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Case Report

Atezolizumab plus bevacizumab-induced intratumoral hemorrhage in a patient with rib metastasis from unresectable hepatocellular carcinoma ☆

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ABSTRACT

Recently, combination therapy with atezolizumab, a humanized monoclonal antiprogrammed death ligand-1 antibody, and bevacizumab, has become available for treatment of unresectable hepatocellular carcinoma (HCC). We herein report a 73-year-old man with advanced stage HCC who developed fatigue during treatment with atezolizumab–bevacizumab combination therapy. Computed tomography identified intratumoral hemorrhage within the HCC metastasis to the right fifth rib metastasis of HCC, which was confirmed on emergency angiography of the right 4th and 5th intercostal arteries and some branches of the subclavian artery confirmed intratumoral hemorrhage, following which transcatheter arterial embolization (TAE) was performed to achieve hemostasis. He continued to receive atezolizumab-bevacizumab combination therapy after TAE, and no rebleeding was seen. Although uncommon, rupture and intratumoral hemorrhage in the HCC metastasis to the ribs can cause life-threatening hemothorax. However, to our knowledge, no previous cases of intratumoral hemorrhage in HCC during atezolizumab–bevacizumab combination therapy have been reported. This is the first report of intratumoral hemorrhage with the combination therapy of atezolizumab and bevacizumab, which was successfully controlled by TAE. Patients receiving this combination therapy should be observed for intratumoral hemorrhage, which can be managed by TAE if it does occur.

☆ Competing Interests: The authors declare that they have no conflict of interest.

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Introduction

Primary liver cancer is the seventh most frequently occurring cancer and the second most common cause of cancer mortality in the world. Hepatocellular carcinoma (HCC) is the dominant type of liver cancer, accounting for approximately 75% of cases [1]. Recently, the indications for various molecular-targeted agents (MTAs) in the treatment of advanced stage HCC have expanded [2]. However, recent studies have described intratumoral hemorrhage caused by lenvatinib, an oral, small-molecule inhibitor of multiple receptor tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors-1, -2 and -3 [3,4]. Although hemorrhage is also one of the well-known adverse events (AEs) of combination therapy with atezolizumab, a humanized monoclonal anti-programmed death ligand-1 antibody, and bevacizumab, a humanized monoclonal VEGF antibody, it typically presents as esophageal and gastric variceal rupture [5], and intratumoral hemorrhage is rare. In fact, to the best our knowledge, no previous report on HCC has identified intratumoral hemorrhage as an AE following atezolizumab-bevacizumab combination therapy. We report a case of intratumoral hemorrhage caused by atezolizumab–bevacizumab combination therapy in a patient with HCC metastasis to the right fifth rib which was successfully controlled by transcatheter arterial embolization (TAE). It is crucial that these AEs are recognized and managed by TAE, to allow continuation of the anticancer therapy.

Case report

A 73-year-old man underwent partial hepatectomy 6 months after being diagnosed with HCC. Five months later, the patient experienced multiple recurrences of HCC and developed metastasis to the right fifth rib. At 1 month after atezolizumab–bevacizumab combination therapy was initiated, he was admitted to the hospital complaining of fatigue.

On admission, his vital signs were as follows: temperature 36.4°C, blood pressure 135/78 mm Hg, pulse 105 bpm, respiratory rate 18 breaths/min, and transcutaneous oxygen saturation 97% (on room air). Physical examination revealed no abnormal breath sounds or abdominal tenderness. Laboratory tests revealed a decrease in hemoglobin from 14.2 g/dL to 13.2 g/dL over the course of one month. There was no evidence of liver dysfunction.

Dynamic contrast-enhanced computed tomography (CT) on admission showed bleeding within the metastatic tumor of the right fifth rib (Fig. 1A and B). Despite the absence of pleural effusion or hemothorax, emergency transcatheter hemostasis was performed due to the identified bleeding. Angiography demonstrated a hypervascular tumor supplied by multiple arteries, including the right fourth and fifth intercostal arteries, the right subclavian artery, right internal thoracic artery, right subscapular artery, and the right external thoracic artery (Fig. 2A–F). Pooling of contrast medium inside the tumor, indicative of intratumoral hemorrhage, was observed in each arteriogram. We performed selective embolization of these vessels using a gelatin sponge (Serescue, Astellas Pharma Inc., Tokyo, Japan) and microspheres (Embosphere 300-500 μm, Merit Medical Japan Inc., Tokyo, Japan). Postembolization angiography of each artery confirmed the complete disappearance of the tumor staining and hemorrhage. After embolization, dynamic contrast-enhanced CT confirmed hemostasis of the intratumoral hemorrhage (Fig. 3A and B).

Following the treatment, the patient's fatigue resolved and there was no worsening of anemia. Atezolizumab–bevacizumab combination therapy was recommenced and continued for more than 6 months after TAE without rebleeding.

Discussion

This is the first report of transcatheter hemostasis for intratumoral hemorrhage associated with atezolizumab–bevacizumab combination therapy. A few previous reports have described intrahepatic hemorrhage and rupture of intrahepatic tumors after administration of lenvatinib, which has a similar pharmaceutical effect against VEGF as bevacizumab

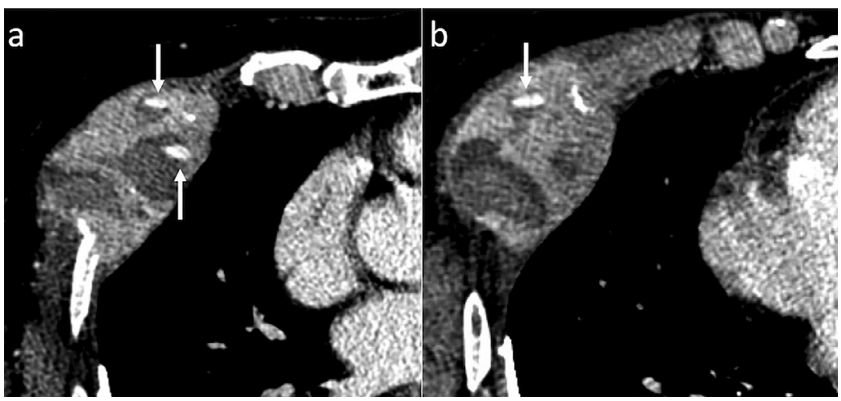

Fig. 1 – Thoracic computed tomography (CT) on admission. Arterial phase of contrast-enhanced CT (A, B). Some arterially enhancing masses were observed in the right fifth rib, indicating HCC metastasis. Intratumoral hemorrhages are also seen (arrows).

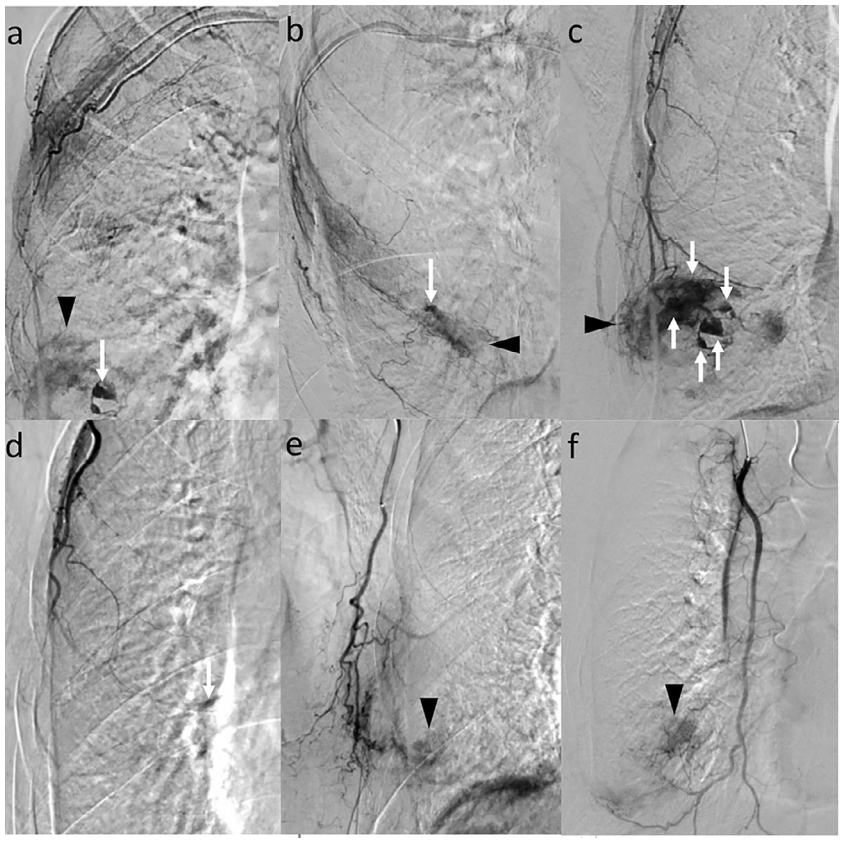

Fig. 2 – Emergency angiography of the right fourth intercostal artery (A), right fifth intercostal artery (B), right external thoracic artery (C), right subclavian artery (D), right subscapular artery (E), and right internal thoracic artery (F) demonstrated leakage of contrast medium, indicating intratumoral hemorrhage. Intratumoral bleeding, referred to as a "vascular lake-like phenomenon" (arrows) was also observed. Tumor staining (is indicated by arrowheads).

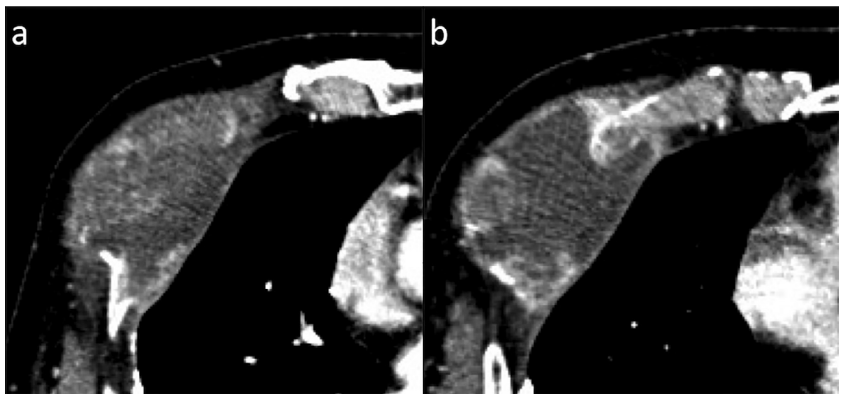

Fig. 3 – Thoracic CT after transcatheter hemostasis. Tumor staining had completely disappeared.

[3,4]. Uchida et al. [3] reported that 5 (7.4%) of 87 patients with unresectable HCC who were treated with lenvatinib developed intratumoral or intra-abdominal bleeding. Tumor hemorrhage has also been reported in patients with advanced thyroid cancer who received lenvatinib [6,7]. One case of intratumoral bleeding was reported in a patient with breast cancer treated with bevacizumab [8], while another report described intratumoral bleeding in a patient with colorectal cancer receiving bevacizumab [9]. Lenvatinib is a VEGF inhibitor and bevacizumab is a VEGF antibody. Both agents have anti-VEGF activity. Hence, it is possible that these anti-VEGF agents are involved in intratumoral hemorrhage.

Dynamic contrast-enhanced CT and angiography showed pooling of contrast material inside the tumor in this case. This contrast material pooling is similar to the vascular lakes occasionally observed during transarterial chemoembolization (TACE) for HCC, resembling tumor extravasation. This angiographic finding is termed as the "vascular lake phenomenon"

(VLP) or the "pooling phenomenon" [10–12]. In the context of the VLP caused by TACE, some authors have suggested that the rapid obstruction of blood flow in HCC might increase the pressure within the fragile tumor microvasculature, causing vascular rupture and blood leakage into the tumor [12]. According to a previous study, angiographic images of lenvatinib-induced tumor related hemorrhages resemble the VLP [3]. Uchida et al. [3] referred to the images of lenvatinib-induced tumor related hemorrhages as a "vascular lake-like phenomenon" [3]. The present case showed imaging findings similar to the "vascular lake-like phenomenon" (Fig. 1C). Therefore, we speculate that anti-VEGF agents trigger a "vascular lake-like phenomenon" similar to the VLP induced by TACE [12].

HCC is known to be prone to rupture, although rupture of metastases is quite rare. Particularly in the thoracic region, rupture and intratumoral hemorrhage have rarely been reported in metastatic HCC. Hemorrhage in HCC metastases in the chest often causes hemothorax [13], and is often associated with dyspnea, shock and pain. Additionally, HCC complicated with hemothorax has an unfavorable prognosis [13]. Transcatheter hemostasis has been reported to be effective in hemothorax associated with HCC metastasis in the thoracic region [13,14]. In this case, transcatheter hemostasis was performed before the intratumoral bleeding and tumor rupture led to the development of hemothorax. We believe that prompt TAE for intratumoral hemorrhage contributed to prevention of life-threatening events in this patient, thereby allowing subsequent continuation of the anticancer treatment.

Conclusion

The findings of this case suggest that careful attention should be paid to intratumoral hemorrhage or rupture in metastases of HCC during drug therapy, especially with MTAs and immune checkpoint inhibitors.

Patient consent

Written informed consent for publication of this case was obtained from the patient.

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