Acquired hyperfibrinolysis as the presenting sign of metastatic breast cancer: A case report

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Abstract. Fibrinolysis is a bleeding disorder characterized by hypofibrinogenemia caused by abnormal activation of fibrinolytic system function. Patients with cancer are prone to hypercoagulable and should be vigilant for the risk of venous thrombosis. However, patients with tumors in which bleeding is the first manifestation are relatively rare. The present study reports the case of a 52-year-old woman with metastatic breast cancer with acquired hyperfibrinolysis as the first manifestation. Hyperfibrinolysis is an important sign and manifestation of disease progression. In this case, fibrinogen was used as a sensitive biomarker of tumor burden to specifically predict the efficacy of the antitumor therapy. Effective antitumor therapy can improve the hyperfibrinolysis of patients, and so the fibrinogen levels gradually increased. In conclusion, the present case showed acquired hyperfibrinolysis with bleeding symptoms, which is an uncommon paraneoplastic phenomenon in breast cancer, especially when combined with bone marrow metastasis, as in the present case. Timely diagnosis and treatment of the primary disease is the fundamental way to improve hyperfibrinolysis. As an effective biomarker, fibrinogen level predicts the changes in a patient's illness and guides the clinical diagnosis and treatment process.

Introduction

The breakdown of fibrin formed during blood clotting is called fibrinolysis (1,2). Fibrinolysis is an important physiological function of the human body and regulates the process of bleeding and hemostasis together with the coagulation system (3,4). Abnormal enhancement of fibrinolytic activity is called hyperfibrinolysis. Hyperfibrinolysis is further divided into the primary and secondary types. Primary hyperfibrinolysis refers to a hemorrhagic syndrome caused by increased plasminogen activator (PA) [such as tissue (t)-PA or urokinase (u)-PA] or decreased fibrinolytic system inhibitor [such as plasminogen activator inhibitor (PAI-1), thrombin-activated plasminogen inhibitor (TAFI) and α2-antiplasmin] levels during the pathophysiological process of the primary disease, causing hyperfibrinolysis (5). Primary hyperfibrinolysis is rare in clinical practice, but can be observed in patients with chronic liver disease, acute leukemia, severe trauma and postpartum hemorrhage (6,7). Secondary hyperfibrinolysis refers to the massive production of fibrin due to the activation of coagulation function [such as thrombosis and disseminated intravascular coagulation (DIC)] in the early stage of the disease, which subsequently causes hyperfibrinolysis (8,9). Malignancies may affect the fibrinolytic process leading to hyperfibrinolysis, and may induce bleeding (1).

The case of a patient with metastatic breast cancer with bleeding caused by hyperfibrinolysis as the first symptom is discussed in the present study. The detailed case history, diagnosis, treatment process and follow-up of this case are reported to provide a reference for the clinical detection and diagnosis of tumor-related coagulation dysfunction. The case is presented in accordance with the CARE reporting checklist. The literature is also reviewed with regard to hyperfibrinolysis in patients with breast cancer or other solid malignant neoplasms. Information was compiled by searching for the role of fibrinolytic function in tumorigenesis and metastasis.

Case report

A 52-year-old woman was admitted to the First Hospital of Jilin University (Changchun, China) in February 2018 due to bleeding as a result of hyperfibrinolysis. There was no history of neoplastic disease. Laboratory results were significant for hyperfibrinolysis: Thrombin time was 15.2 sec (normal range, 11.0-17.8 sec), prothrombin time (PT) was 14.9 sec (normal range, 9.0-13.0 sec) and activated partial thromboplastin time (APTT) was 36.6 sec (normal range, 20.0-40.0 sec), while the fibrinogen level was very low at 0.5 g/l (normal range, 1.8-4.0 g/l), the D-dimer assay result was 7,070 μg/l (normal range, 0-232 μg/l) and the fibrin (fibrinogen) degradation products (FDP) level was 129.4 μg/ml (normal range, 0-5 μg/ml). Meanwhile, the blood routine suggested anemia and thrombocytopenia [red blood cell count, 2.41×10^{12}/l (normal range, $3.8\text{-}5.1 \times 10^{12}$/l); hemoglobin level, 77 g/l (normal

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range, 115-150 g/l); platelet count, $62x10^9$/l (normal range, 125-350$x10^9$/l); and white blood cell count, $4.22x10^9$/l (normal range, 3.5-9.5$x10^9$/l)]. A bone marrow biopsy revealed abnormal cell clusters, and the pathological report revealed primary tumors of the breast, with estrogen receptor (ER)-positive (+80%), progesterone receptor (PR)-negative and Ki-67 (+20%) results by immunohistochemistry. Human epidermal growth factor receptor 2 (HER2) testing was not performed due to limited specimen availability. A mammogram and breast MRI revealed a mass in the upper outer quadrant of the left breast, ~1.8x1.4 cm in size, of Breast Imaging-Reporting and Data System category 4C (10) (Fig. 1A). The systemic evaluation suggested metastatic cancer in liver segments S5 and S8 (liver function tests showed no significant abnormalities) and multiple bone metastases throughout the body. The diagnosis was infiltrating ductal carcinoma with immunohistochemical expression of ER (+90%), PR (+45%), Ki-67 (+35%), but not HER-2, as indicated by breast mass puncture pathology. The TNM stage was stage IV (cT1N0M1) according to the 8th edition of the American Joint Committee on Cancer staging manual (11). Genetic testing suggested no treatment-related genetic variations. Fibrinogen and blood transfusions were administered during the course of the disease to improve the patient's coagulation function based on the patient's condition.

In January 2019, the patient was administered 200 mg nab-paclitaxel weekly as first-line treatment (Fig. 2). After 4 cycles (3 months) of chemotherapy, the liver metastases had shrunk (from 1.1 to 0.5 cm; Fig. 3) and the breast lesions had shrunk (from 1.8x1.4 to 0.3x0.4 cm) compared with previously; the evaluation of the response was of a partial response. Meanwhile, the blood routine suggested that the bone marrow suppression due to bone marrow metastasis had improved (red blood cell count, $3x10^{12}$/l; hemoglobin level, 94 g/l; platelet count, $139x10^9$/l; and white blood cell count, $4.93x10^9$/l) and liver function tests showed no significant abnormalities. After 7 cycles of nab-paclitaxel treatment (5 months) in total, the breast lesions were still enlarged (0.6x0.3 cm; Fig. 1B), and new S8 liver lesions appeared (Fig. 3), suggesting disease progression. Blood routine analysis indicated a decrease in white blood cells and platelets compared with previously (red blood cell count, $2.94x10^{12}$/l; hemoglobin level, 90 g/l; white blood cell count, $3.33x10^9$/l; and platelet count, $121x10^9$/l). The progression-free survival (PFS) time was 5 months. A decrease in neutrophil count was recorded as a grade 2 adverse event in this period, and no grade 3-4 adverse events occurred, based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (12). During treatment, the hemogram values were higher than before, and hyperfibrinolysis was relieved.

Second-line treatment for the patient was palbociclib and letrozole. Oral letrozole (2.5 mg) was administered once daily for 28 days and palbociclib (125 mg) once daily for 21 days. Each cycle was a 28-day cycle. After 2 months of treatment, the evaluation of response was of stable disease (SD). At this time, the patient's ancillary tests suggested a decrease in the number of red blood cells, white blood cells and platelets (red blood cell count, $2.79x10^{12}$/l; hemoglobin level, 90 g/l; white blood cell count, $1.74x10^9$/l; platelet count, $34x10^9$/l), and liver function tests showed no significant abnormalities. The patient's coagulation function and imaging assessment were not abnormal, so the changes in blood routine were considered to be treated-related adverse effects. The patient received palliative surgery for the breast cancer. The pathological report revealed that only a few invasive ductal carcinomas remained in the breast tissue, with a maximum diameter of 0.2 cm, no cancer invasion of the vessels and nerves, and no cancer metastasis in the axillary lymphoid tissue (0/19). The patient continued to receive palbociclib and letrozole treatment at the same dose for 6 months after surgery. In April 2020, imaging suggested an increased number of liver metastases compared with before (the liver function tests showed no significant abnormalities). The PFS time was 10 months. During this period, due to the antitumor drugs, the patient experienced a decrease in neutrophil count and platelet count, which were recorded as grade 3 adverse events. This improved with granulocyte colony-stimulating factor administration and platelet transfusion after discontinuation, based on the patient's condition.

Third-line treatment for the patient was capecitabine chemotherapy. Oral capecitabine (1,500 mg) was administered twice daily for 14 days. Each cycle was a 21-day cycle. After 4 cycles of treatment, the liver metastases showed no significant change compared with before, while the evaluation of response was of SD. At this time, the patient's blood routine suggested a decrease in the number of red blood cells and platelets (red blood cell count, $2.3x10^{12}$/l; hemoglobin, 87 g/l; and platelet count, $57x10^9$/l), and liver function tests showed no significant abnormalities. The patient exhibited a progressively decreased level of fibrinogen, and physical examination showed skin ecchymosis at the right chest wall port, lower limbs and buttocks, and atypical cell clusters on bone marrow puncture. Laboratory tests showed a fibrinogen level of 0.38 g/l, which was considered progression of the bone marrow metastasis and aggravation of the hyperfibrinolysis. The third-line treatment produced a PFS time of 5 months. Aminocaproic acid antifibrinolytic therapy, a fibrinogen intravenous drip, thrombopoietin and other symptomatic treatments were administered to the patient based on the patient's condition.

Fourth-line treatment was eribulin chemotherapy (2 mg on day 1 and 8, every 3 weeks). After 4 cycles of treatment, the liver metastases were not significantly changed compared with previously, while the evaluation of response was of SD. The patient had poor disease control due to the progressive decline in fibrinogen level and the hyperfibrinolysis aggravation, with a PFS time of 5 months. Meanwhile, the patient's blood routine suggested a decrease in the number of red blood cells, white blood cells and platelets (red blood cell count, $2.62x10^{12}$/l; hemoglobin level, 95 g/l; white blood cell count, $1.31x10^9$/l; and platelet count, $47x10^9$/l), and liver function tests showed liver injury caused by liver metastases and antitumor therapy (aspartate aminotransferase, 127.9 U/l; alanine transaminase, 54.6 U/l; γ-glutamyl transferase, 335.3 U/l; and blood bilirubin, 43.1 μmol/l).

In February 2021, the patient started to receive fulvestrant as endocrine therapy (500 mg administered intramuscularly every 4 weeks after an initial 2-week induction). After 4 cycles of treatment, the liver metastases showed no significant change from previously. Routine blood and liver function tests indicated that the degree of bone marrow suppression and liver

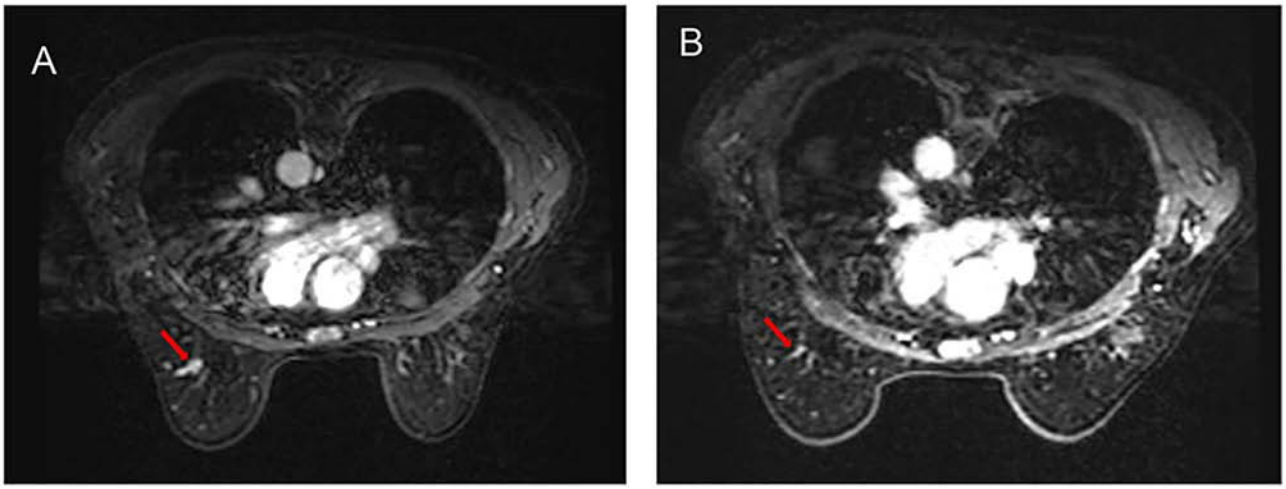

Figure 1. Breast MRI (A) before treatment and (B) after 7 cycles of nab-paclitaxel. The lesion of the breast is indicated with a red arrow.

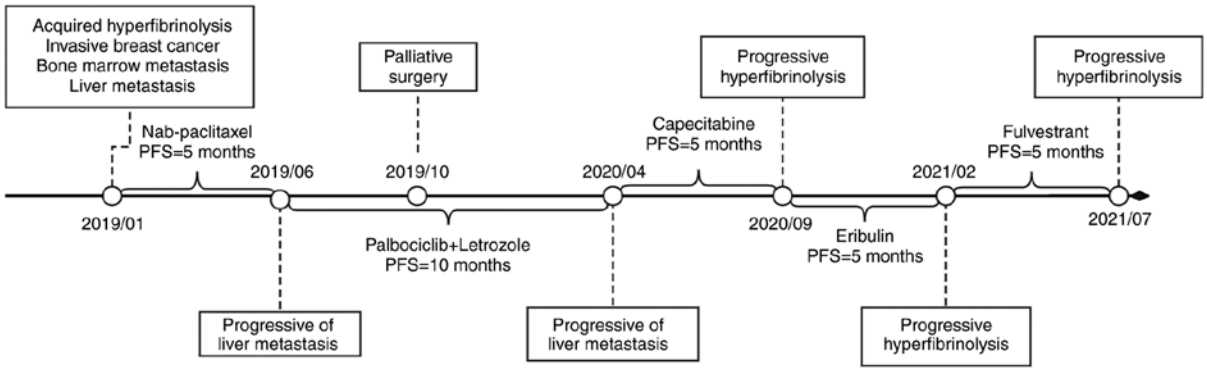

Figure 2. Timeline of antitumor treatments and outcomes. PFS, progression-free survival.

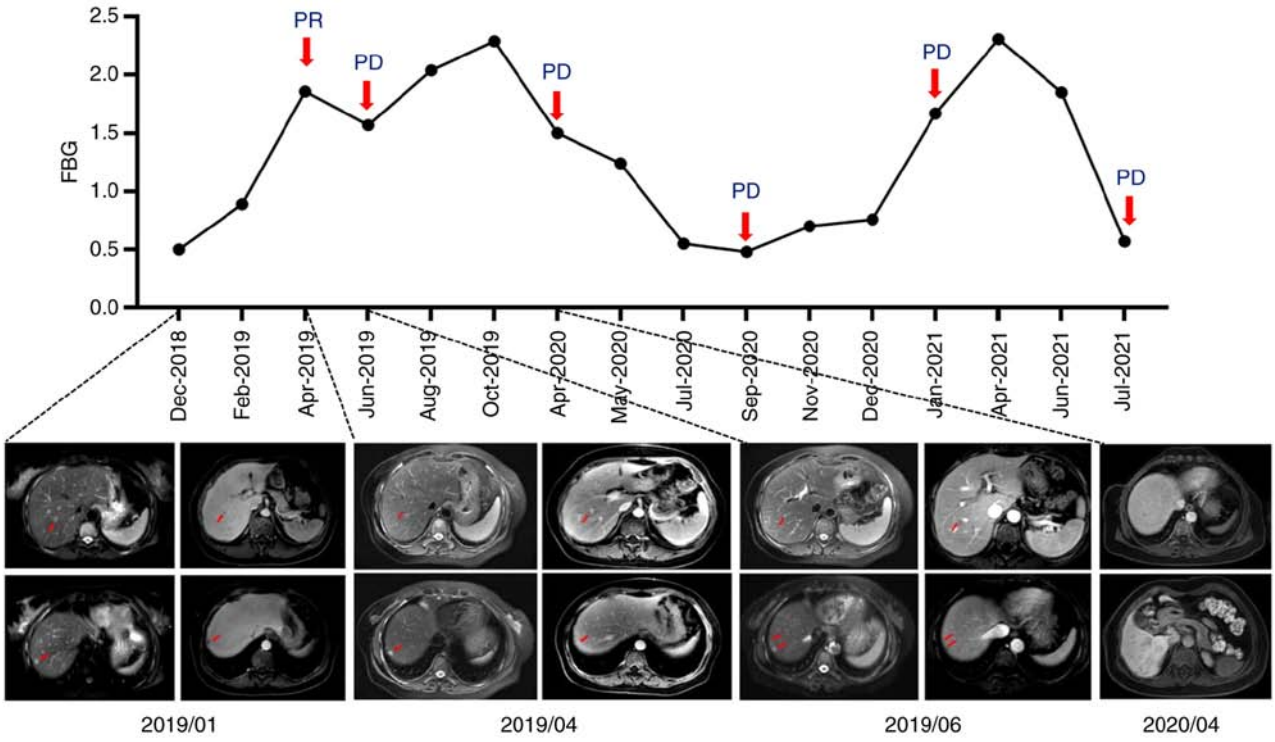

Figure 3. Radiological evaluation and altered levels of fibrinogen during the treatment. The presence of tumor lesions is indicated with red arrows. FBG, fibrinogen; PD, progressive disease.

damage was improved. In July 2021, the patient experienced subcutaneous bleeding in the lower abdomen and left lower extremity, with a low platelet count and fibrinogen level, which was considered as aggravated hyperfibrinolysis (fibrinogen, 0.84 g/l; platelet count, $29x10^9$/l). The patient died due to a cerebral hemorrhage in September 2021. The overall survival time of the patient was 30 months.

Discussion

Paraneoplastic syndrome (PNS) refers to a series of diseases caused by malignant tumors that are not associated with direct tumor invasion; it is caused by immune cross-reactivity between tumor-produced bioactive substances (e.g., hormones, peptides and cytokines) and normal tissues (13). PNS may affect multiple organ systems throughout the body, especially the endocrine, nervous, rheumatic and hematological systems. Some patients with malignant tumors such as small cell lung cancer often present with PNS as the first manifestation before the diagnosis of the tumor is confirmed (14). Correct identification of PNS can allow the timely diagnosis of the primary disease and avoid a missed diagnosis. The present study reports a case of metastatic breast cancer with hemorrhage as the first manifestation, and acquired hyperfibrinolysis, which is a rare paraneoplastic phenomenon in breast cancer.

Hyperfibrinolysis is uncommon in clinical practice, and in most cases is secondary to severe diseases such as DIC, liver disease and trauma. Hyperfibrinolysis is divided into the primary and secondary types. Primary hyperfibrinolysis refers to the release of plasminogen activators (t-PA and u-PA) into the blood under the condition of basically normal coagulation function, which promotes the activation of plasminogen to become plasmin or decreases PAI-1 and TAFI levels, increases the activity of plasmin and finally leads to hyperfibrinolysis (1,6,15). Secondary hyperfibrinolysis, on the other hand, refers to extensive microthrombosis in the setting of abnormal coagulation, such as DIC, leading to the generation of large amounts of coagulant active substances and excessive consumption of hemostatic components, followed by activation of the fibrinolytic system (16). Hyperfibrinolysis is mainly manifested as bleeding, such as skin petechiae, ecchymosis, wounds, wound bleeding, and in severe cases, hematemesis, hematochezia, intracranial hemorrhage and other manifestations.

In the present case, hyperfibrinolysis was the first manifestation, and fibrinogen levels were examined. Combined with the results of a bone marrow aspiration examination, the findings revealed that the possible cause of thrombocytopenia was bone marrow hematopoietic suppression caused by bone marrow metastasis of breast cancer. The patient showed no abnormality in liver function and had no history of hepatitis or liver cirrhosis. Decreased fibrinogen synthesis caused by liver disease could therefore be excluded. PT and APTT were approximately normal, and D-dimer and FDP levels were significantly increased. At the same time, active antitumor therapy and antifibrinolytic therapy significantly improved the fibrinogen levels, which also provided strong evidence for the diagnosis of hyperfibrinolysis. Low-grade DIC occurs in patients with extensive systemic metastases and may be one of the causes of hyperfibrinolysis (17). Although there was ample evidence that the cause of bleeding symptoms in the present patient was tumor-associated hyperfibrinolysis, hyperfibrinolysis is uncommon in association with solid tumors (18).

The mechanism of tumor-induced primary hyperfibrinolysis is not fully understood. Possible causes include: i) Tumor cells themselves can produce proteins during fibrinolysis, such as u-PA and PAI-1 (19,20). Urinary tract and genital tract tumors are rich in u-PA, which releases large amounts of u-PA into the blood during surgical or traumatic injuries and triggers primary hyperfibrinolysis (21). Winther-Larsen *et al* (18) systematically evaluated hyperfibrinolysis in 21 patients with malignant solid tumors, with prostate cancer (76%) being the most common type, while there have been few reports of hyperfibrinolysis in patients with breast cancer (17,21). Breast cancer cells contain abundant plasminogen activators (t-PA and u-PA), and with the progression of tumors, plasminogen activator in tumor cells is released into the blood in large amounts, causing enhanced fibrinolytic system function (22-24). ii) The tumor cell membrane also carries a specific u-PA-receptor (u-PAR), which contributes to the assembly of fibrinolytic components and promotes the activation of the fibrinolytic cascade (24,25).

In addition, the fibrinolytic system plays an important role in the process of tumor invasion and metastasis (19,26). Studies found that u-PA and u-PAR levels were significantly higher in patients with breast cancer with regional lymph node metastasis and other organ metastasis (27,28). The invasion of breast cancer cells is closely associated with u-PA and u-PAR activity, and is an independent risk factor. Levels of u-PA in tumor specimens can also be used to assess prognosis in breast cancer (27). Distant metastases have already developed in 85% of patients at the time of a hyperfibrinolysis diagnosis (18). u-PA is involved in multiple stages of tumor formation and development through the regulation of invasion, metastasis and cell adhesion (29). u-PA effectively degrades the extracellular matrix and basement membrane by binding to specific receptors (u-PAR) on the surface of tumor cells and activating the formation of plasmin (30). At the same time, u-PA and u-PAR form complexes with vitronectin and integrins, which can promote the adhesion of tumor cells to the extracellular matrix and promote cell proliferation by binding to G-protein-coupled receptors (19,31). PAI-1 can inhibit apoptosis and improve the survival rate of tumor cells (32). Therefore, hyperfibrinolysis can reduce the adhesion and stability of tumor cells, and promote tumor metastasis.

Bone marrow metastases from solid tumors are common in breast, prostatic and gastric adenocarcinomas, and can lead to hematological disorders such as anemia, leukopenia and thrombocytopenia (33,34). For patients with hormone receptor-positive and HER2-negative metastatic breast cancer with visceral crisis such as bone marrow metastasis, chemotherapy is the primary means of treatment (35), and its purpose is to rapidly control the tumor burden and provide opportunities for subsequent antitumor therapy. Combined endocrine therapy with CDK4/6 inhibitors is a promising regimen after effective control of tumor burden by chemotherapy. In the present study, the administration of palbociclib combined with letrozole after nab-paclitaxel monotherapy for the patient resulted in a PFS time of 10 months, which was significantly longer than the PFS time after the other treatments, such as chemotherapy

or single drug endocrine therapy The overall survival time was also longer than the average of 19 months recorded previously in patients with bone marrow metastases (33,34). This result may be associated with the application of CDK4/6 inhibitors combined with endocrine therapy. There are also studies on the clinical attempts using CDK4/6 inhibitors combined with endocrine therapy as first-line treatment for patients with metastatic breast cancer with hormone receptor-positive, HER2-negative and visceral crisis (34).

In conclusion, patients with breast cancer who exhibit bleeding as the first symptom are rare, and attention should be focused on them in the process of diagnosis and treatment to avoid misdiagnosis or a missed diagnosis. Early recognition and appropriate treatment can improve the clinical symptoms and prognosis, which improves the quality of life. For patients with cancer and acquired hyperfibrinolysis, in addition to the inhibition fibrinolytic therapy, the active treatment of the primary disease and the effective control of the tumor burden while experiencing hyperfibrinolysis can also be improved. Fibrinogen levels can be used as biomarkers for efficacy prediction and specifically reflect the tumor burden and disease changes in patients. This process may be associated with u-PA secreted by breast malignancies. Furthermore, for patients with HR-positive/HER2-negative breast cancer with a visceral crisis such as bone marrow metastasis, CDK4/6 inhibitors combined with endocrine therapy can potentially improve the survival time and quality of life, and provide evidence for subsequent treatment strategies for patients with a visceral crisis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GL and RY were involved in the identification and selection of patient cases and drafted the manuscript. LJ and ZL reviewed and edited the manuscript. GL, LJ, RY, ZL and JC were involved in the patient's clinical management. LJ, ZL and JC were involved in the identification, selection and management of patient cases, and reviewed and edited the manuscript. GL, ZL and JC confirm the authenticity of all the raw data. All authors contributed to the article and read and approved the final version.

Ethics approval and consent to participate

All procedures performed in studies involving human participants followed the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This case report was approved by The Ethics Committee of the First Hospital of Jilin University (Changchun, China).

Patient consent for publication

The patient's family provided oral consent for the article and accompanying images to be published. The Ethics Committee of the First Hospital of Jilin University approved that oral consent was sufficient in this case report.

Competing interests

The authors declare that they have no competing interests.

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