

Case Report

A rare case of hepatic sarcomatoid carcinoma: exceeding expectations in a stage IV primary hepatic sarcomatoid carcinoma patient

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Abstract: A 41-year-old man was admitted to the hepatobiliary surgery department of West China Hospital for right upper abdominal pain lasting for more than three months. The local hospital's abdominal computed tomography (CT) showed an unclear low density shadow in the right and lateral lobes of the liver and nodules on the abdominal wall. A histologic analysis of an ultrasound guided percutaneous hepatic biopsy revealed it was hepatic sarcomatoid carcinoma (HSC). This stage IV highly aggressive liver cancer patient received chemotherapy, radiotherapy, and thermotherapy at the same time. An important result of this treatment was the rapid relief of pain and symptoms of nausea, vomiting, and decreased appetite. His quality of life improved quite a lot. Clinicians and patients usually have negative attitudes when they face stage IV cancer, especially in cases like this one. Through multimodal anti-tumor treatment, the patient felt much better and became more cooperative, which gave both the clinicians and the patient more confidence in the treatment and produced a better than expected outcome. We summarize the treatment of this rare case in order to share the experience and affirm confidence in both patients and clinicians in treating this condition.

Keywords: Hepatic sarcomatoid carcinoma, radiochemotherapy, thermotherapy

Introduction

Hepatic sarcomatoid carcinoma (HSC) is also known as spindle cell carcinoma, pseudosarcoma, carcinosarcoma, and metaplastic cancer [1, 2]. It is biphasic in morphology and mixed with carcinomas and sarcomas. HSC only accounts for about 2% of all resected hepatocellular carcinoma specimens, and approximately 3.9%-9.4% have been found in autopsies [3].

It is a tumor of monoclonal origin, but its histological origin is still in dispute. It is remarkably rare in clinical practice and is predominant in middle-aged men. It can occur in multiple organs throughout the body or in several organs at the same time, but the lung and bladder are the most common sites [4, 5]. Lesions are usually found in the right liver lobe, and the clinical

manifestations are similar to those of primary liver cancer. Surgical resection is a significant and efficient way to treat it, and adjuvant radiotherapy and chemotherapy are also required if the HSC has aggressive margins. Due to its high degree of malignancy, a poor prognosis is very common in these patients. In the past ten years, there were fewer than 30 HSC patients who were diagnosed and treated in our hospital, and most of these patients usually didn't follow up on the doctor's orders, resulting in incomplete clinical data which we could use for follow up.

Case summary

Clinical summary

A 41-year-old man was admitted to the hepatobiliary surgery department of West China

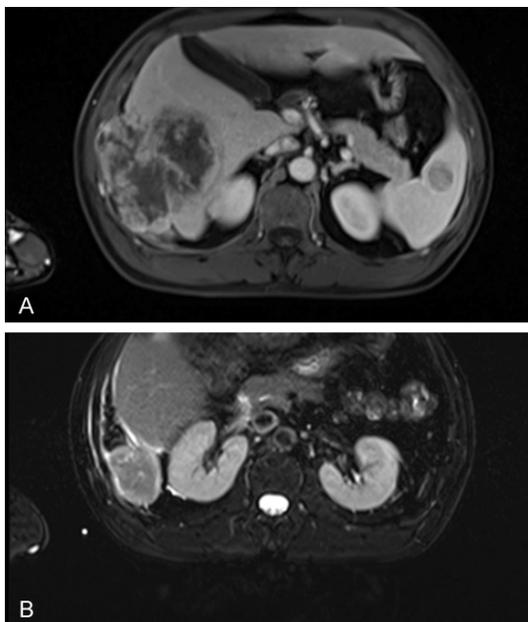


Figure 1. A. The patient's first enhanced abdominal MRI T1 showed the maximum cross section of the mass in the liver. Several nodules and masses can be seen in the right lobe of the liver, the demarcation between the larger mass and diaphragm is unclear, and liquefactive necrosis can be seen in the large mass. A suspicious focal metastasis is seen in the spleen. B. Another section of enhanced abdominal MRI T2 showed a giant mass adjacent to the peritoneal wall between the liver and kidney.

Hospital because of right upper abdominal pain that had lasted for more than three months. The pain was aggravated by pressure and had associated nausea, vomiting and radiation to the back and shoulder. The local hospital blood test showed an alpha fetoprotein (AFP) level of 3.07 ng/ml and a carcinoembryonic antigen (CEA) level of 0.69 ng/ml. Abdominal computed tomography (CT) showed an unclear low density shadow in the right and lateral lobes of the liver and nodules on the abdominal wall. After administering antibiotics, abdominal magnetic resonance imaging (MRI) showed that the right diaphragm was unevenly thickened and partially clumped, extending down to the liver and kidney crypt. The lesion pushed the right lobe of the liver, and several nodules and masses were seen in the right lobe of the liver. Multiple anterior abdominal wall and liver and kidney crypts had multiple nodules. Multiple T1 short T2 signal nodules about 2.1 to 3.4 cm large were seen in the spleen. This combination of right chest wall, right abdominal wall, anterior abdominal wall, liver and kidney crypt, and multiple spleen nodules was considered to be a

metastatic tumor (**Figure 1**). Our chest computed tomography (CT) showed the right hydrothorax. When this patient turned to the oncology department for further treatment, we did a thoracentesis to alleviate his shortness of breath and then sent a sample of the fluid to cytology. The patient underwent three rounds of intrapleural chemotherapy starting on May 25th, 2015 after the final diagnosis of HSC was made. The first two weeks consisted of 90 mg cisplatin, and the third week was Interleukin IL 2,000,000 IU. We simultaneously proceeded with thermal therapy for the right pleural effusion. Further chemotherapy from June 12th till November 2015 consisted of gemcitabine and ifosfamide every three weeks for six cycles, and meanwhile radiotherapy was in preparation. In August of the same year, the patient started volumetric-modulated arc therapy image guided radiation therapy (VAMT IGRT) every other day consisting of GTV 3600cGy/600cGy/6f. Rapid reduction of the hepatic mass occurred after six rounds of radiotherapy, so we adjusted the plan to GTV 2800cGy/700cGy/4f. There was a remarkable response in the right pleural effusion and liver mass, and according to the RECIST 1.1 evaluation criteria, the curative effect was determined to be a partial response (**Figure 2**). It's uncommon to see this malignancy have such a prompt response to this comprehensive regimen with relief of the patient's discomfort in such a short time.

Past medical history

No history of infectious diseases. The patient has a family history of renal clear cell carcinoma in his father, breast cancer in his sister, and liver, lung, and colorectal cancers in other relatives.

Pathological findings

Liver: Based on the morphology and immunohistochemical staining, a histologic analysis of ultrasound guided percutaneous hepatic biopsy revealed it was a malignant neoplasm (**Figure 3**). Immunohistochemical staining revealed that the tumor component was positive for pancytokeratin (PCK), cytokeratin 8 (CK8), smooth muscle actin (SMA), and Ki-67 (MIB-1), the level of which was approximately 20% (**Figure 4**). It was negative for cytokeratin 5/6 (CK5/6), cytokeratin 7 (CK7), cytokeratin 19 (CK19), epithelial membrane antigen (EMA), anaplastic lymphoma kinase (ALK), ALK-1, DOG1, CD117,

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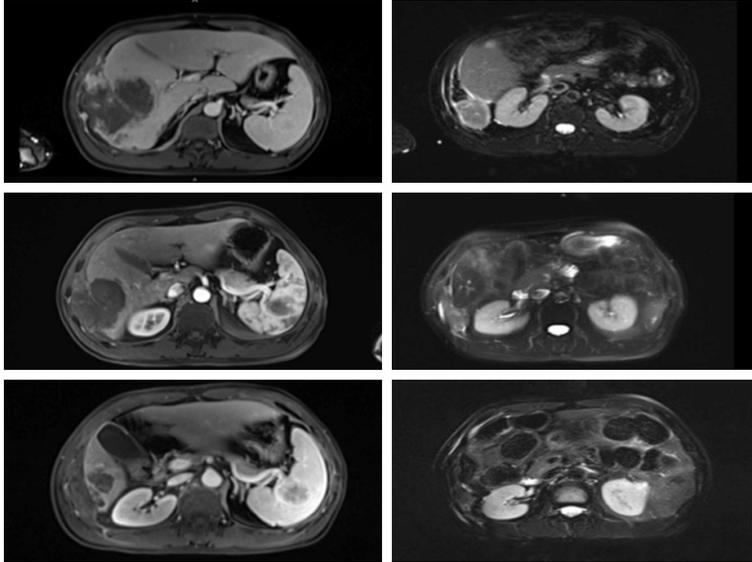


Figure 2. The images from top to bottom show the patient's abdominal MRI from three different points in time. The first line is from the first time the patient was admitted to the hospital, and the second and third lines are the images after 4 and 6 cycles of chemotherapy respectively. It can be seen that both the liver mass and the mass between the liver and kidney were greatly reduced in size after chemotherapy, radiation, and thermotherapy.

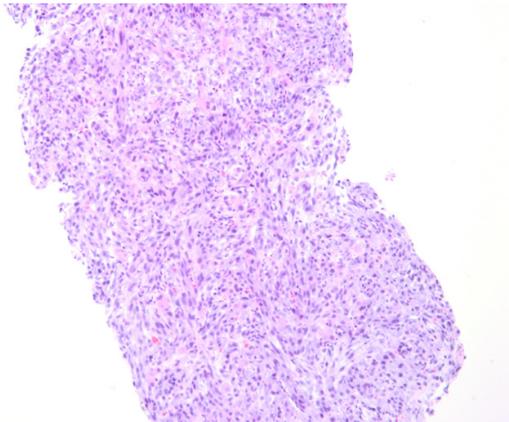


Figure 3. Under the microscope after the HE staining, some of the tumor cells were epithelioid, stellate and polygonal, with abundant eosinophilic cytoplasm, large dark nuclei, and obvious heterogeneity.

CD34, CD31, S-100, desmin, WT-1 (negative for nucleus), and Calretinin. Spindle-shaped tumor cells and mitotic figures were seen under a high-powered microscope, so hepatic sarcomatoid carcinoma was the preliminary diagnosis.

Pleural effusion

Immunohistochemical staining showed that the cell blocks in the pleural effusion were positive for epithelial membrane antigen (EMA), D2-40,

cytokeratin 5/6 (CK5/6), CR, DES, and EC, and negative for carcinoembryonic antigen (CEA) and thyroid transcription factor-1 (TTF-1). A diagnosis of mesothelial hyperplasia was made according to the patient's history.

Discussion

Hepatic sarcomatoid carcinoma (HSC) is a unique and rare type of primary hepatocellular carcinoma (HCC) that accounts for around 2% of all resected hepatocellular carcinomas, of which, approximately 3.9%-9.4% are found in necropsies. According to the World Health Organization (WHO) tumor classification of 2000, sarcomatoid carcinoma is defined as a malignant tumor that contains cancerous and sarcomatoid components,

shows epithelial features, and has a larger proportion of sarcomatoid tissue. It is also known as spindle cell carcinoma or pseudosarcoma as it has spindle and epithelial cells [6]. Primary Hepatic Sarcomatoid Carcinoma may be a tumor of monoclonal origin [7], but the histological origin remains controversial. The mainstream theories are embryonic residual theory, totipotent stem cell theory, interstitial induction theory, and metaplasia theory. The etiology of secondary HSC may be related to cirrhosis, viral infection, radiotherapy and chemotherapy, interventional therapy, long-term chronic stimulation of biliary inflammation, or other factors. It has also been reported in the literature that primary hepatocellular carcinoma can gradually develop into HSC during its process of development [8].

The etiology and pathogenesis are still unclear due to the carcinoma's lack of specific biomarkers and clinical manifestations. However, it has a high degree of malignancy with rapid tumor growth, which indicates aggressive tumor behavior and a poor prognosis. About 93% of patients already have extrahepatic metastases when they are admitted to the hospital, thereby losing the opportunity for surgery. Approximately 64% of these patients had more than 3 to 9 organ metastases, and the most common

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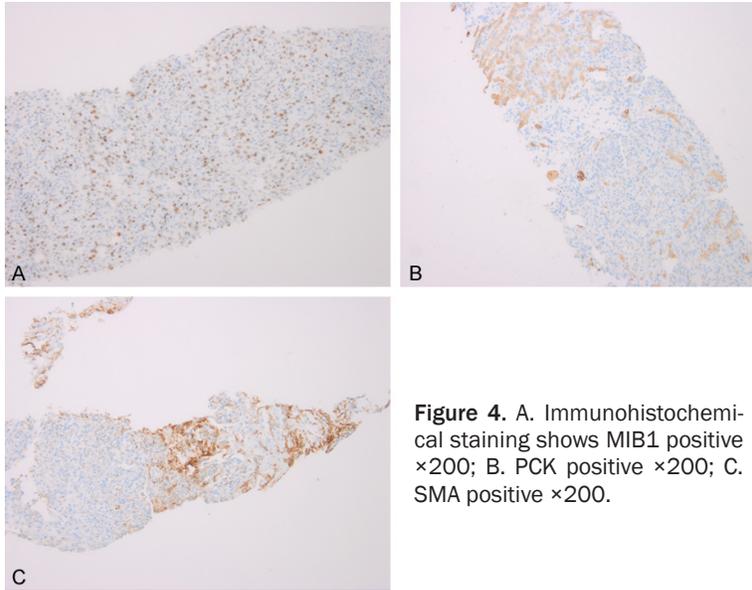


Figure 4. A. Immunohistochemical staining shows MIB1 positive $\times 200$; B. PCK positive $\times 200$; C. SMA positive $\times 200$.

HSC from primary liver cancer. As HSC often grows quite fast and causes tumor center necrosis, the enhancement of irregular flaps or circles around the tumor can be seen in the arterial phase of an enhanced CT, but the enhancement in the central region is not as obvious. The liquefactive necrosis area, however, can be seen, and needs to be distinguished from the giant HCC. Primary HCC is characterized by uniform tumor enhancement, or uneven tumor internal enhancement [9], but imaging cannot be used as the method for definite diagnosis.

metastasis sites are the lung, peritoneum, pleura, pancreas, adrenal glands, intestine, spleen, etc. Surgical resection is the only curative method. Adjuvant treatment, including radiotherapy, chemotherapy, interventional therapy and other comprehensive treatments, is needed since there is a high recurrence after surgical resection.

The diagnosis of HSC relies on pathologic biopsy, clinical features, and other auxiliary examinations. However, these serve merely as a reference and not a differentiating factor. Clinical manifestations such as abdominal pain and distension are one of the key features of early prognosis, but they are nonspecific and are also seen in other types of HCC. Jaundice, fever, abdominal distension, and weight loss are typical systemic symptoms caused by decompensated liver function. Only a fraction of patients are diagnosed without any symptoms. The value of tumor markers such as serum AFP, CEA, and CA-125 in the diagnosis are very limited as they can be normal or slightly elevated. Therefore, the diagnostic value of this patient's increased serum CA-125 is limited. However, patients with HSC also have nonspecific clinical manifestations like persistent right upper quadrant pain, nausea, vomiting, weight loss, palpable xiphoid mass, and other gastrointestinal symptoms. Imaging examinations such as enhanced CT and MRI can detect lesions and provide preliminary screening for hepatic sarcomatoid carcinoma. Enhanced CT has a certain value in differentiating primary

The imaging findings in this case are similar to those reported in the literature. An enhanced MRI of the liver showed several nodules and masses in the right lobe and markedly uneven liquefactive necrosis. Pathological and immunohistochemical examinations are important ways to diagnose HSC. Pathological features of both the tumor and sarcoma tumor components of HSC are often dominated by sarcomatoid tissue, which is usually greater than 50%. Under the electron microscope, some sarcoma cells have desmosomal connections and the ultrastructural features of epithelial cells, such as tension microfilaments in the cytoplasm, which clearly demonstrate the morphological characteristics of the two components. Epithelial components of adenocarcinoma-based stained deep nuclei show the common features of being multi-nucleated, megakaryocytic, and mitotic. Immunohistochemical staining showed that the sarcomatoid component markers were positive for vimentin, while the epithelial component was positive for the markers CK, Keratin and EMA [10, 11]. In this case, no obvious sarcomatoid or epithelial-like component markers were found through immunohistochemistry. It is possible that too little tumor tissue was obtained by the ultrasonography guided liver biopsy. However, the expression of the epithelial-like component marker CK was found through thoracentesis, and EMA was found to be positive through cell smear immunohistochemistry. The diagnosis of hepatic sarcomatoid carcinoma was made based on the three

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components of clinical findings, imaging, and pathological aspects.

Because HSC lacks specific clinical manifestations and biomarkers, and has a high degree of malignancy, and because it is aggressive, easily metastasizes, grows rapidly, and has a high postoperative recurrence rate [12, 13], the prognosis is extremely poor. The pathogenesis of HSC is not yet clear, and an exploration of the in-depth knowledge of the etiology and mechanisms is key to finding an effective means of treatment [14]. Currently, surgery is the first option for an HSC patient, as well as adjuvant treatment including radiotherapy, chemotherapy, interventional therapy, and other comprehensive treatment. Despite these treatments, it recurs very easily because of its biological behavior, poorly differentiated cancerous properties, and aggressive nature, even in the early stages of the disease. Approximately 93% of patients with HSC have extrahepatic metastases at the time of their visit, and about 64% of them have metastasis in 3 or more organs, the maximum being 9. The most common metastatic organs are the lung, peritoneum, pleura, pancreas, adrenal glands, intestines, and spleen [15]. For those with multiple metastases, the combination of chemoradiotherapy, intra-body chemotherapy, hyperthermia and other comprehensive treatment can relieve the symptoms, but the overall survival can't be changed. Our patient had multiple sites of invasion including the right diaphragm, the thoracic and abdominal walls, the first rib, liver, kidney crypt, right pleura, lung and the abdominal cavity. He had more than three sites of metastases when he was first admitted and therefore was not a candidate for surgery. After the final diagnosis was made, the patient received chemotherapy, radiotherapy and hyperthermia therapy. The tumor had an interestingly quick response to these therapies, and the patient was relieved of his symptoms.

According to a retrospective analysis of 28 patients with resected hepatic sarcomatoid carcinoma in our department of biliary surgery in 2014 [16], the median overall survival rate is 11.5 months. The total survival rate of patients undergoing surgical resection was 15.6 months, and 7.6 months for the total survival for the patient who received palliative treatment. The overall survival rates at 1 year, 2 years and 3

years were 50%, 21.4% and 14.3% respectively. It has also been reported [17] that 83.3% of the patients who underwent radical resection of the tumor died of tumor recurrence with a total survival of 3 to 11 months. Only 16.7% of the patients had a survival time of over 6 months. Therefore, in the early stages of HSC, surgical resection is still the most effective treatment with a median overall survival of up to 12 months [18]. Our patient died 3 months after discharge, making his overall survival about 8 months, which was similar to what was found in a literature review and which exceeded our expectations. The reason we presented this case was to provide more clinical data and treatment information about hepatic sarcomatoid carcinoma due to its rare occurrence in practice and to give both patients and doctors more confidence in the treatment of this condition.

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Disclosure of conflict of interest

None.

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