Synchronous liver metastasis at initial diagnosis of adrenal pheochromocytoma by CT: A case report

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Abstract. Pheochromocytoma is a tumor of the sympathetic nervous system, characterized by atypical symptoms and signs. Pheochromocytoma metastases can be found in various tissues and organs. However, synchronous metastasis at the initial diagnosis of pheochromocytoma is rare. The present study described a case with synchronous liver metastasis at the initial diagnosis of adrenal pheochromocytoma based on imaging findings. A 41-year-old woman presented with liver pain and fatigue for 1 month. Physical examination showed increased blood pressure and heart rate with sinus tachycardia. Laboratory examination revealed normal levels of liver tumor markers and increased levels of serum or urine epinephrine and norepinephrine. CT examination revealed a large cystic solid mass in the right lobe of the liver and right adrenal gland, and the solid part of the mass was enhanced after enhancement. The pathological diagnosis was pheochromocytoma of the right adrenal gland with liver metastasis. The patient underwent right hepatectomy and right adrenal tumor resection. During the postoperative follow-up, the patient's blood pressure and catecholamine levels were within the normal range. Three years after surgery, the CT examination revealed multiple liver metastases. Chemotherapy was administered to the patient. A year later, re-examination revealed an increase and enlargement of the metastases, and the mass of the right adrenal gland remained similar to the previous one. After 6 months of follow-up, the patient succumbed to recurrence and metastasis. Preoperative diagnosis of metastatic pheochromocytoma is challenging. This case mainly emphasizes that imaging findings can help the clinical diagnosis of metastatic pheochromocytoma.

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Introduction

Pheochromocytoma, also known as paraganglioma, is a catecholamine-secreting tumor originating from the adrenal medulla, with only 15% of cases occurring outside the adrenal gland (1), making it a rare neuroendocrine tumor. It has an estimated annual incidence of 2-8 cases per million people, typically occurring between the ages of 40-50 years, with an equal proportion of cases among men and women (2). The clinical symptoms of pheochromocytoma are primarily attributed to the excessive secretion of catecholamines, including epinephrine, norepinephrine and dopamine (3), which can lead to abnormal fluctuations in blood pressure and metabolic dysfunction. Persistent or paroxysmal hypertension is a prominent and significant feature of pheochromocytoma, representing its most common symptom, occurring in 80.7% of patients (4). Long-term hypertension can cause significant damage to vital organs such as the heart, brain and kidneys, and sudden severe hypertension may also lead to pheochromocytoma crisis, which is life threatening. Malignant pheochromocytoma accounts for ~10-15% of all pheochromocytoma cases (5). Distinguishing between benign and malignant tumors using histopathological methods is often challenging. Historically, the presence of distant metastases has been the sole reliable criterion for diagnosing malignancy (2). The treatment of malignant pheochromocytoma has always been a challenge and its prognosis is poor, with a 5-year overall survival rate of 30-60% (6). Pheochromocytoma metastases are mostly found in bone, lung, liver and regional lymph nodes (7). The malignant pheochromocytoma with liver metastasis reported in the past mostly occurred several years after the resection of the primary tumor, and synchronous metastasis at the first diagnosis is rare (7-10). The present study described a case of metastatic pheochromocytoma that occurred synchronously in the adrenal gland and liver. After surgical resection, the patient developed recurrence and metastasis, which is different from previously reported cases (7-10).

Case report

A 41-year-old female patient was admitted to The Affiliated Hospital of Yanbian University (Jilin, China) in March 2010 due to right upper quadrant abdominal pain and fatigue for one month. Physical examination showed that there was no obvious tenderness, rebound pain or muscle tension in the

abdomen. The liver was palpable with a hard texture. No mass was palpable. There was no percussion tenderness over the kidney region and no costovertebral angle tenderness. The blood pressure was measured at 150/110 mmHg, exceeding the reference value of 120/80 mmHg, indicating increased blood pressure. The heart rate was recorded at 102 beats/min, slightly above the normal range of 60-100 beats/min.ECG examination showed sinus tachycardia, mild ST-segment depression and low T wave. Laboratory examinations revealed that the levels of serum bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea and serum creatinine were within normal ranges, suggesting normal liver function. The hepatitis virus markers were negative and levels of tumor markers for liver cancer were within normal ranges. However, serum norepinephrine (4.7 ng/ml; normal reference <0.6 ng/ml) and epinephrine (0.3 ng/ml; normal reference <0.1 ng/ml), as well as 24-h urine epinephrine (50 μg/day; normal reference <20 μg/day) and norepinephrine (161 μg/day; normal reference <90 μg/day) levels were increased. CT of the upper abdomen showed a huge cystic solid mass with a clear boundary in the right lobe of the liver. The size was ~14x12 cm. The adjacent inferior vena cava was compressed by the mass. After enhancement, the solid part and separation of the mass were enhanced in the arterial phase, while there was no enhancement in the cystic necrosis area (Fig. 1A). Continuous enhancement of the mass was observed in the portal venous phase (Fig. 1B). In the delayed phase, the density of the mass was the same as that of the normal liver parenchyma (Fig. 1C). The blood supply was mainly from the right hepatic artery (Fig. 1D). CT of the upper abdomen also revealed another cystic solid mass in the right adrenal gland involving the upper pole of the right kidney, with a size of 7.6x7.3 cm. After enhancement, the solid part of the mass was enhanced, but not the cystic lesion (Fig. 1E). On the coronal section, it can be seen that the adrenal mass was surrounded by circular calcification (Fig. 1F). No enlarged lymph node was observed in the abdominal cavity. Based on the imaging results, the diagnosis was determined as space-occupying lesions in the right adrenal gland and right hepatic lobe, not excluding metastasis.

Subsequently, under general anesthesia, a right hemihepatectomy and surgical resection of the right adrenal mass were performed. During surgery, the 17x11 cm gray brown liver tissue lesion and the 10x7 cm gray brown cystic wall tissue lesion from the right adrenal gland were completely removed. HE staining, which was performed according to standard procedures (11), showed that the adrenal fibrous membrane thickened to ~1 mm. (Fig. 2A). Fibrous tissue hyperplasia with hyaline degeneration was observed. Tumor cells were arranged in patterns of nests or patches accompanied by massive hemorrhage. There were rich cytoplasm and nuclear atypia in tumor cells, which is consistent with that of liver tumors (Fig. 2B). Immunohistochemical analysis of liver tissues, which was performed according to standard procedures (11), showed chromogranin A (+), synaptophysin (+), cytokeratin (CK) 20 (-), CK7 (-), α-fetoprotein (-), and α-inhibin (-) (Fig. 2C-E). The antibodies against chromogranin A (cat. no. #ZM-0076; dilution 1:200), synaptophysin (cat. no. #ZM-0246; dilution 1:200), CK7 (cat. no. #ZA-0573; dilution 1:200), CK20 (cat. no. #ZA-0574; dilution 1:200), α-fetoprotein (cat. no. #ZM-0009; dilution 1:200), and α-inhibin (cat. no. #ZM-0460; dilution 1:200) were from Origene Technologies, Inc. Thus, the pathological diagnosis was right adrenal pheochromocytoma with liver metastasis.

Postoperatively, the patient's condition was stable. The patient was followed up every 6 months for the first 2 years post-surgery and then annually thereafter. The follow-up included CT examination and routine biochemical analysis, along with morning blood pressure monitoring. During long-term follow-up, the previously elevated levels of blood and urine catecholamine (including epinephrine, norepinephrine and dopamine), and blood pressure were within normal ranges. Three years after the operation, upper abdominal CT showed that the left lateral lobe of the liver was enlarged and there were multiple low-density nodules in the liver parenchyma. In the arterial phase, nodular enhancement was obvious and some larger nodules showed ring enhancement (Fig. 3A). A soft tissue mass with a size of ~3.9x2.6 cm was newly observed in the right adrenal area and spotted calcification was observed locally, which was unevenly enhanced after enhancement (Fig. 3B). There were no enlarged lymph nodes in the abdominal cavity. Therefore, adrenal pheochromocytoma recurrence and metastasis after surgery were diagnosed. The patient received chemotherapy with cyclophosphamide, vincristine and dacarbazine according to the Averbuch scheme (12). One year later, a plain CT scan of the upper abdomen indicated that the mass in the liver was increased and enlarged, with uneven density (Fig. 4A). The largest lesion was ~5.1 cm in diameter. The soft tissue mass in the right adrenal area showed no obvious change compared to its condition 1 year ago (Fig. 4B). Furthermore, no enlarged lymph nodes in the abdominal cavity were observed. Follow-up examinations (such as routine biochemical analysis) were performed every 3 months to monitor the physical condition and provide support and encouragement. After 6 months of follow-up, the patient succumbed to recurrence and metastasis.

Discussion

In the past, benign pheochromocytoma was treated by a single surgical resection (laparoscopic or open surgery) based on imaging findings, such as tumor size, morphology and density (13). However, the treatment methods for malignant pheochromocytoma still pose challenges. Patients with synchronous liver metastases of pheochromocytoma should undergo adjuvant chemotherapy after surgical resection to improve treatment outcomes (2). In the present case, the patient did not undergo chemotherapy immediately after the surgical resection and only received regular follow-ups due to financial constraints, thereby delaying the chemotherapy. Additionally, the patient experienced a recurrence of the right adrenal gland, along with multiple new metastases in the liver, rendering the patient unsuitable for further surgical intervention. The experience of this case highlights the necessity of postoperative chemotherapy for synchronous liver metastases of pheochromocytoma, and it is crucial to carefully select the treatment regimen of chemotherapy to prolong the life of the patient. Furthermore, the patient already had synchronous liver metastases at the initial examination, indicating a high degree of malignancy of the tumor. In addition, the patient underwent comprehensive surgical resection of the right lobe of the liver and the tumor in the right adrenal gland at the initial

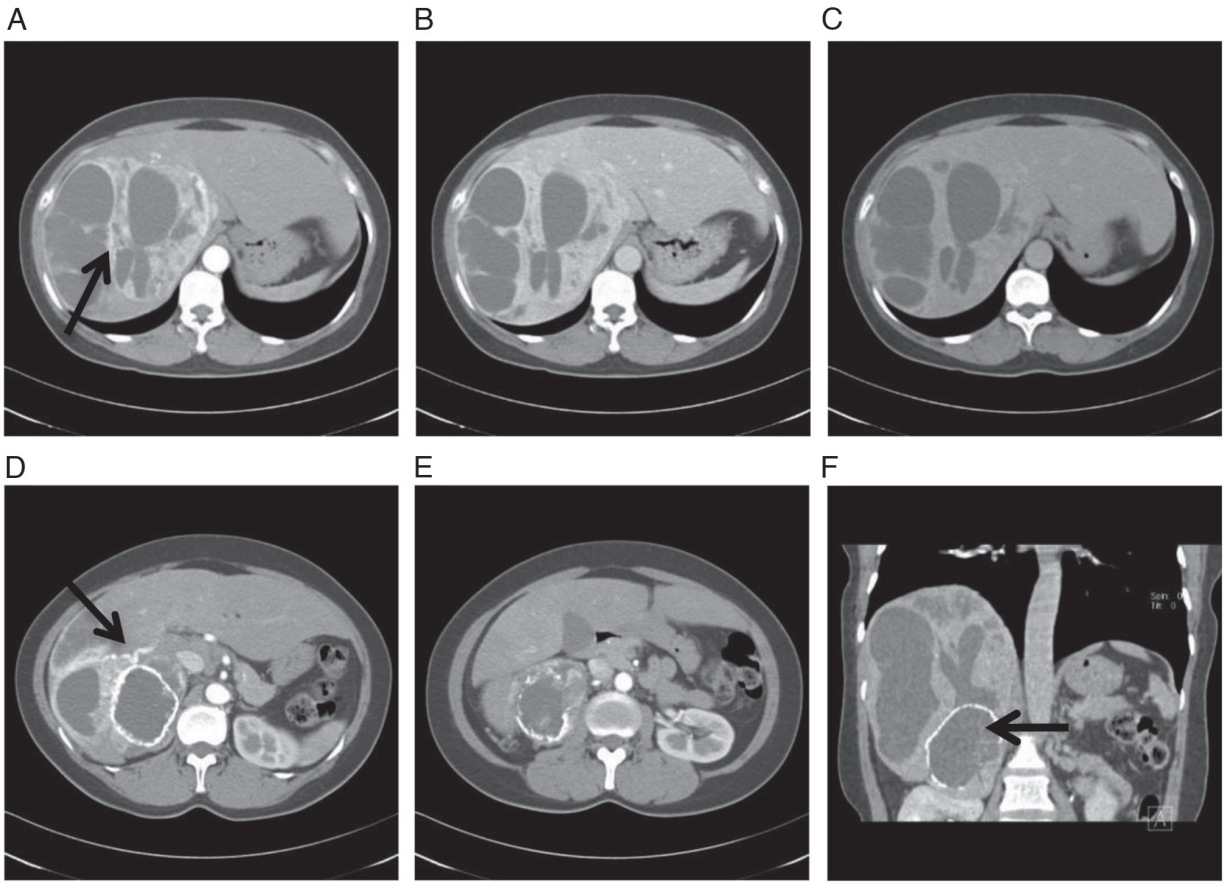

Figure 1. CT enhanced images of the upper abdomen at diagnosis. (A) CT image of arterial phase. A huge cystic solid mass was observed in the right lobe of the liver, with an obvious enhancement of solid parts and separations but no enhancement in the cystic area (black arrow). (B) CT image of portal venous phase. There was continuous enhancement of the mass. (C) CT image of delayed phase. The density of the mass was similar to that of liver tissue. (D) The right hepatic artery was enlarged, providing blood to the mass (black arrow). (E) The density of the mass in the right adrenal gland was uneven, with annular calcification. After enhancement, the solid part was obviously enhanced, but the cystic area was not enhanced. (F) The coronal image clearly showed the positional relationship between the liver and adrenal masses and the adrenal tumors on the right side were surrounded by circular calcifications (black arrow).

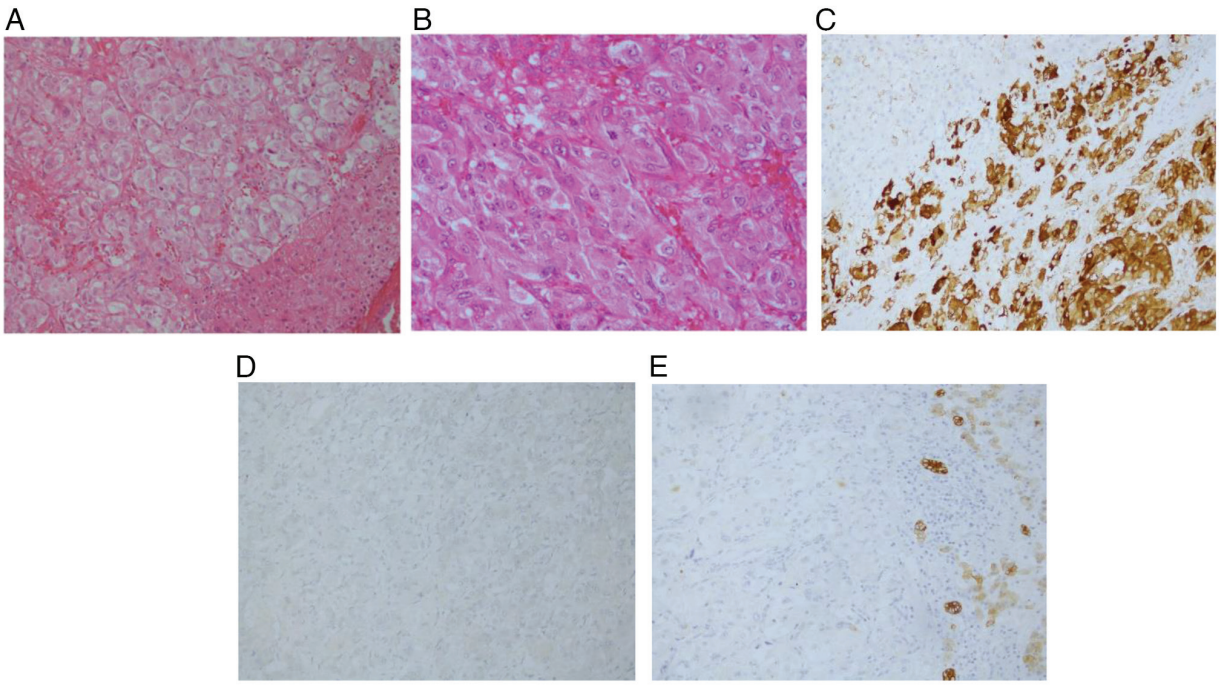

Figure 2. Postoperative pathological analysis. (A) HE staining results of adrenal mass. (B) HE staining results of liver mass. (C-E) Immunohistochemistry of liver mass: (C) Chromogranin A (+) and synaptophysin (+); (D) α-fetoprotein (-); and (E) cytokeratin (-) (magnification, x400). Blue staining indicates negative expression, whereas brown staining indicates positive expression.

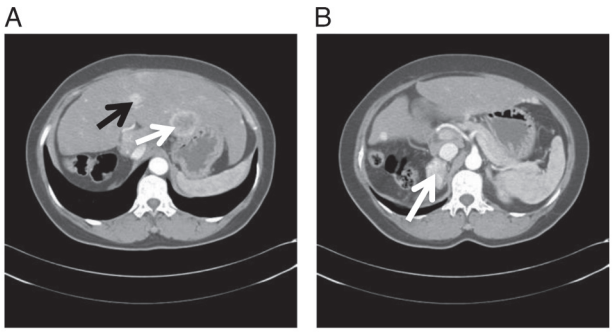

Figure 3. CT enhanced images of the upper abdomen at three years after surgery. (A) Hepatic arterial stage: The right lobe of the liver was absent. The left lobe of the liver increased in volume and there were multiple nodular (black arrow) and annular (white arrow) enhancements in the liver. (B) A mass in the right adrenal gland area was unevenly enhanced after enhancement (white arrow).

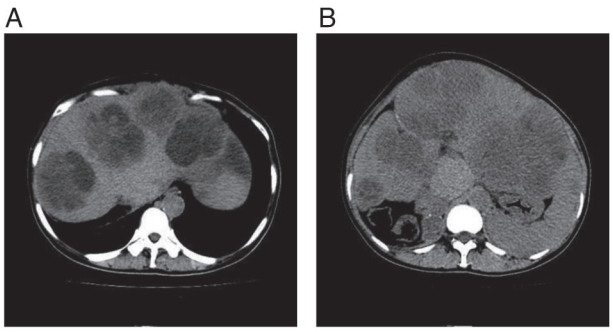

Figure 4. CT enhanced images of the upper abdomen at four years after surgery. (A) There was a progressive enlargement of the liver, obvious increase, enlargement of intrahepatic metastases and uneven density. (B) The mass in the right adrenal area was similar to that before and there were spotted calcifications.

stage. Subsequent follow-ups showed that blood pressure and catecholamine levels remained within the normal range. The delayed postoperative adjuvant chemotherapy increased the risk of tumor metastasis and recurrence.

Benign pheochromocytoma is more common, but it also has the potential to become malignant. Unlike other malignant tumors, even if surgical resection is performed, pheochromocytoma can still metastasize to distant sites after several years (7). The clinical manifestations of pheochromocytoma, which are mainly related to catecholamine, usually include paroxysmal or sustained hypertension, headaches, palpitations and sweating (10), as well as atypical symptoms, such as abdominal pain, constipation and progressive weight loss. A small proportion of patients have an insidious onset. CT examination has an important role in revealing the location and distant metastasis of pheochromocytoma. The typical CT manifestation of pheochromocytoma is a large tumor with uneven density, often accompanied by hemorrhage, cystic changes, necrosis and calcification (14). The attenuation value of pheochromocytoma on CT is generally >10 Hounsfield units (15) and the attenuation value of a very small number of lipid-containing pheochromocytomas is reduced, similar to adenomas (16). Due to the rich capillary network in the tumor, in the arterial phase, the solid part is enhanced, while the part with cystic necrosis is not enhanced. In the present case, pheochromocytoma was found in both adrenal gland and liver. Both of them were cystic and solid masses, and the liver masses were larger. However, they had their own characteristics. There was annular calcification in the edge and scattered patchy calcification in the central area of the adrenal mass. After enhancement, the solid part of the adrenal mass was enhanced. However, there was no calcification but separations in the liver mass. In the arterial phase of enhancement, the solid part and separation of the liver mass were enhanced. The discovery of liver lesions through CT was not accidental. It may be suggested that when pheochromocytoma is discovered, CT should be used simultaneously to examine common sites of metastasis for pheochromocytoma; this is particularly important for the choice of treatment plan and the prognosis of the patient. The patient received surgery for treatment. At 3 and 4 years after surgery, adrenal pheochromocytoma recurrence and metastasis in the adrenal gland and liver were observed. The patient passed away 4.5 years after the first surgery.

Due to the various imaging presentations of pheochromocytoma, adrenal pheochromocytoma should be differentiated from adrenal cortical adenoma, adrenal cortical adenocarcinoma, adrenal lymphoma and adrenal metastasis. Adrenal cortical adenoma is the most common benign adrenal tumor. It has even density and is rich in fat tissues. The enhancement of adrenal adenoma is lower than that of pheochromocytoma on enhanced CT. The clearance rate of contrast reagents in the delayed phase is faster (17).

Adrenal cortical adenocarcinoma is a rare and invasive malignant tumor in the clinic and most cases have the clinical manifestations of excessive secretion of cortisol or androgen (18). Its typical CT manifestations are huge mass, hemorrhage, necrosis, calcification, unclear boundary and infiltration into the surrounding tissue. Infiltration of the inferior vena cava and distant metastasis are more common. The solid part of the tumor shows continuous progressive enhancement, but its degree of enhancement is lower than that of pheochromocytoma.

Adrenal lymphoma is more common in elderly men. The tumor on a CT scan is usually large and uniform in density (19). There is mild to moderate enhancement on enhanced CT. Part of the density is uneven due to cystic degeneration, necrosis and hemorrhage (19). Most metastatic adrenal tumors have irregular margins, uneven density, visible necrotic areas and invasion of adjacent tissues. There is an obvious uneven enhancement on enhanced CT (19).

Treatment options for metastatic pheochromocytoma include surgical resection, chemotherapy, ^{131}I-m-iodobenzylguanidine therapy and transcatheter arterial chemoembolization (TACE). For pheochromocytoma with liver metastasis, surgical removal of the primary tumor and metastasis is the main treatment method. Wei *et al* (7) and Morikawa *et al* (8) reported that after surgical removal of the primary pheochromocytoma and liver metastases, the patients obtained a good prognosis. For patients with advanced or inoperable resection, chemotherapy and/or TACE can be used. Chemotherapy can alleviate the progression of the tumor in most patients, but it is ineffective in a small number of patients, which may be related to the high degree of tumor malignancy and the limited cytotoxicity

of chemotherapeutics (20). In the present case, the patient succumbed to a large tumor and synchronous liver metastasis characterized by a high degree of malignancy and poor response to chemotherapy. Postoperative extensive metastasis was not due to incomplete surgical removal or the presence of undetected tiny metastatic foci, but rather because no adjuvant chemotherapy was administered early after surgery, combined with the high degree of malignancy of malignant pheochromocytoma, which led to recurrence and metastasis. Consequently, the challenge of effectively treating pheochromocytoma with synchronous liver metastasis persists.

It should be acknowledged that the preoperative examination of the patient of the present study was not sufficiently comprehensive. On the one hand, during the CT examination, liver right lobe and right kidney adrenal masses were found, but no clear abnormal images were found in other examination sites and organs. To avoid increasing physical damage to the patient, no examinations such as metaiodobenzylguanidine scanning, DOTA-Tyra3-octreotide scanning or positron emission tomography-CT were performed. Meanwhile, the clinical symptoms of this patient were typical and the imaging presentation was prominent, making clinical diagnosis based on these presentations straightforward. On the other hand, the patient's economic condition was poor and the cost of the above examinations was high, which were thus not performed. In our future work, these examinations will be conducted when necessary. However, these examinations will not be performed if the patients cannot afford them and if they have a damaging effect on the patients.

In conclusion, pheochromocytoma and synchronous metastasis is relatively rare, and pheochromocytoma is similar to other adrenal tumors. Imaging examination is conducive to the diagnosis of tumor occurrence, metastasis and recurrence. An effective treatment plan should be selected to improve the prognosis of patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Conceptualization: GJ. Data curation: ZZ, XJ, YG, XL and KX. Formal analysis: ZZ, XJ, YG, XL and KX. Funding acquisition: GJ. Writing-original draft: ZZ. Writing-review and editing: GJ. ZZ and GJ checked and confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Yanbian University (approval no. 2022121;Yanbian Hospital; Yanbian, China).

Patient consent for publication

Written informed consent for the publication of case data and images was obtained from the relatives of the patient.

Competing interests

The authors declare that they have no competing interests.

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