

Zygomatic bone metastasis from hepatocellular carcinoma and the therapeutic efficacy of apatinib

A case report and literature review

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Abstract

Rationale: Hepatocellular carcinoma (HCC) metastases to the zygomatic bone are extremely uncommon, and the treatment of target drugs against such case is unknown.

Patient concerns: A 48-year-old male patient was admitted to our hospital under suspicion of an advanced liver tumor due to an increase in levels of alpha-fetoprotein (AFP) after radiofrequency ablation for independent nodule in his liver 1 month before. He had a hepatitis B virus (HBV) history for 20 years without treatment.

Diagnosis and interventions: A diagnosis of primary HCC was made based on pathological examination following right hepatectomy. Seven months after the surgery, a mass in S8 was identified and treated by ARF. Twenty days later, a right zygomatic mass was observed and the incisional biopsy revealed metastasis from HCC. Due to side effects of chemotherapy, the metastatic zygomatic mass was treated with radioactive seed implantation. Despite these interventions, there was steady increase in AFP values as well as increase in size of the zygomatic mass. Hence, the patient was started on apatinib with a dose of 500 mg/day from 1 to 28 days per cycle for a duration of 10 months.

Outcomes: The AFP values were significantly decreased but the size of the zygomatic mass continued to increase indicating progression of disease. But the progression-free survival was more than 10 months. The patient exhibited adverse reactions which were controllable by symptomatic treatments. As of last follow-up, the patient is unwell with pain in the face, blurred vision in the right eye, dyscrasia, and exhibited difficulty in opening his mouth.

Lessons: HCC metastases to the zygomatic bone are very aggressive with a very low incidence and immunohistochemistry is useful diagnostic indicators. Still now, there is no optimal treatment strategy for these patients. Apatinib may be a promising drug in the treatment of HCC metastases to the zygomatic bone.

Abbreviations: AFP = alpha-fetoprotein, ARF = radiofrequency ablation, CK = cytokeratin, CT = computed tomography, FDG = fluorodeoxyglucose, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = Hepatocellular carcinoma, HE = hematoxylin-eosin staining, IV = intravenous, MR = magnetic resonance, PET/CT = positron emission tomography/ computed tomography, TACE = transcatheter hepatic arterial chemoembolization.

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1. Introduction

Liver cancer is one of the commonest cancers and specifically hepatocellular carcinoma (HCC) is the sixth most common cancer and second leading cause of cancer death worldwide.^[1,2] Approximately, 85% of HCCs occur in developing countries, and 54% occur in China.^[3] A literature review showed that HCC ranks fifth in the number of new cases each year and second in cancer-related deaths annually among men.^[4] HCC usually metastasizes through blood or lymphatic dissemination; metastasis to the lungs (55%) is the most common, followed by the abdominal lymph nodes (41%) or bones (28%).^[5] According to the English-language literature, metastases from HCC to osseous structures in the head are extremely rare, particularly to the zygomatic bone.^[6] Here, we report a case of HCC metastasizing to the zygomatic bone. To the best of our knowledge, only 3 other cases similar to ours have been previously reported.

Apatinib, a new and highly selective small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptor-2, was approved for advanced gastric cancer in China in Oct 2014.^[7] It is reported to markedly improve the overall survival of patients with metastatic gastric adenocarcinoma.^[8] Some clinical

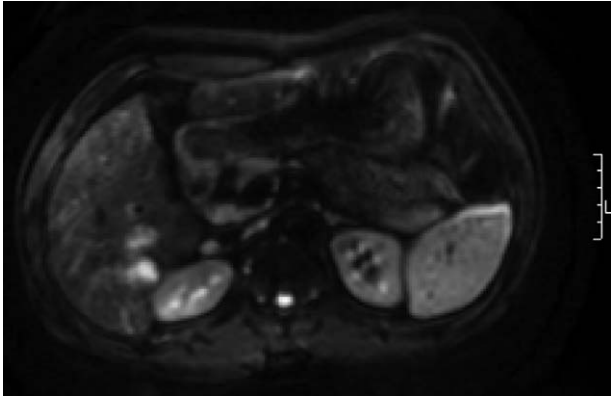


Figure 1. Abdominal magnetic resonance (MR) scan showing 2 independent masses in the right posterior liver.

studies showed that multiline treatment combined with apatinib may prolong the survival of patients with advanced HCC.^[9,10] A phase II randomized, open-label trial also indicated that apatinib is well tolerated and effective for the treatment of advanced HCC and has potential survival benefit.^[11] So far, there is no report to evaluate its efficacy and safety in patient with advanced HCC with a zygomatic bone metastasis. Here, we reported 1 case using apatinib on treatment of advanced HCC with bone metastasis.

2. Case report

On April 6, 2016, a 48-year-old Chinese patient was admitted to our hospital under suspicion of an advanced liver tumor due to an increase in levels of alpha-fetoprotein (AFP) after radiofrequency ablation. Before being referred to our hospital, an independent nodule in his left lobe and liver cancer were diagnosed via computed tomography (CT) and were treated using radiofrequency ablation (ARF) 1 month before at a local hospital. Family, alcohol consumption, and smoking histories were otherwise unremarkable, except for the history of clonorchis sinensis, with his last rhinological examination being conducted 3 months before. He presented with hepatitis B virus (HBV) history for 20 years without treatment. Examination showed no abdominal distension or pain. Initial investigations revealed raised levels of AFP (2004 ug/L) and HBV DNA (<500IU/mL), and the laboratory tests did not reveal any liver dysfunction. Ultrasonography indicated hepatocirrhosis, with a right posterior liver lobe mass (S6) 3 cm in diameter. On the magnetic resonance (MR) scan, some areas of necrosis in the left lobe (post-treatment change), 2 independent nodules in the right posterior liver, and several swollen lymph nodes in the hepatic portal and retroperitoneum were observed (Fig. 1). Whole-body positron emission tomography/CT (PET/CT) showed a heterogeneous, encapsulated, hypodense right lobe mass with one area of high fluorine-18 fluorodeoxyglucose (FDG) metabolism (Fig. 2). The

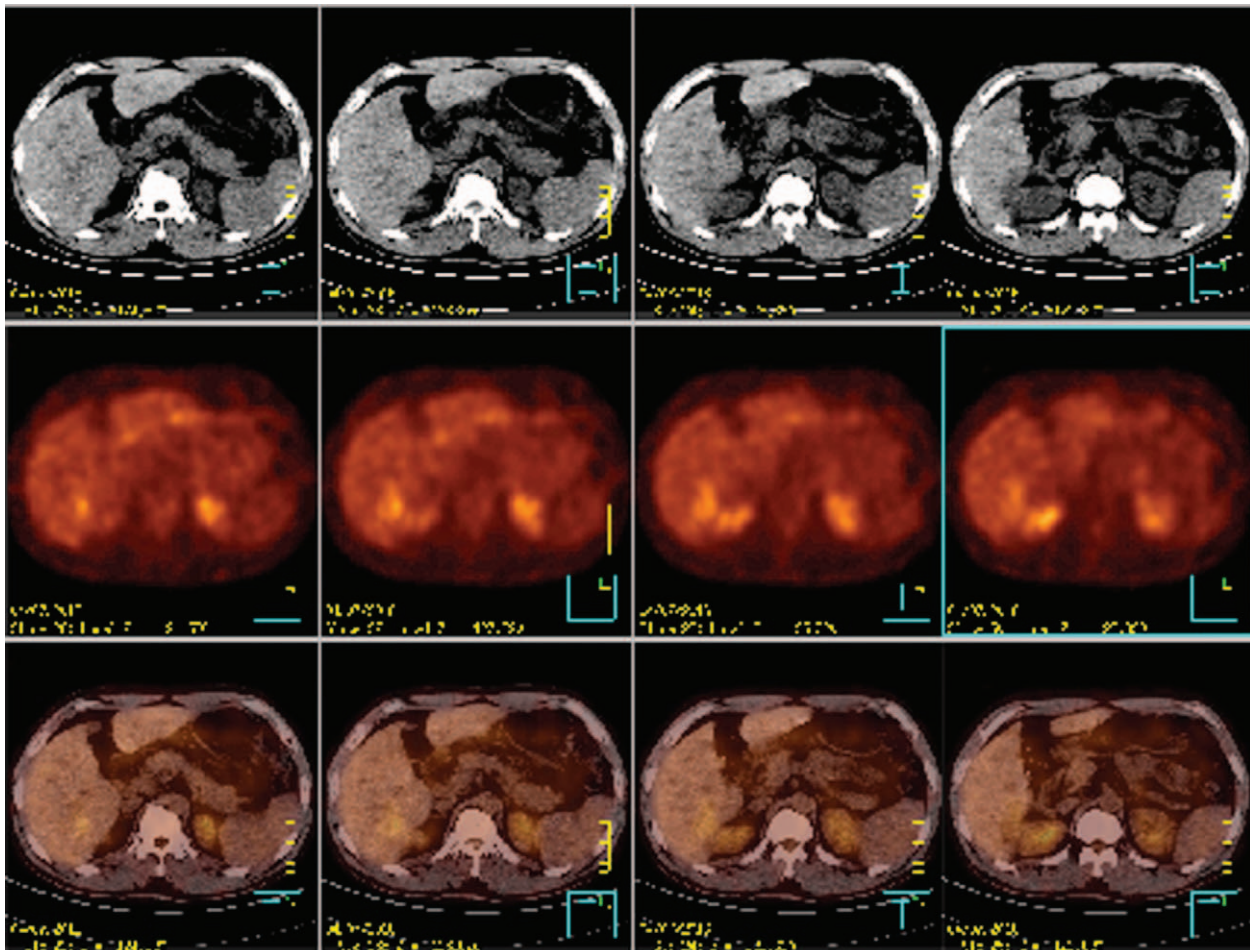


Figure 2. Positron emission tomography/CT (PET/CT) demonstrating 2 hepatic mass. PET/CT=positron emission tomography/ computed tomography.

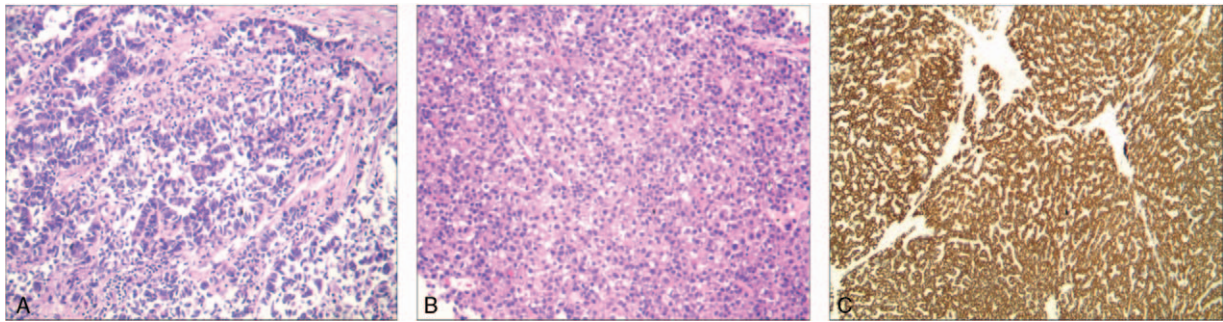


Figure 3. A: Photomicrographs showing a large mass of tumor cells in the liver tissue (Hematoxylin-eosin $\times 10$); B: Biopsy findings of the right zygomatic bone metastasis showing a large of polygonal tumor cells (Hematoxylin-eosin $\times 10$); C: Hepatocyte immunohistochemical stain showing strong and diffuse positivity in the cytoplasm of tumor cells (Streptavidin-biotin $\times 10$).

lesion was hyper-vascular and was supplied mainly by the right hepatic artery, suggesting a diagnosis of intrahepatic metastasis from the left HCC.

On April 12, 2016, a right hepatectomy enlarged to segment VI was performed. Histological examination of the lesion suggested primary HCC (Fig. 3A). The tumor cells were immunohistochemically positive for hepatocytes, AFP, and hepatitis B surface antigen (HBsAg). The patient successfully recovered after surgery and all biochemical marker levels returned to normal. Chemotherapy was not given after the hepatectomy. Seven months after the surgery, an ultrasonography was performed, which showed a liver lobe mass 2cm in diameter in the right lobe (S8). Upon admission to our hospital, his laboratory test results were normal except for raised AFP levels of 281.3 ug/L (normal range, 0–20 ug/L). Abdominal imaging methods (contrast-enhanced ultrasound and MR imaging) successfully revealed metastatic disease in the liver. Because of the small size of the tumor, the patient was planned for an ARF treatment.

Twenty days later, he developed a tender, light zygomatic mass. At that time, physical examination revealed a 4 \times 3-cm²

bony mass in the right zygomaxillary region. The skin of the right zygomatic was slightly inflamed, but not ulcerative. The mucosa overlying the oral cavity was normal. A CT scan of the jaw demonstrated a mixed-density mass in the zygomatic arch (Fig. 4A). The mass included bony material and a cyst-like area, along with destruction of the bone. Whole-body bone scanning detected a solid and soft-tissue mass, along with increased metabolism in the right zygomatic arch. Laboratory analysis showed elevated AFP levels (4315 ug/L). An incisional biopsy was conducted, and histopathologic examination revealed a neoplasm that was composed of large heteromorphic cells (Fig. 3B). Immunohistochemical analysis showed strong and diffuse cytoplasmic positivity with hepatocytes (human hepatocyte-specific antibody) (Fig. 3C). The tumor was also positive for cytokeratin (CK) and CK19 staining. The Ki-67 proliferative index was 40% in the tumor cells. Based on the pathology results of tumor biopsy, the zygomatic mass was diagnosed as metastasis from HCC. The patient had been treated only with 2 cycles of chemotherapy (gemcitabine 1.6g intravenous (IV) drip + oxaliplatin 135mg IV drip + calcium levofolinate 300mg IV

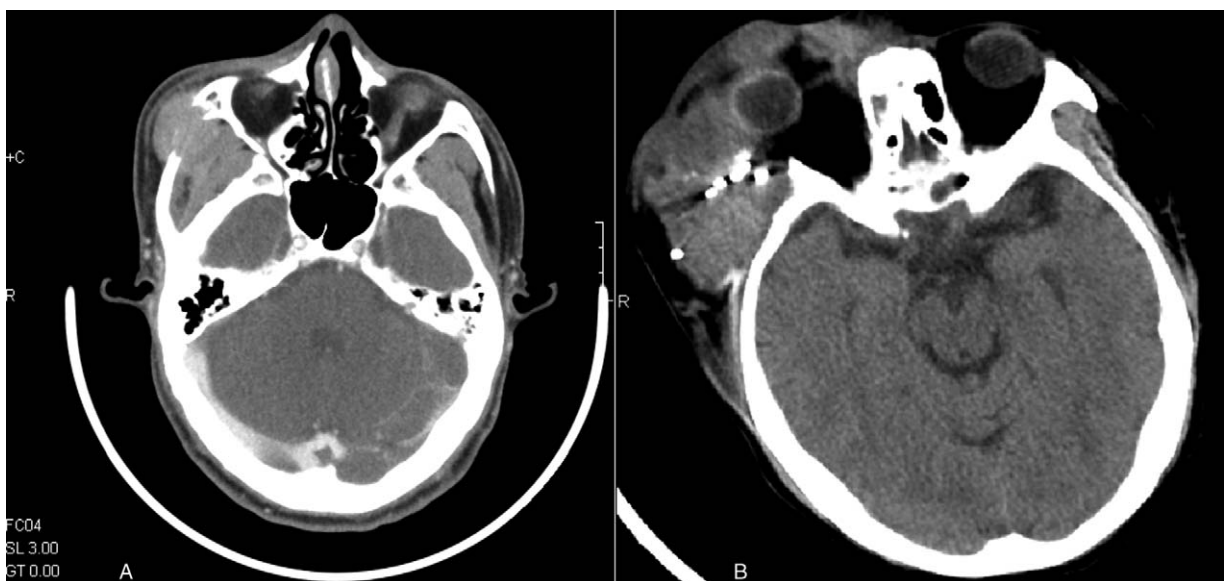


Figure 4. A: Facial computed tomography (CT) scan revealing a mixed-density mass in the right zygomatic arch; B: CT scan showing enlarged metastatic lesions in the right zygomatic arch.

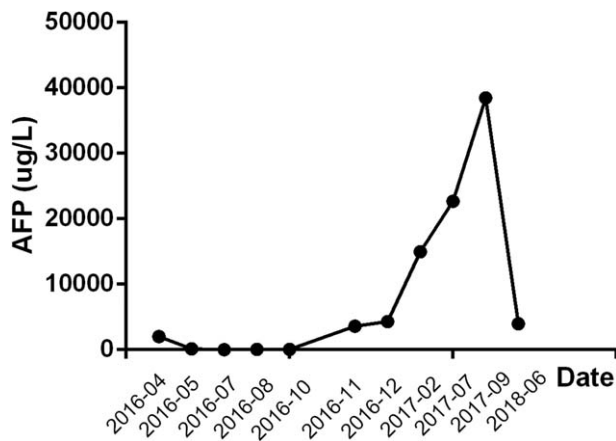


Figure 5. The changes of AFP levels for this patient during the follow-up. AFP = alpha-fetoprotein.

drip + 5-Fluorouracil 4.35g IV drip) in the cancer center of our hospital; subsequently, he suffered severe myelosuppression and the relevant therapy was administered. He then underwent 2 courses of oral and maxillofacial radioactive seed implantation at Sun Yat-sen University Cancer Center (Guangzhou, China).

In September 2016, he presented to the clinic with a complaint of a painful, soft mass in the right zygomatic region that had been slowly enlarging during the previous 16 months. Examination showed an 8 × 5-cm² mass in the right face and laboratory tests revealed raised AFP levels (38,475.0 ug/L, normal range: 0–20). During treatment, the AFP marker levels continuously increased (Fig. 5). Due to chemotherapy intolerance, he started taking orally apatinib with a dose of 500mg/day from 1 to 28 days per cycle. He accepted the treatment for 10 months from August 2017. At the last follow-up in June 2018, the AFP marker levels decreased to 3992 ug/L, but the follow-up CT scan showed that zygomatic target lesions were much bigger. (Fig. 4B). The patient suffered a slight impairment of liver function and mildly elevated blood pressure, but these adverse effects were controllable. He was unwell with a pain in the face, blurred vision in the right eye, dyscrasia, and exhibited difficulty in opening his mouth. He was treated only with symptomatic therapy. This report was approved by the institutional review board of the First People’s

Hospital of Foshan, and the patient provided written informed consent.

3. Discussion

HCC is a prominent malignancy that is clinically silent for most of its course, and most patients are diagnosed at an advanced stage of the disease. Despite considerable knowledge about its nature and pathological process, this malignancy remains incurable. The general prognosis of HCC is poor with 5-year survival rate of less than 20%.^[12] Most patients succumb to HCC within a year of diagnosis, and the survival is only 5 months if left untreated.^[13,14] Metastases from HCC have extremely poor prognoses. Extrahepatic spread is also common with the most common sites of metastasis being the lungs, intra-abdominal lymph nodes, bones, and adrenal glands.^[4] Bone metastases from HCC are uncommon, with a reported incidence ranging from 3 to 20%.^[15,16] However, metastases to the bones of the head and neck region are extremely rare. In a study by Chin et al, 48 cases of metastatic HCC presented in the head and neck region, and most of them were usually observed in the oral cavity, maxilla, or mandible.^[17]

Until recently, zygomatic bone involvement from HCC was very rarely described. Only 3 cases have been reported thus far (Table 1).^[6,18,19] All patients with metastases of HCC in the zygomatic region were men, with a mean age of 60 years (range: 52–70 years).^[6,18,19] Our patient was a 48-year-old man, who was younger than the patients of other published cases. The histology of the primary liver tumor was HCC in 2 of the reported cases and the other case was not reported. Two cases reported that the HCC metastasized to the left zygomatic bones; metastasis of the other case was to the right zygomatic arch, which is similar to that in our case. Dimensions of primary liver tumors have been declared only in one of the published papers (114 mm), which is much larger than the primary liver tumor in our patient (4 mm). In the previous cases, the dimensions of zygomatic metastases range from 30mm to 60mm. The metastasis in our case was larger, that is, 80 mm in diameter (anaphase), which was because of the 18-month duration of metastatic growth after the diagnosis.

Clinically, HCC is diagnosed when the tumor shows diffuse cell proliferation without the typical histological patterns of liver cells using routine hematoxylin - eosin staining (HE). Immunohistochemistry might be very useful for the diagnosis of maxillary

Table 1
Summary of the cases reporting of zygomatic bone metastasis from hepatocellular carcinoma.

Parameters	Reichbach et al ^[13]	Neff et al ^[14]	Tomanovic et al ^[15]	Present case
Age (yr)	52	59	70	48
Gender	M	M	M	M
Initial symptom	Pain and decreased hearing in the left ear	None	A painless mass in the left zygomatic region	None
Location of primary tumor	Liver	Right and left lobes of the liver	Right liver	Left liver
Size of primary tumor (mm)	NS	30	114	30
Location of zygomatic arch	Left	Right	Left	Right
Size of metastasis (mm)	30	39	60	40
Histology	HCC	HCC	HCC	HCC
Treatment	Partial resection for metastasis	LT for primary tumor, resection and reconstruction of facial bones	Symptomatic therapy	ARF, liver resection, chemotherapy And symptomatic therapy
Outcome	Death after 3 months	Death after 12 months	Death after 6 months	Still alive after 10 months

ARF = radiofrequency ablation, HCC = hepatocellular carcinoma, LT = Liver transplantation, NS = not stated.

metastasis from HCC.^[20,21] Hepatocyte antigens are widely distributed in the hepatic cells and are considered the most useful markers to confirm HCC. In the present case, the tumor was positive for hepatocyte antigens upon incisional biopsy of the right zygomatic mass, and an enhanced Ki-67 proliferative index was observed. Therefore, the tumor was diagnosed as a zygomatic bone metastasis from HCC. For the diagnosis of zygomatic bone metastasis from HCC, HCC as an initial presentation is also vital. The patient in our study was already aware of the presence of the primary liver tumor, similar to the case reported in a study by Neff et al^[19] Hence, in the studies by Reichbach et al^[18] and Tomanovic et al^[6], the zygomatic metastasis from HCC was an initial presentation of a malignant liver tumor.

None of the 3 previous cases harbored any background liver disease, such as cirrhosis or hepatitis.^[6,18,19] One reported case exhibited a 30-year history of consuming large amounts of alcohol daily.^[18] In the present case, our patient suffered hepatitis B liver cirrhosis for 20 years. No cases have been reported with changes in AFP levels. Our patient's preoperative (liver resection) AFP levels were elevated. Postoperatively, the AFP levels decreased, but did not return to normal. After finding the zygomatic malignant lesion, the AFP levels continuously increased, indicating an unfavorable prognosis. There have been 2 reports describing the imaging characteristics of zygomatic bone metastases from HCC.^[6,19] According to these cases, zygomatic bone metastases from HCC corresponded to a soft-tissue-density characteristic observed on CT and bone scans. There was no report of MR images of this type of tumor. In the present case, as in other malignant tumors, the tumor was observed as a low-intensity mass on T1-weighted MR images and as a high-intensity area on T2-weighted MR images. All imaging findings suggested that the present tumor was a hypovascular mass.

Bone metastases from HCC, in particular, result in extremely poor patient prognosis, with a median survival of only 1 to 2 months.^[22] Because of the rarity of zygomatic bone metastases from HCC, optimal treatment strategies are not well-defined. The prognosis of patients with zygomatic bone metastases from HCC is unfavorable, even when complete resection of the tumor is performed. Two studies reported surgical resection for metastasis, with 3 and 12 survival months after the diagnosis, respectively.^[18,19] In our case, surgery was not recommended because of widespread metastases in the liver and high surgical risk. Our patient was treated with chemotherapy and radioactive seed implantation in consideration of the patient's age and performance status; however, the therapy was ineffective. Huang et al reported a case of sinonasal metastases from HCC, with a survival of only 5 months.^[23] There is no solid evidence for the efficacy of those treatments in patients with bone metastases from advanced HCC. Treatment for bone metastases from HCC might be aimed at palliation of symptoms. Radiation therapy has previously been shown to provide effective palliation for skeletal metastases in patients with HCC. A study by Seong et al revealed that the median survival from the occurrence of bone metastasis from HCC was 5 months, with a 1-year survival of 15%.^[24] Another study conducted by Choi et al reported the effectiveness of palliation for spinal metastases from HCC.^[25] In our case, radiation therapy was not recommended because of high hemorrhage risk.

A lot of target drugs against advanced HCC are constantly emerging from clinical trials. So far, sorafenib is still the standard treatment for advanced HCC, and it has been proved

to be effective in prolonging overall survival in those patients.^[26] However, the response rates of HCC to sorafenib were relative low, and the extended survival was also limited.^[9] In recent years, apatinib, a small-molecule orally antiangiogenic agents that highly selectively and strongly inhibits vascular endothelial growth factor receptor 2, came to light due to its positive clinical efficacy on some advanced solid tumors, such as gastric cancer,^[8] non-small cell lung cancer^[27] and HCC.^[9] Apatinib shows antitumor efficacy in several established human tumor xenograft models when administered alone or in combination with chemotherapeutic drugs.^[28] According to the English literature, there are 5 reports on the therapeutic efficacy of apatinib alone or combined with radiotherapy/transcatheter hepatic arterial chemoembolization (TACE) to advanced liver cancer thus far.^[29–32,10] All of them nearly exhibited that exhibited exciting effects and good safety profile. Zhu et al^[32] reported that apatinib was efficient for HCC patient with big paraspinal metastasis and they think that it may function as a radiosensitizer of HCC. In our case, the patient took apatinib for maintenance therapy, and AFP marker levels were decreased, the zygomatic tumor mass have become bigger and he was confirmed as progressive disease by the Response Evaluation Criteria in Solid Tumors, however, the progression-free survival time is more than 10 months. It seems that apatinib extended his progression-free survival time and may be pays a potential antitumor role on the course of this patient's treatment to some extent. However, more research is needed to prove the clinical benefits of apatinib.

In summary, HCC metastases to the zygomatic bone are very aggressive with a very low incidence; this case is, to our knowledge, the fourth recorded case of zygomatic bone metastasis from HCC. Immunohistochemistry results with hepatocytes, combined with raised AFP levels and primary liver cancer, are useful diagnosis indicators. Because of their rarity, there is no optimal treatment strategy for these patients and their outcome is poor. In a word, zygomatic bone metastases from HCC represent a challenging clinical problem, and further large-scale prospective studies are needed to prove the therapeutic efficacy of apatinib.

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