSE (ng/ml)	10.76	0-16.3
TAM(U/ml)	102	0-95

CEA –Carcinoembryonic Antigen; CA125 –Carbohydrate Antigen 125; CA153 –Carbohydrate Antigen 153; CA199 –Carbohydrate Antigen 199; NSE –Neuron Specific Enolase; TAM –Tumor Associated Material

Table 3: Results of tumor markers test (Now).

Tumor markers	Values	Normal ranges
CEA (ng/ml)	726.3	0-4.3

CA125 (U/ml)	31.22	0-35
CA153 (U/ml)	19.95	0-25
CA199 (U/ml)	43275	0-27
NSE (ng/ml)	9.85	0-16.3
TAM(U/ml)	123	0-95

CEA –Carcinoembryonic Antigen; CA125 –Carbohydrate Antigen 125; CA153 –Carbohydrate Antigen 153; CA199 –Carbohydrate Antigen 199; NSE –Neuron Specific Enolase; TAM –Tumor Associated Material

Initial coagulation testing was performed: Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), and Thromboplastin Time (TT) were mildly extended (16.9 s, 52.6 s, and 26.3s respectively) as well as D-dimer 1.0 mg/L, while fibrinogen level was very low (0.74 g/L) and the fibrinogen degradation product was extremely high 66.51ug/ml **(Table 4).** The patient received plasma and cryoprecipitate in an unsuccessful attempt to stop the bleeding. Comparing coagulation, platelet, and tumor markers in the past three months illustrated that the levels of fibrinogen and tumor markers were significantly negatively correlated, while platelet count, PT, and APTT did not change obviously **(Figure 4).** To further clarify the diagnosis, other tests were performed. Antithrombin III was within normal limits at 90% (NV 80-125%). The plasma protamine para coagulation test was negative. No schistocytes were found in the peripheral blood smear. We realized that refractory bleeding was most probably the result of primary hyperfibrinolysis secondary to pancreatic cancer. Treatment with Tranexamic Acid (TXA) and Aminocaproic Acid (EACA) was started. He was also given maintenance therapy of plasma and cryoprecipitate with a goal for fibrinogen >1.25 g/l during active bleeding. No new subcutaneous hemorrhage was developed. The fibrinogen level was normalized within three days (2.1 g/L). He was discharged to another hospital for further treatment of pancreatic head cancer.

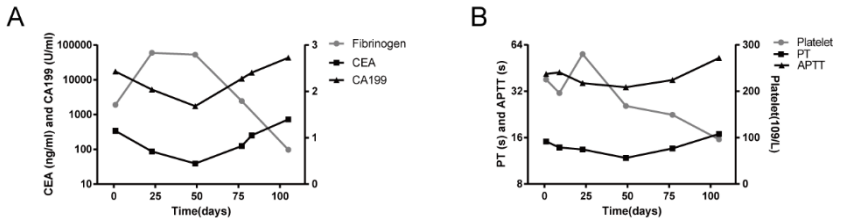

Figure 4: Comparing coagulation, platelet, and tumor markers in the past three months, it illustrated that the levels of fibrinogen and tumor markers were significantly negatively correlated, while platelet count, PT, and APTT did not change obviously.

Table 4: Results of coagulation test (Now).

Coagulation test	Values	Normal ranges
PT (s)	16.9	11-15
APTT (s)	52.6	23-43.5
TT (s)	26.3	14-21
Fibrinogen (g/L)	0.74	2-4
INR	1.39	0.8-1.25

FDP (ug/mL)	66.51	0-5
D-dimer (mg/L)	1.0	0-0.5

PT – Prothrombin Time; APTT – Activated Partial Thromboplastin Time; TT – Thrombin Time; INR – International Standardization Ratio

Discussion

We presented a case of a patient with a recent history of subcutaneous hemorrhage and metastatic pancreatic head cancer. The most striking findings of routine laboratory tests were remarkably low levels of fibrinogen, normal levels of platelet, antithrombin III, and elevated level of FDP. The plasma protamine para coagulation test was negative. No schistocytes were found in the peripheral blood smear. The results of the bone scan and abdominal enhancement CT verified tumor progression. The rise of CEA and CA199 further indicated the progression of the tumor. The levels of fibrinogen and tumor markers were significantly negatively correlated, while platelet count, PT, and APTT did not change obviously in the past three months. Therefore, we speculated that the progressive decline of fibrinogen was caused by tumor progression. Based on the malignant neoplasm and laboratory results, we considered the diagnosis of primary hyperfibrinolysis. An elevated level of D-dimer might support Disseminated Intravascular Coagulopathy (DIC), but could also be caused by fibrin deposition at the site of bleeding. Antifibrinolytic therapy improved clinical symptoms and the course of laboratory parameters, which fitted primary hyperfibrinolysis better than DIC. Probably, refractory bleeding in our case was that as the tumor progresses, pancreatic cancer cells released a large amount of uPA and tPA, resulting in fibrinogen lysis. Only by controlling the progression of pancreatic head cancer could the fibrinogen be further reduced. Therefore, the patient was discharged to another hospital for further treatment of pancreatic head cancer. Malignancy is recognized as the cause of hyperfibrinolysis **[11].** Reports have been published on the fibrinolytic activity of tumor cells from melanoma **[12,13],** mammary carcinoma **[14],** lung adenocarcinoma **[15],** prostate cancer **[16],** acute promyelocytic leukemia **[17]** and giant-cell carcinoma of the lung **[18].**The pathophysiology of hyperfibrinolysis as a paraneoplastic phenomenon is unknown. The fibrinolytic pathway is activated in two ways. At first, cancer cells generate an abnormally large number of the t-PA and u-PA **[3].** Secondly, tumor cells also carry specific Urokinase Plasminogen Activator Receptor (uPAR), which is conducive to the assembly of all fibrinolytic components and promotes the extreme activation of the fibrinolytic cascade **[19].** The increased rate of plasminogen to plasmin conversion and fibrin breakdown illustrated the low levels of plasminogen and fibrinogen, as well as elevated D-dimer in our patient. It resulted in speedy clot breakdown with consequent bleeding.

Primary hyperfibrinolysis in a patient with solid malignant neoplasms is often very difficult to distinguish from secondary hyperfibrinolysis, particularly DIC **[20,21].** In patients with pancreatic cancer, DIC is the more frequent coagulation disorder than primary hyperfibrinolysis. Differential diagnosis with DIC is important because of differences in pathophysiology and therapy. DIC designates a fibrinolytic response to intravascular thrombin generation and fibrin deposition and is usually provoked in response to abnormal activation of the blood coagulation system, while primary hyperfibrinolysis implies an excessive fibrinolytic activity generated without association with a hypercoagulable or prothrombotic state **[22].** Therefore, laboratory assessment is different in primary hyperfibrinolysis and DIC. In the DIC coagulation test the results demonstrate in this order: platelets decreased, FDP increased, PT and APTT prolonged, fibrinogen decreased, and D-dimer increased

[23,24]. Our patient had normal platelets count, PT, APTT, and antithrombin III, elevated D-dimer, and significantly decreased fibrinogen, thus leading us to a diagnosis of primary hyperfibrinolysis. Laboratory diagnosis of primary hyperfibrinolysis is highly heterogeneous, and the biochemical tests used in each patient vary evidently. Overall, there is no clear definition of fibrinolysis and no diagnostic criteria for primary fibrinolysis. Therefore, the biochemical diagnosis of primary hyperfibrinolysis is not standardized and requires the nature of the fibrinolysis process and clinical conditions of this pathological state. Treatment of hyperfibrinolysis should mainly direct towards the cure of the underlying disease and give supportive therapies, such as transfusion of plasma and cryoprecipitate and treatments that inhibit plasminogen activation and fibrin breakdown **[22,25].** Lysine analogs TXA and EACA have been known for many years as inhibitors of fibrinolysis. Lysine analogs bind to kringle domains to block fibrin interactions. TXA and EACA are effective and well-tolerated antifibrinolytic agents and reduce excess blood loss and mortality after accidents **[25,26].** However, care should be taken when starting treatment for hyperfibrinolysis, because the use of lysine analogs in DIC is contraindicated because of the high risk of thrombosis **[27]**. It is therefore of outstanding clinical importance to distinguish these two diseases. Aprotinin is another drug commonly used in hyperfibrinolysis **[28,29].** It works as a serine-protease inhibiting plasmin and kallikrein **[1].** However, due to its increased risk of renal failure, myocardial infarction, and stroke, the license was revoked in Europe and the US **[30].** In our patient, plasma, cryoprecipitate, TXA, and EACA were used to stop bleeding, which led to perfect results. In the previously reported of primary hyperfibrinolysis secondary to metastatic breast cancer and prostate cancer, the combination of antifibrinolytics and chemotherapy showed beneficial effects **[15,21,31].** In our case, chemotherapy should also be shown excellent efficacy for metastatic pancreatic cancer with hyperfibrinolysis.

Conclusion

Learning through literature, we present the first case of a patient with metastatic pancreatic cancer complicated by intractable bleeding due to primary hyperfibrinolysis. When we confront a bleeding patient, thrombocytopenia, coagulopathy, and primary hyperfibrinolysis should be considered. Laboratory tests are required to rightly diagnose hyperfibrinolysis and distinguish it from other causes of bleeding, including DIC. Early recognition of primary hyperfibrinolysis and prompt treatment of cancer and inhibition of fibrinolysis by administration of lysine analogs may provide an effective management for life-threatening bleeding and improve quality of life.

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Citation of this Article

Heng C and Xiangke X. Primary Hyperfibrinolysis as the Presenting Sign of Metastatic Pancreatic Cancer- A Case Report and Literature Review. Mega J Case Rep. 2022; 5: 2001-2009.

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