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CASE REPORT

# Response of Scalp and Skull Metastasis to Anti-PD-1 Antibody Combined with Regorafenib Treatment in a Sorafenib-Resistant Hepatocellular Carcinoma Patient and a Literature Review

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Video abstract

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**Background:** Scalp and skull metastasis of hepatocellular carcinoma (HCC) is extremely rare. Modalities for the treatment of this disease include craniotomy, radiotherapy and chemotherapy, which are unsatisfactory. We report a case of HCC with scalp and skull metastasis and review similar cases from the literature to accumulate experience for better management of this type of HCC metastasis.

**Case Presentation:** A 54-year-old female was diagnosed with advanced HCC with posterior portal vein tumor thrombus (PVTT) at admission. She received laparoscopic microwave therapy for a large tumor in Segment 6, which was then followed by sorafenib therapy. One year later, sorafenib resistance developed, metastasis occurred in the scalp and skull, left sacroiliac joint, and lung; PVTT extended into the main portal vein and alpha-feta protein (AFP) levels exceeded 65,000 ng/mL. Systemic therapy was then substituted by regorafenib combined with sintilimab. Three months later, AFP decreased to 2005 ng/mL; meanwhile, skull and lung metastatic lesions shrank significantly. Furthermore, both lump and limp disappeared. One year after the combination of regorafenib and sintilimab, skull and lung metastasis, and PVTT were completely relieved. Moreover, primary liver lesions showed no sign of activity. With comprehensive therapy, the patient has survived for 5 years and 7 months.

**Conclusion:** Sorafenib-regorafenib sequential treatment combined with sintilimab is safe and effective when used to treat HCC skull metastasis, for which high-level evidence is needed to support this treatment strategy.

**Keywords:** hepatocellular carcinoma, scalp and skull metastasis, sorafenib-resistant, anti-PD-1 antibody, regorafenib

## Introduction

Primary liver cancer can seriously influence life expectancy and quality of life. Liver cancer is the sixth most common malignancy and the third leading cause of mortality worldwide.[1] Approximately 45% of new cases and 47% of deaths of hepatocellular carcinoma (HCC) occur in China, which, respectively, ranks liver cancer fourth in the incidence of the most common cancer and second among cancer-induced deaths in the country.[2,3] HCC accounts for 90% of primary liver cancers[3] and is closely related to liver cirrhosis and results from various factors, such as chronic viral hepatitis including hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, excessive alcohol consumption, non-alcoholic steatohepatitis (NASH), parasite infection including liver *flukes* and *schistosomes* in endemic regions, long-term consumption of food and water contaminated with aflatoxins, family history of liver cancer, as well as genetic alterations.[1,4] The underlying pathobiology and molecular mechanisms of HCC have been widely investigated but have not been completely clarified.[1] However, the diagnostic criteria are well established and include history of liver disease, elevated tumor

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markers, and typical imaging findings.[5] However, HCC is mostly found at an advanced stage, and the patients lose the opportunity to receive curative therapies.[6]

Controversies regarding treatment for advanced HCC persist between eastern and western guidelines.[7–9] The China's liver cancer staging (CNLC) system recommends TACE, systemic treatment, liver resection as well as radiotherapy for HCC with vascular invasion, and systemic treatment, TACE and radiotherapy for HCC with extrahepatic metastasis.[10] Only systemic therapy is recommended for advanced HCC in the Barcelona Clinic Liver Cancer (BCLC) system.[9] However, systemic therapy is the cornerstone of treatment for advanced HCC.

Sorafenib, challenged by several studies which have yet failed, was prominent as systemic therapy between 2007 and 2017.[11] In 2018, the REFLECT study introduced lenvatinib, another first-line tyrosine kinase inhibitor (TKI) for unresectable HCC, especially for HBV-induced patients.[12] TKIs combined with immune checkpoint inhibitors (ICIs), such as atezolizumab with bevacizumab and sintilimab plus IBI305 (a bevacizumab biosimilar), outperformed the therapeutic efficacy of sorafenib and subsequently emerged as super first-line options for unresectable HCC.[13–15] Given the success of the clinical trials, TKIs plus ICIs have become the focus of growing research, involving lenvatinib plus pembrolizumab (LEAP-002) (see ClinicalTrials.gov for trial information: NCT03713593), lenvatinib plus nivolumab (Study 117) (ClinicalTrials.gov: NCT03418922), and regorafenib plus pembrolizumab.[16] Furthermore, regorafenib is considered the first choice for second-line systemic therapy if disease progresses on sorafenib treatment.[11,17] Other second-line treatments include ramucirumab (when AFP is >400 ng/mL), cabozantinib, pembrolizumab, tislelizumab, and apatinib.[10,18]

With the appearance of new agents and the publication of clinical trial results, first- and second-line treatment options have become plentiful for advanced HCC.[19] Moreover, there is no specific marker for HCC management, which reduces the difficulty of drug selection.[20] Therefore, selection of first- and second-line drugs or different combinations largely depends on personal experience and following of guidelines. Previously, we reported an advanced HCC case with liver recurrence and lung metastasis 18 months after radical resection, which was completely relieved after treatment with sorafenib followed by regorafenib plus sintilimab.[21] Based on our experience of using TKIs and ICIs, we describe a special case with skull and lung metastasis, and portal vein invasion, classified as IIIb in CNLC system and stage C in BCLC system, which was successfully managed by systemic therapy, with a review of the related literature. These findings will hopefully contribute to the therapeutic options available for treatment of advanced HCC, particularly for skull metastasis.

## Case Report

A female patient aged 54 years with HCC and portal vein tumor thrombus, classified as Barcelona clinic liver cancer (BCLC) stage C, was admitted to our department in July 2018. The patient had been diagnosed with HCC and HBV-induced hepatic cirrhosis 2 years prior and received ten courses of transhepatic arterial chemotherapy and embolization. Entecavir had been used as an antiviral agent at another medical center before presentation to our medical group. On admission, the patient presented with good performance status. Physical examination failed to reveal any obvious positive signs. The patient did not report any history of hypertension, diabetes mellitus, drug allergy, or tuberculosis except for the more than 10 years history of HBV infection with antiviral therapy with lamivudine and adefovir, which were replaced by entecavir upon development of drug resistance. She received an ectopic pregnancy surgery in 1989. Blood examination showed AFP levels of 46,502 ng/mL, liver function indices including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), and albumin were within normal ranges. Liver function was classified as Child-Pugh A. Hepatitis B infection markers of HBsAg, HBeAg, and HBcAb were positive. The HBV-DNA load was less than 100 IU/mL. Liver magnetic resonance imaging (MRI) after admission showed multiple lesions in the right lobe, the largest of which was located in Segment 6 with a diameter of around 50 mm (Figure 1), and a tumor thrombus in the right posterior portal branch (Figure 1). Ultrasonography confirmed the above findings. Magnetic resonance imaging (MRI) and ultrasonography identified hepatic cirrhosis and presentation of portal hypertension consisting of enlargement of portal vein, splenomegaly, and esophagogastric varices. Chest computed tomography (CT) demonstrated no sign of metastasis (Figure 2). Gastroscopy revealed severe esophagogastric varices and multiple gastric ulcers. Therefore, the main diagnosis of the patient after evaluation was one of the liver multiple HCC with portal

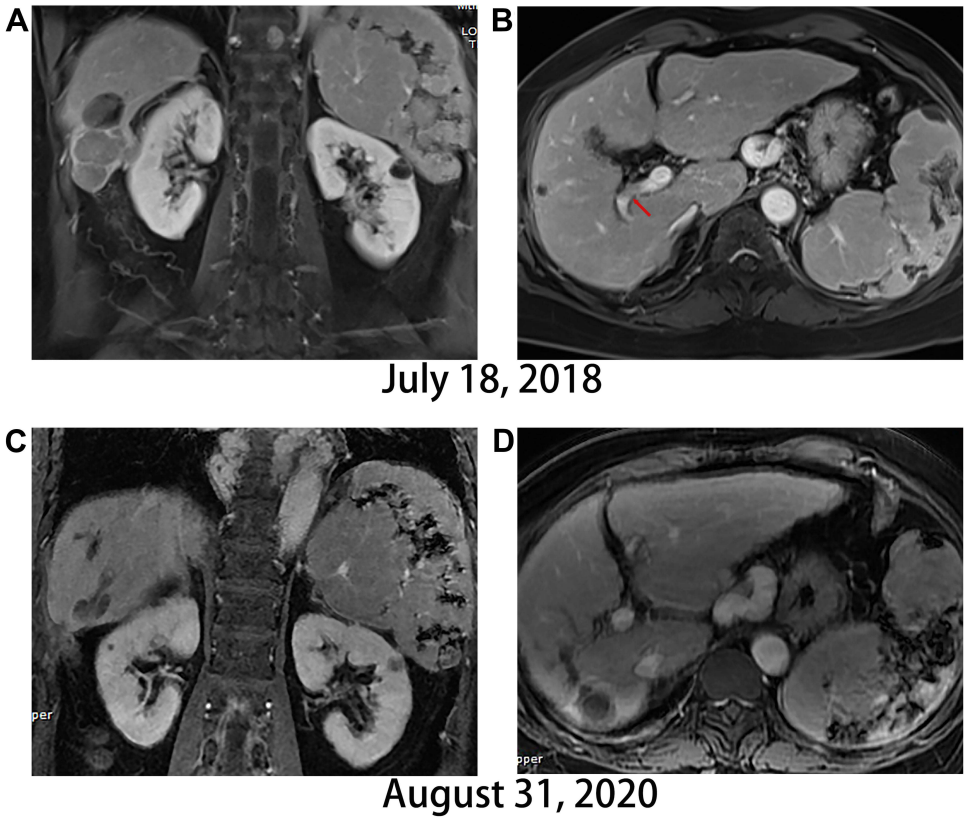


**Figure 1** Contrast imaging of primary liver lesions on MRI subsequent to sorafenib-regorafenib therapy combined with sintilimab. (**A**) The largest liver lesion in Segment 6 at admission. (**B**) A posterior portal vein tumor thrombus indicated by the arrow at admission. (**C**) Tumor in Segment 6 is rendered inactive by treatment. (**D**) Disappearance of PVTT.

vein tumor thrombus (PVTT) and suspected lung metastasis (BCLC C), HBV-induced hepatic cirrhosis, and portal hypertension. Sorafenib, 400 mg, twice per day, was recommended at that time.

To alleviate tumor load, the patient underwent laparoscopic microwave therapy of the tumor in Segment 6. Three months later, levels of AFP decreased to 1453 ng/mL. Unfortunately, the patient developed a complication due to perforation in the hepatic flexure of the colon and was obligated to undergo an ileostomy. The patient recovered well after the surgery. In April 2019, 1 year after receiving sorafenib therapy, AFP values decreased to 29.42 ng/mL; however, the lesion in Segment 6 began to enlarge (Figure 3). The patient exhibited hypertension, proteinuria, diarrhea, and hand-foot syndrome which manifested as red spots, swelling, pain in the palms of the hands and soles of the feet 2 months after using sorafenib, but she was able to endure all of the side effects with appropriate symptomatic treatment. In June 2019, the levels of AFP increased to 95 ng/mL and the lesion in Segment 6 continued to increase in size. At the 3-month follow-up, levels of AFP exceeded 60,500 ng/mL; PVTT was extended into the main portal vein (Figure 3), and lung metastasis (Figure 2) and scalp metastasis presented as a frontal lump and bone lesions including skull and left sacroiliac joint leading to a limp were observed (Figure 4). Considering the tumor progression observed following treatment of sorafenib, regorafenib was recommended, and sintilimab (200 mg per 3 weeks) was also introduced as anti-PD-1 therapy. After treatment with sintilimab for three rounds and its combination with regorafenib (160 mg per day), AFP levels decreased to 2005 ng/mL (Figure 5); meanwhile, the skull and lung metastatic lesions shrank (Figures 2, 4 and 5). Besides, both the lump and limp disappeared. During the combined treatment of regorafenib and sintilimab, a high fever (exceeding 39°C) appeared but could be controlled by dexamethasone. Due to the outbreak of Coronavirus disease 2019 (COVID-19), the patient was unable to visit hospital; thus, targeted and immune therapies were suspended. The patient revisited our medical centre in August 2020, approximately 7 months later. Amazingly, AFP had returned to normal levels at 0.89 ng/mL (Figure 5). The skull and lung metastasis and PVTT disappeared (Figures 1, 2 and 4). The tumor

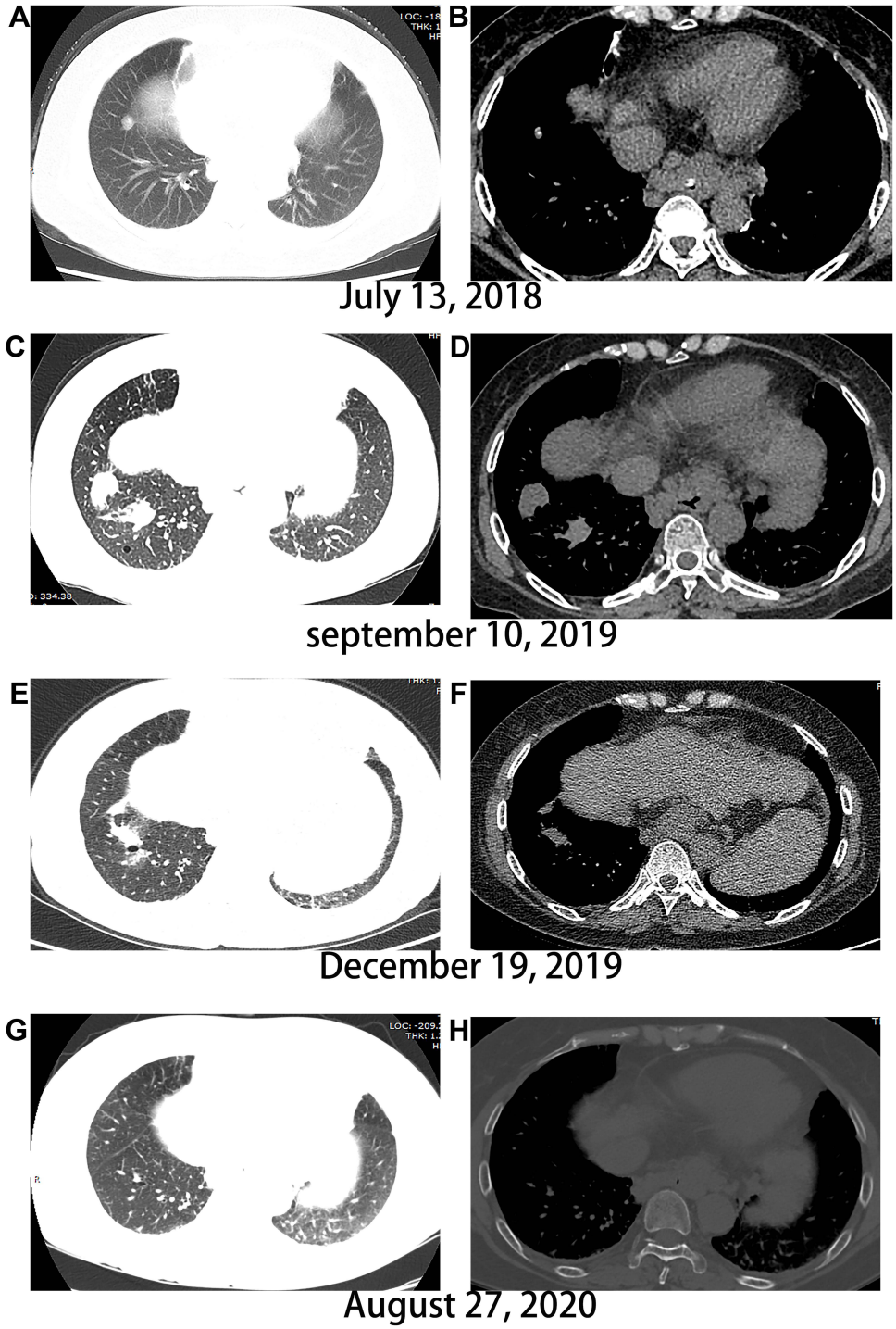


**Figure 2** Evolution of HCC lung metastasis. (**A** and **B**) No signs of metastasis at admission, (**C** and **D**) Multiple lung lesions after therapy with sorafenib for 1 year, (**E** and **F**) Volume of lung lesions decrease after treatment with regorafenib combined with sintilimab for 3 months. (**G** and **H**) Complete remission of lung metastasis.

size also reduced significantly in the right lobe of the liver and was inactive (Figure 1). During hospitalization, the ileostomy was closed, and then, the patient continued with treatment using regorafenib and sintilimab. The patient then returned to the local referral hospital and the use of the combination lasted 8 months and then ceased in April 2021 after visiting our clinics, as a result of severe liver function damage that was graded 3 to 4 in terms of adverse reactions. The liver function recovered with the use of dexamethasone and liver-protecting agents in the local hospital. The follow-up

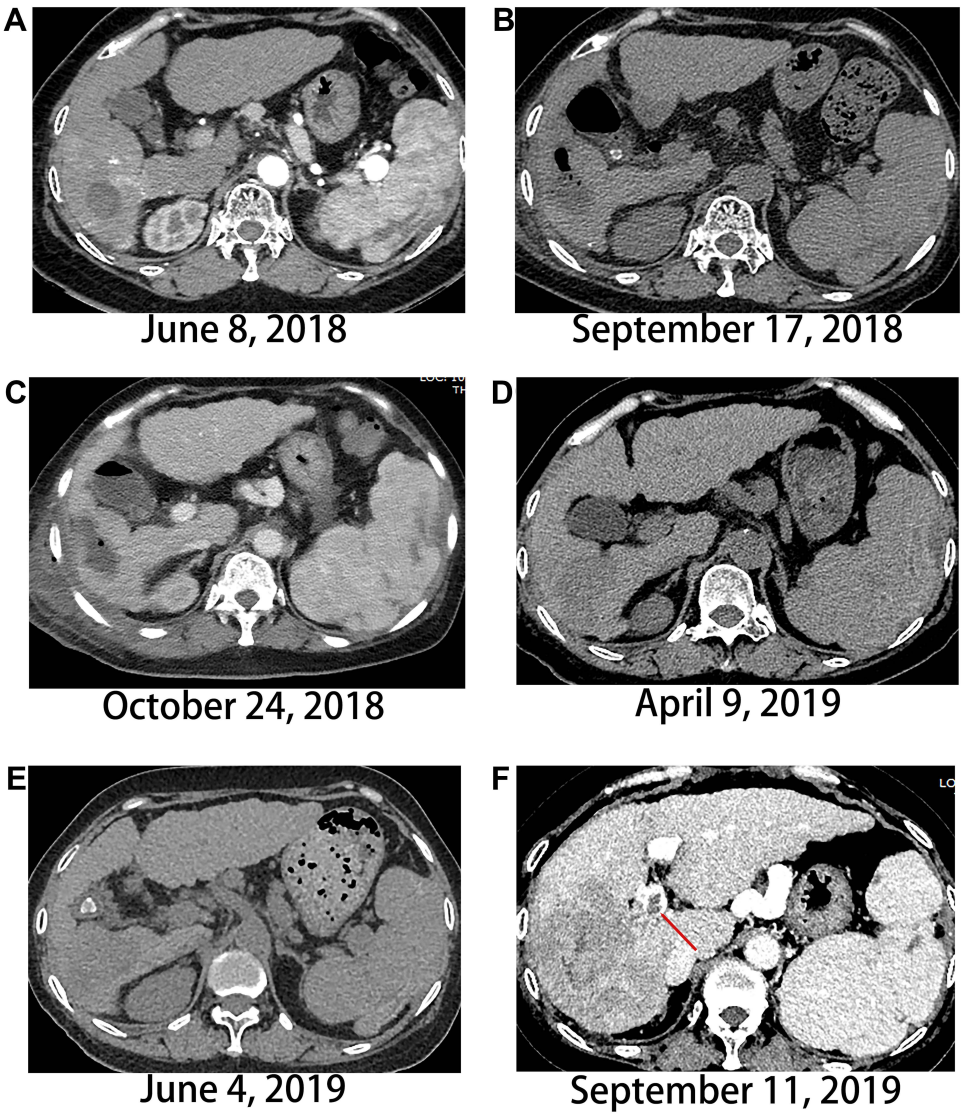


**Figure 3** Evolution of the primary liver lesion on computed tomography. (**A**) Liver lesion in Segment 6 at admission, (**B** and **C**) Changes in the segment 6 lesion post-microwave irradiation, (**D** and **E**) The tumor continually progresses. (**F**) Main portal vein tumor thrombus emerges. Red arrow indicates main portal vein tumor thrombus.

results revealed that AFP values were normal; ultrasonography only indicated cirrhotic nodules in the liver; bone and lung metastases were absent.

## Discussion

Distant metastasis of HCC, as an indicator for poor quality of life and survival, is quite common, with an incidence as high as 72%.[22] The lung is the most common metastatic site of HCC, followed by intra-abdominal lymph nodes, and bone.[23] HCC is prone to metastasize to vertebrae, spine, pelvis and ribs, as well as long bones, but rarely to the skull.[24] We present a case with scalp and skull metastasis, which was successfully managed by TKIs combined with an immune checkpoint inhibitor. Furthermore, we reviewed reported cases of HCC with skull metastasis, to increase the knowledge base of experience regarding diagnosis and treatment of advanced HCC with skull metastasis. Our case is a 54-year-old female with HBV infection, which is in line with the basic characteristics of HCC.

All the HCC cases with scalp and skull metastasis, from 1992 to 2020, were extracted from PubMed and reviewed (Table 1). The age of the 27 patients (4 females and 23 males) ranged from 52 to 77 years, with a mean age of 59 years. The dominant risk factor related to HCC was HBV infection, followed by HCV, alcohol abuse, and parasitic disease,

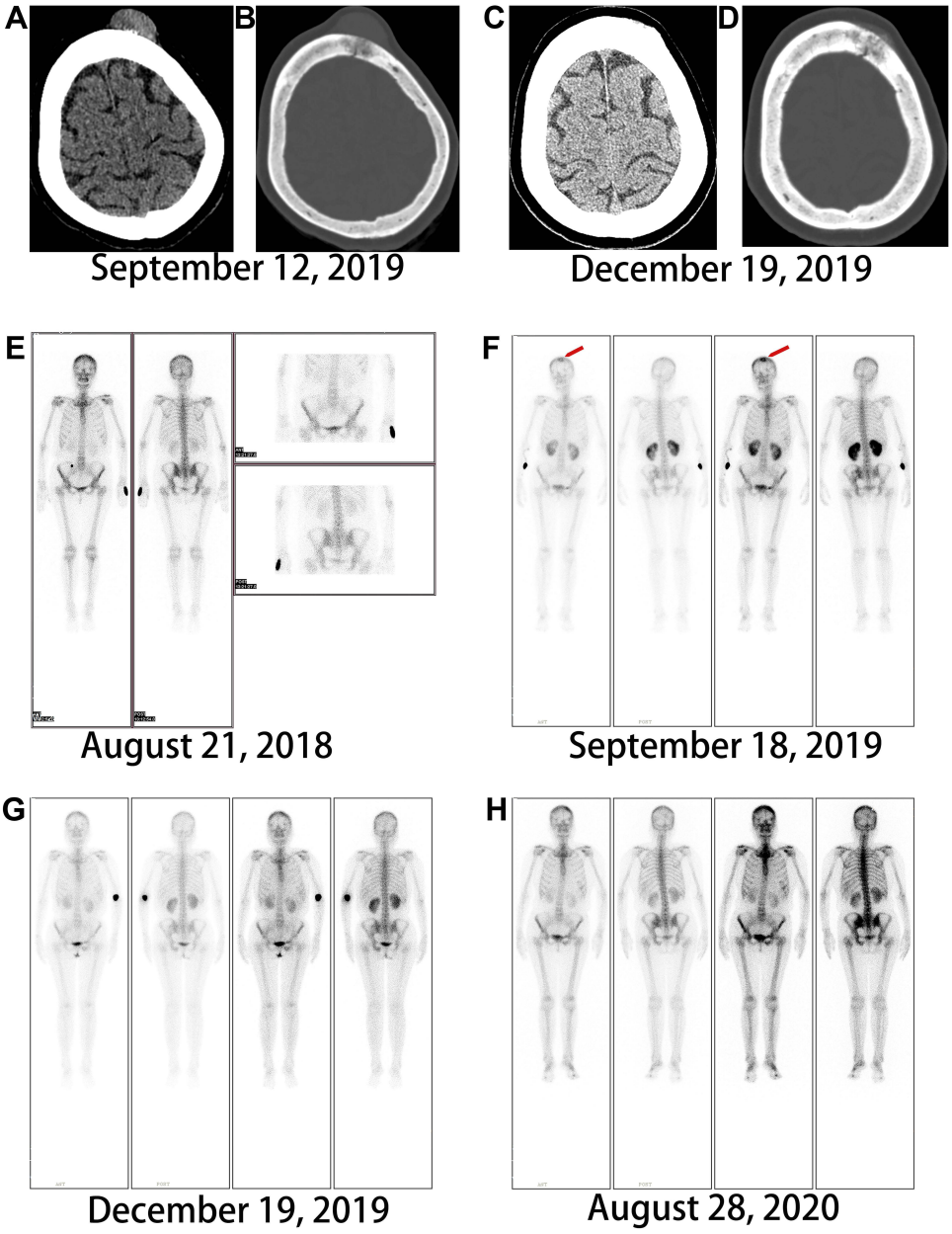


**Figure 4** Evolution of the scalp and skull metastasis on computed tomography and whole-body bone scan by single-photon emission computed tomography (SPECT) using 99mTc. (**A** and **B**) the scalp and skull metastases occur on the frontal site, (**C** and **D**) the scalp and skull lesions shrink significantly, (**E**) SPETCT shows no active signal at admission, (**F**) SPECT indicates frontal skull marked by arrow, left sacroiliac joint, and left iliac increased radioactivity, (**G** and **H**) radioactivity of the skull disappears.

which was in agreement with HCC epidemiology.[1] Most patients present with a scalp mass involving the scalp and skull, several of whom describe this as the chief complaint provoking them to seek medical help, followed by definitive diagnosis of metastatic HCC by surgery or biopsy. As the rupture of the tumor led to an epidural hematoma, five patients showed progressive headache, nausea, vomiting, dizziness, or unconsciousness; one patient reported a visual defect, and another presented left-sided hemiparesis, due to tumor compression of the brain tissue. Fortunately, our patient presented a head lump without nervous symptoms. Based on primary tumors with vascular invasion, distant metastatic lesions, such as lung, adrenal glands, and bone, and history of HCC, diagnosis of skull metastasis is not difficult to make. However, two of the cases showed no signs of primary or metastatic lesions, which undoubtedly added difficulty to the diagnosis, which was finally defined by craniotomy.[25,26] In the reported cases, 59.3% (16/27) of the patients accepted craniotomy, 18.5% (5/27) biopsy, 29.6% (8/27) radiotherapy, 11.1% (3/27) chemotherapy, 7.4% (2/27) systemic therapy, sorafenib,

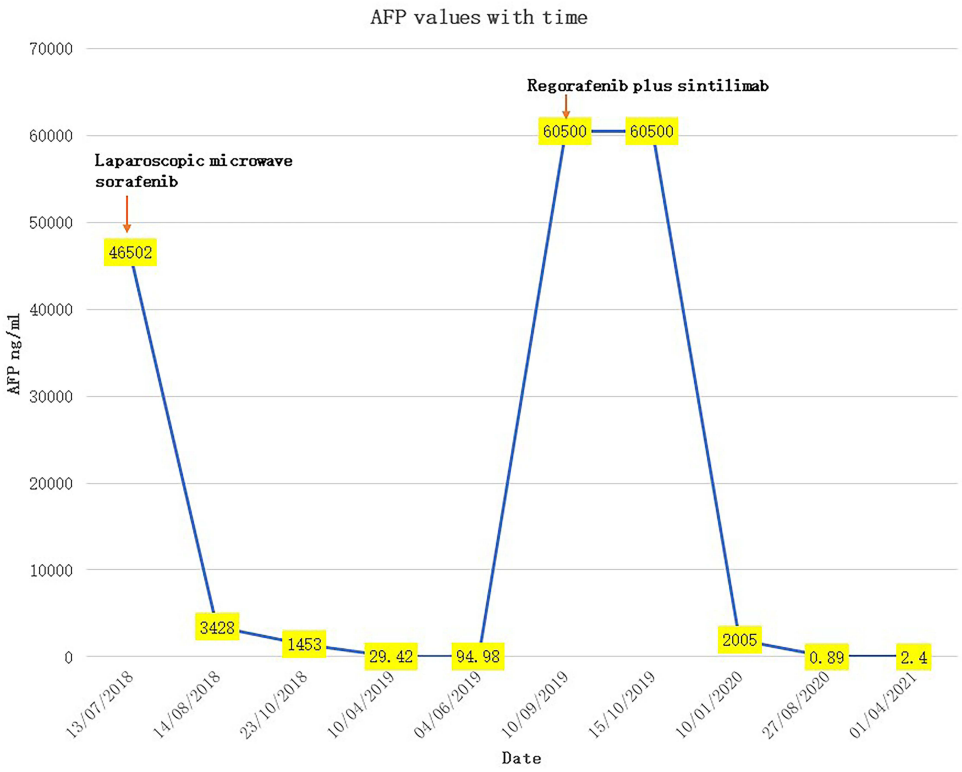


**Figure 5** AFP levels over time. The first red arrow indicates the treatment of laparoscopic microwave and sorafenib after finding AFP level is 46,502 ng/mL, and second red arrow indicates the use of regorafenib and sintilimab after AFP level elevates to more than 65000ng/mL.

and 7.4% (2/27) only best supporting care (BSC). In addition, 11.1% (3/27) of the patients received TACE for primary lesions. Surgery is the main approach to treat skull metastasis, accompanied by radiotherapy, chemotherapy, and other measures, which do not achieve satisfactory results. The follow-up periods ranged from 5 days to 26 months and 68.4% (13/19) died of multi-organ failure or liver failure. As shown in Table 1, craniotomy increased the risk of death. Conversely, patients receiving radiotherapy seem to have better survival compared to patients subject to surgery alone. For our patient, scalp and skull metastases disappeared 3 months after receiving regorafenib and sintilimab treatment. At the time of writing, 29 months has passed, and no signs of recurrence were detected. Thus, our patient was the first case of HCC skull metastasis remission without surgery and had the longest survival time compared to the previously reported cases.

Primary HCC metastasizing to distant sites is a multiple and complex process. Cancer cells acquire the ability of epithelial to mesenchymal transition (EMT) in order to exudate from basement membrane; cells then enter the blood stream or lymphatic vessels and become circulating tumor cells (CTC) that reach metastatic sites, by adhering, anchoring, and exudating across blood vessels. Mesenchymal–epithelial transition (MET) allows cancer cells to adapt to the new environment and form metastatic lesions.[27] The underlying mechanisms of HCC cells involve cells breaking away from the primary site, which then escape from immune surveillance in case of elimination, selectively migrate to the bone microenvironment, and survive. Although several cellular and animal models of HCC bone metastasis have been established to explore these issues, the underlying mechanisms remain unclear.[28,29] Furthermore, trauma sites of the skull are prone to be the destination of HCC metastasis, which is attributed to the skeletal wound healing microenvironment containing vascular endothelial growth factor (VEGF), tumor growth factor-β (TGF-β), and base fibrous growth factor (bFGF), which promote metastasis.[26,30] This phenomenon warrants deeper investigation.

Angiogenesis and immune escape are two hallmarks of cancer.[27] VEGF is able to increase vascular permeability and promote extracellular matrix degeneration, vascular endothelial cell migration and proliferation, and angiogenesis, which in turn plays an important role in the invasion and metastasis of cancer.[31] Thus, the current first- and second-line target

**Table 1** Clinical Characteristics of the Reported HCC Scalp and Skull Metastasis

| No. | Reference | Year | Age | Sex | Risk Factor | Manifestation | Primary Lesion | Vascular Invasion | Skull Spread | Involvement | Other Spread | Management | Follow-Up | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Sanders et al[40] | 2020 | 77 | F | HBV | Scalp mass | Multiple, infiltrative | None | Frontal region | Scalp, skull | None | BSC | 2 months | Expired |
| 2 | Sadik et al[41] | 2019 | 54 | M | HCV | Scalp mass | Single | IVC, RAT | Superior sagittal sinus | Scalp, skull | Lung, rib | Craniotomy | 26 days | Expired |
| 3 | Han et a[25] | 2017 | 66 | M | *S.J.* | Scalp mass, headache, dizziness | None | None | Left occipital region | Scalp, skull, dura | None | Selective embolization, craniotomy | 9 months | Alive |
| 4 | Ferraz et al[42] | 2016 | 55 | M | None | Scalp mass with local pain | Single, infiltrative | None | Right frontal region | Scalp, skull | Clavicle, sternum, hip, lumbar spine | Craniotomy, radiotherapy | 6 months | Expired |
| 5 | Kim et al[43] | 2015 | 41 | M | ND | Sudden headache, vomiting, drowsiness | Multiple | ND | Right occipital region | Skull, epi-dura | Ribs, pelvis | BSC | 4 months | Expired |
| 6 | Subasinghe et al[44] | 2015 | 56 | M | None | Scalp mass | Single | None | Occipital region | Scalp, skull | Left scapula | Excision of the scalp mass, RFA for liver mass | ND | ND |
| 7 | Susheela et al[45] | 2015 | 40 | M | HBV | Scalp mass | Multiple | ND | Frontal region | Scalp, skull | Lung, dorsal vertebrae | Radiotherapy, sorafenib | 12 months | Expired |
| 8 | Chye et al[46] | 2015 | 69 | F | HCV | Headache, nausea, vomiting, dizziness | Single | None | Left temporal region | Scalp, skull, epi-dura, dura | None | Radiotherapy for brain, TACE for liver mass | ND | ND |
| 9 | Guo et al[47] | 2014 | 49 | M | HBV | Scalp mass | Single | None | Right parietal-occipital region | Scalp, skull | None | Craniotomy, TACE for liver mass | 18 months | Expired |
| 10 | Azarpira et al[48] | 2014 | 38 | M | HBV | Scalp mass | None | None | Right temporal region | Scalp, skull, dura | None | Radiotherapy, chemotherapy | 3 months | Alive |


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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | Turan et al[49] | 2013 | 70 | M | HBV | Scalp mass | Single | None | Frontal region | Scalp, skull | Lung, adrenal glands, ribs, lumbar vertebrae, and pelvis | Craniotomy, sorafenib | 11 months | Expired |
| 12 | Brunetti et al[50] | 2012 | 79 | M | ND | Scalp mass | Multiple | ND | Parietal-occipital region | Scalp, skull | Mandible | Biopsy | ND | ND |
| 13 | Ermis et al[51] | 2012 | 72 | M | HCV | Scalp mass | Multiple | PVTT | Right frontal-parietal region | Scalp, skull | Thoracic vertebrae, ribs, sternum, right sacroiliac joint | Biopsy | ND | ND |
| 14 | Goto et al[52] | 2010 | 56 | M | HBV | Scalp mass | Multiple | None | Left occipital-temporal region | Scalp, skull | Thoracic vertebrae | Radiotherapy for brain, TACE for liver mass | ND | Expired |
| 15 | Woo et al[53] | 2010 | 46 | M | ND | Severe headache, unconsciousness | ND | ND | Right temporal region | Skull, epi-dura, dura | ND | Craniotomy | 5 days | Expired |
| 16 | Fukushima et al[26] | 2010 | 58 | M | ND | Scalp mass | None | None | Left temporal region | Scalp, skull | None | Craniotomy | ND | ND |
| 17 | Kanai et al[54] | 2009 | 56 | M | HCV | Severe headache, unconsciousness | Single, huge | None | Left occipital region | Scalp, skull, epi-dura | ND | Craniotomy | 21 days | Expired |
| 18 | Shim et al[55] | 2008 | 71 | M | HCV, alcohol | Scalp mass | Two | None | Occipital region | Scalp, skull | None | Craniotomy, TACE for liver mass | 9 months | Alive |
| 19 | Hsu et al[56] | 2008 | 53 | M | HBV | Scalp mass, visual field defect | Multiple | None | Left parietal-occipital region | Scalp, skull, epi-dura | None | TACE, craniotomy, radiotherapy | 10 months | Alive |
| 20 | Hsieh et al[57] | 2006 | 46 | M | HBV | Scalp mass | None | None | Left frontal region | Scalp, skull | Spine, left femur | Craniotomy, radiotherapy, chemotherapy | 15 months | Alive |

(*Continued*)



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**Table 1** (Continued).

| No. | Reference | Year | Age | Sex | Risk Factor | Manifestation | Primary Lesion | Vascular Invasion | Skull Spread | Involvement | Other Spread | Management | Follow-Up | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | Simone et al[30] | 2005 | 61 | M | HCV | Scalp mass | Multiple | None | Left parietal region | Scalp, skull | Sternum, lung | Craniotomy, chemotherapy | ND | ND |
| 22 | Nam et al[58] | 2005 | 65 | M | HCV, alcohol | Scalp mass | Multiple | None | Frontal region | Scalp, skull, dura | Sternum, ribs | Biopsy, radiotherapy | 26 months | Alive |
| 23 | Jegou et al[59] | 2004 | 55 | M | ND | Scalp mass | Single | None | Left frontal region | Scalp, skull | Adrenal gland | Biopsy | ND | ND |
| 24 | Chan et al[60] | 2004 | 75 | F | None | Scalp mass | Single | None | Right frontal region | Scalp, skull | None | Craniotomy | ND | ND |
| 25 | Torres et al[61] | 2002 | 66 | F | HCV | Scalp mass | Two | None | Occipital region | Scalp, skull | None | Biopsy | 42 days | Expired |
| 26 | Hayashi et al[62] | 2000 | 70 | M | ND | Left-sided hemiparesis | ND | ND | Right parietal region | Scalp, skull, epi-dura | ND | Craniotomy | 2 months | Expired |
| 27 | Nakagawa et al[63] | 1992 | 52 | M | ND | ND | ND | ND | ND | Scalp, skull, epi-dura | ND | Craniotomy | ND | Expired |

**Abbreviations**: F, female; M, male; ND, not described; BSC, best supportive care; IVC, inferior vena cava; RFA, radiofrequency ablation; PVTT, portal vein tumor thrombus; S.J., Schistosoma japonicum; RAT, right atrium thrombus.

drug treatments, including sorafenib, lenvatinib, donafenib, regorafenib, apatinib, ramucirumab, and cabozantinib, for treating advanced HCC, are designed to block the VEGF signaling pathway.[32–34] Monotherapy for advanced HCC is unsatisfactory as sorafenib only prolongs median overall survival (OS) by 2.8 months compared to placebo, lenvatinib is non-inferior to sorafenib, and the median OS of donafenib is just 12.1 months although it is superior to sorafenib.[12,32,35] Given the systemic blockade of tyrosine kinases, adverse events (such as hand-foot skin reactions, hypertension, proteinuria, diarrhea, and weight loss) have been reported,[12,32,36] which were also manifest in our patient but were controlled by symptomatic treatment. Moreover, drug resistance is an unavoidable issue when using target therapy because of the remarkable heterogeneity of HCC. Because drug resistance occurs and given the uncertain duration of TKI treatment, there is no protocol to guide switching drugs from a number of available first- and second-line TKIs after the primary TKI resistance has developed. In our case, sorafenib resistance appeared after 11 months, and treatment was switched to regorafenib in accordance with effective and accomplished clinical trial protocols (RESORCE).[17]

ICIs targeting PD-1 on immune cells and its ligand PD-L1 on tumor cells have shown efficacy in managing advanced HCC but are currently classified as second-line options and are used as monotherapy.[37] In addition, the combined use of ICIs induces elevation of autoantibodies and inflammatory cytokines, which activate T cells to attack normal tissues, potentially leading to immune-related adverse events (irAEs) including thyroiditis, pneumonia, myocarditis, and hepatitis.[38] irAEs also occurred in our patient, which manifested as high fever, the presence of an itchy maculopapular rash over the entire body, and severe liver function damage with elevated bilirubin levels that directly resulted in the suspension of target and immune therapy.

Blockade of VEGF not only suppresses angiogenesis but also inhibits functions of regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), up-regulates PD-L1 expression on endothelial cells (ECs) and tumor cells and turns the immunosuppressive microenvironment into an anti-tumor microenvironment.[39] This finding justified why anti-angiogenic therapy could enhance cancer immunotherapy and why the combination of atezolizumab (anti-PD-L1 antibody) with bevacizumab (anti-VEGF antibody) allows advanced HCC patients to achieve a significantly prolonged OS and progression-free survival,[14] which has also been verified by sintilimab plus IBI305 treatment.[15] In our previous study, a postoperative patient with liver recurrence and lung metastasis achieved complete remission using sorafenib-regorafenib sequential therapy combined with sintilimab.[21] The same combination was applied to the case presented herein, surprisingly, skull metastasis disappeared after 3 months and lung metastasis after 1 year. Fortunately, the skull and lung metastases of our patient are currently still in the state of persistent complete remission even after discontinuing regorafenib and sintilimab. How long the non-tumor state will last and what type of therapeutic option should be chosen if recurrence was to occur remain unknown.

This study holds the potential that regorafenib plus sintilimab is an ideal means to manage HCC skull or lung metastasis, especially for patients with sorafenib resistance. However, this report belongs to case observation and personal clinical experience, which is unable to provide high-level evidence, and therefore is the main limitation of this study. At present, the ongoing clinical trials of regorafenib combined with PD-1/PD-L1 inhibitors for advanced HCC include nivolumab, tislelizumab and pembrolizumab, except sintilimab, which makes the promising combination of regorafenib and sintilimab worth studying to clinical researchers.

## Conclusion

Regorafenib combined with sintilimab is safe and effective when used to treat HCC skull metastasis and is a treatment strategy that warrants evaluation in high-level clinical trials.

## Informed Consent

The patient and her family provided informed consent for the case details and images to be published. Our institution approved the publication of the details of this case.

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## Disclosure

The authors report no conflicts of interest in relation to this work.

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