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CASE REPORT

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Lenvatinib-associated hemoperitoneum in a patient with primary angiosarcoma of the breast

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Key Clinical Message

We highlight the risk of lenvatinib drug toxicity when high-risk anatomic regions are affected by angiosarcoma.

KEYWORDS

angiosarcoma, embolization, hemoperitoneum, lenvatinib

1 | INTRODUCTION

Angiosarcoma is a rare and aggressive soft tissue sarcoma associated with a high risk of local recurrence and widespread metastasis.[1] Due to its increased vascularity, it is prone to spontaneous rupture. Lenvatinib is a multi-kinase inhibitor with anti-angiogenic effects used in treating various cancers like endometrial carcinoma, hepatocellular carcinoma, renal cell carcinoma, differentiated thyroid cancer, and advanced soft tissue sarcoma.[1,2] Common side effects associated with lenvatinib include elevated blood pressure, which occurs in hypertensive and non-hypertensive patients and may aggravate bleeding, proteinuria, diarrhea, hand-foot syndrome, thrombocytopenia, and delayed wound healing.[2] In addition to these, lenvatinib is associated with the occurrence of hemorrhagic events, including cerebral hemorrhage, intra-tumoral hemorrhage, and rupture of hepatocellular cancers.[3] In this report, we discuss a 32-year-old female with primary angiosarcoma of the breast with metastases to the liver complicated by hemoperitoneum while on lenvatinib.

2 | CASE PRESENTATION

A 32-year-old nursing mother with no significant medical history presented to urgent care with a 5-day history of subjective fever, chills, myalgia, swelling, and discomfort of her left breast, accompanied by an inability to express milk. She had been breastfeeding her 6-month-old son up until 1 month before her presentation when she stopped breastfeeding, due to inability to express milk. She had no previous surgeries, she never smoked cigarettes or drank alcohol, and her only daily medication was a multivitamin. She had no known family history of malignancy. Vitals on presentation were a temperature of 99F, blood pressure 142/89 mmHg, SpO_2 of 98% on room air, and heart rate

of 72 beats/min. She tested COVID-19 positive. Physical examination revealed a large area of firm left breast tissue encompassing the upper two-thirds of the breast without rash or visible erythema to the overlying skin. She was sent home with gynecology follow-up and recommendations for an ultrasound of the breast and a biopsy of the left breast mass.

3 | INVESTIGATIONS AND TREATMENT

She underwent an ultrasound-guided core biopsy of the left breast, which revealed tumor cells positive for CD31 and CD34, consistent with mammary angiosarcoma. She completed four cycles of doxorubicin 60 mg/m^2 every 21 days and ifosfamide 1500 mg/m^2 for 4 days every 21 days and underwent a mastectomy without axillary lymph node dissection. After completion of chemotherapy, she began targeted therapy with lenvatinib 20 mg daily as she was enrolled in an ongoing clinical trial. She presented to the emergency department 9 months after lenvatinib initiation with epigastric pain, nausea, and vomiting. Her vitals on presentation were temperature of 98.2 F, blood pressure 98/65 mmHg, heart rate 59 beats/min, and SpO_2 95% on room air. Physical exam was pertinent for generalized abdominal tenderness. Her laboratory values were white cell count of 11.4×10^9/L (normal range 3.5–10×10^9/L), Hgb of 9.5 g/dL (normal range 12–16 g/dL), platelets of 148×10^9/L (normal range 150–400×10^9/L). CT abdomen and pelvis (Figures 1–3) revealed a ruptured caudate lobe hepatic mass with hemoperitoneum requiring emergent embolization of the segment three hepatic artery (Figure 4).

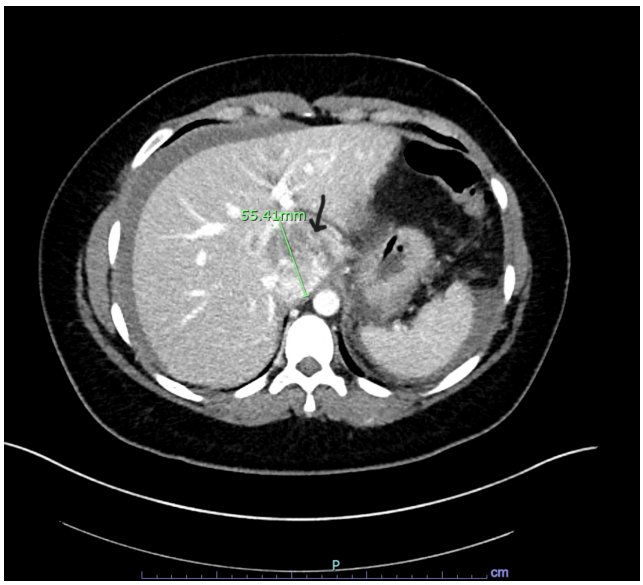

FIGURE 1 CT of the abdomen and pelvis with IV contrast: A large heterogeneously enhancing mass (black arrow) is centered in the caudate lobe, measuring approximately 5.5 cm. This mass appears to have ruptured with associated hemoperitoneum. Evaluation for active extravasation is somewhat limited on this single-phase scan; however, based on the appearance, active hemorrhage is suspected.

4 | OUTCOME AND FOLLOW-UP

Lenvatinib was discontinued upon discharge, and she was instructed to follow-up with her outpatient oncologist. She had no recurrence of bleeding, but due to disease progression in the form of an increased number of metastatic liver lesions, ascites, and deteriorating quality of life, she was transitioned to comfort care and hospice until she passed away.

5 | DISCUSSION

Angiosarcoma is a rare tumor that accounts for <1% of all sarcomas. The incidence of primary angiosarcoma in the breast is about 0.05%, and among all breast tumors, 0.1%–0.2%.[4,5] They are usually characterized by the presence of epithelial markers like pan-cytokeratin or endothelial markers such as CD31 and CD34 and are likely to hemorrhage due to frailty of the neovascular tissue.[6,7] With hepatocellular carcinoma, the likelihood of tumor hemorrhage is increased when it is in the caudate lobe as well as in Segments II, III, and VI of the liver. This is because the caudate lobe is thinner than other segments.[8] Furthermore, these segments have a relatively small room for the space-occupying lesions to expand, resulting in rupture when the tumor grows.[3,9] The caudate lobe was the location of our patient's tumor and could have contributed to her tumor rupture and hemoperitoneum. Other hypothesized mechanisms of hemorrhage include the increased expression of collagenase, proliferation of elastin, and breakdown of collagen fibrils in small arteries of the carcinomas, resulting in stiff and brittle vessels that rupture easily.[3,9] Another possible reason for hemorrhage is the invasion and occlusion of the hepatic vein, resulting in intra-tumoral hemorrhage.[3,9]

Lenvatinib is a multi-tyrosine kinase inhibitor developed as targeted therapy against the vascular endothelial growth factor receptor (VEGFR 1–3), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (KIT). These receptors play an essential role in tumor angiogenesis and the proliferation of cancer cells.[2] Inhibiting angiogenesis in cancerous cells causes the remaining poorly developed tumor micro-vessels to collapse easily.[3] As VEGF

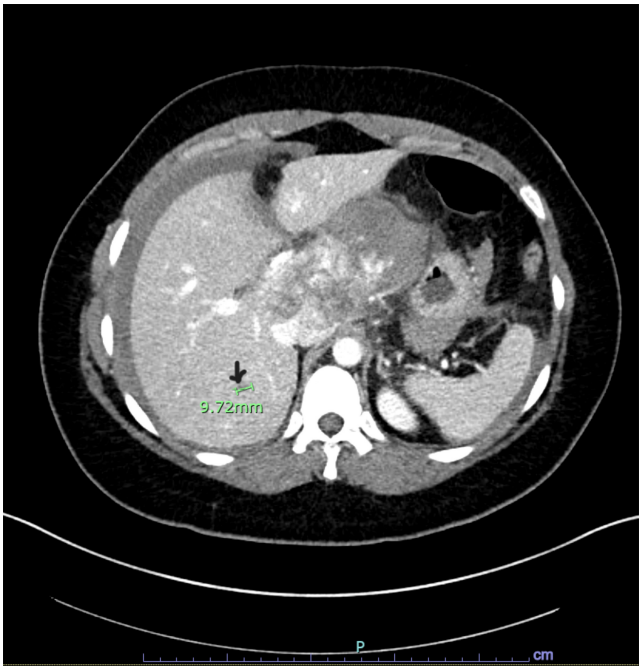

FIGURE 2 CT of the abdomen and pelvis with IV contrast: one (black arrow) of five heterogeneously enhancing hepatic lesions suspicious for metastases.

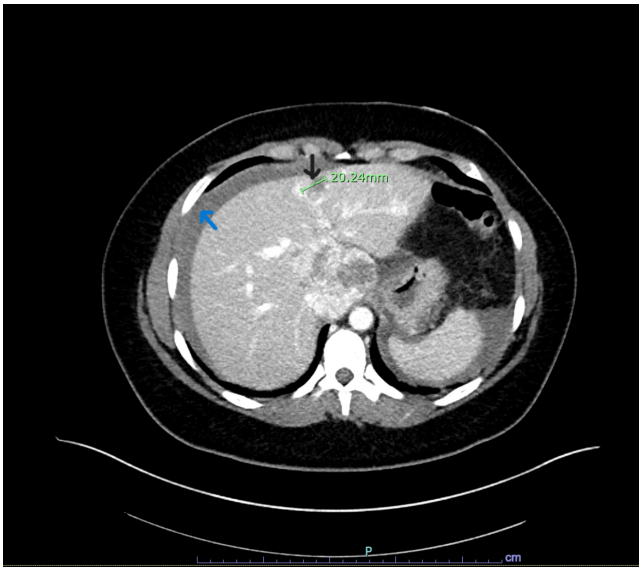

FIGURE 3 CT of the abdomen and pelvis with IV contrast: one (black arrow) of five heterogeneously enhancing hepatic lesions suspicious for metastases. The blue arrow points to the hemoperitoneum.

is important for the survival of endothelial cells and the maintenance of blood vessel integrity, inhibiting this pathway can reduce the regeneration potential of the damaged endothelial cells, increasing the risk of hemorrhagic events. The time to hemorrhagic event from lenvatinib initiation is typically between 3 and 93 days.[8,10] Lenvatinib

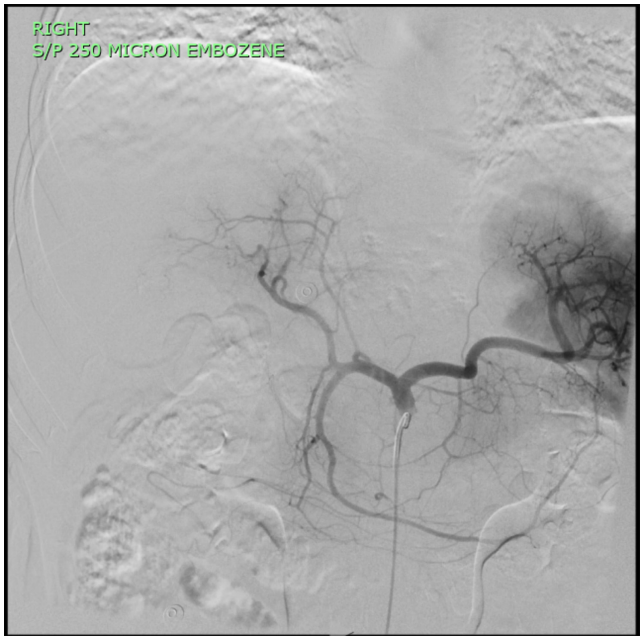

FIGURE 4 Post embolization angiogram with no further extravasation.

can also cause drug-induced disruption of circulatory development within the tumor, leading to tumor necrosis followed by hemorrhage.[3,8,10] Because bleeding can occur in regions where hemostasis is difficult to achieve, lenvatinib-exacerbated bleeding can be life-threatening. Other case reports have recommended drug interruption and dose modification or dose interruption. Identifying high-risk areas of bleeding, depending on the site of metastases, before administering tyrosine kinase inhibitors is recommended, together with close follow-up.

6 | CONCLUSION

Although other case reports[3,8,10] demonstrated lenvatinib-associated tumor rupture within 30 days of use, ours occurred 9 months after, showing that it could occur at any time during therapy, especially when the tumor is located in high-risk areas of the liver. In our patient, lenvatinib was used as secondary therapy after the failure of primary therapy because she was enrolled in an ongoing clinical trial[11] involving patients with rare angiosarcomas. As lenvatinib is not the standard treatment for breast cancer and much of the information we have on its use in angiosarcomas is from ongoing trials, it is possible that the rupture of the liver tumor could have been prevented if secondary standard treatment of mammary angiosarcoma had been used. It is essential to keep this side effect in mind as we find out more about the drug to ensure patient safety and prevent lethal outcomes.

AUTHOR CONTRIBUTIONS

Ijeoma Orabueze: Conceptualization; formal analysis; methodology; supervision; validation; writing – original draft; writing – review and editing. **Inemesit Akpan:** Conceptualization; validation; writing – original draft; writing – review and editing. **Ryan Denley:** Project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within this article. Raw Data that support the findings of the case are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This case report was conducted in accordance with the declaration of Helsinki. The collection and evaluation of all protected patient health information were performed in a health insurance portability accountability Act (HIPAA)-compliant manner.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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REFERENCES

1. Gaballah AH, Jensen CT, Palmquist S, et al. Angiosarcoma: clinical and imaging features from head to toe. *Br J Radiol*. 2017;90(1075):20170039.
2. Suyama K, Iwase H. Lenvatinib: a promising molecular targeted agent for multiple cancers. *Cancer Control*. 2018;25(1):1073274818789361.
3. Ishihara K. A case of multiple intratumoral hemorrhage and rupture of hepatocellular carcinoma after starting lenvatinib. *Case Reports Hepatol*. 2020;19:2020-2024.
4. Lee SW, Song CY, Gi YH, et al. Hepatic angiosarcoma manifested as recurrent hemoperitoneum. *World J Gastroenterol: WJG*. 2008;14(18):2935-2938.
5. John Hopkins University. Angiosarcoma of the Breast [Internet]. 2021 Accessed February 13, 2024. https://www.hopkinsmedicine.org/health/conditions-and-diseases/breast-cancer/angiosarcoma-of-the-breast
6. Bennani A, Chbani L, Lamchahab M, et al. Primary angiosarcoma of the breast: a case report. *Diagn Pathol*. 2013;8(1):1-5.
7. Bhaludin BN, Thway K, Adejolu M, et al. Imaging features of primary sites and metastatic patterns of angiosarcoma. *Insights Imaging*. 2021;12(1):1-8.
8. Sato A, Imai Y, Uchiya H, et al. Two cases of intraabdominal bleeding caused by hepatocellular carcinoma rupture soon after the initiation of chemotherapy with lenvatinib. *Intern Med*. 2022;61(15):2301-2305.
9. Li J, Huang L, Liu CF, et al. Risk factors and surgical outcomes for spontaneous rupture of BCLC stages a and B hepatocellular carcinoma: a case-control study. *World J Gastroenterol*. 2014;20(27):9121-9127. doi:10.3748/wjg.v20.i27.9121
10. Uchida-Kobayashi S, Kageyama K, Yamamoto A, et al. Lenvatinib-induced tumor-related hemorrhages in patients with large hepatocellular carcinomas. *Oncology*. 2021;99(3):186-191.
11. ClinicalTrials.gov [Internet], Movva S. National Library of Medicine (US). 2021-03-18. Identifier NCT04784247, Lenvatinib and Pembrolizumab in People With Advanced Soft Tissue Sarcoma. Accessed February 27, 2024. https://clinicaltrials.gov/study/NCT04784247

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