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Lenvatinib-Induced Intraparenchymal Hemorrhage in a Patient with Hepatocellular Carcinoma: A Case Report

Dr Abhishek Gote Senior Resident

Corresponding Author: Dr Danish H Memon Head of Department and Senior Consultant

Department of Medicine Noble Hospitals and Research Centre, Pune

Abstract

Background: Lenvatinib is an oral multikinase inhibitor targeting VEGFR, FGFR, PDGFR RET and KIT signaling pathways. It is widely used as first line systemic therapy in patients with unresectable hepatocellular carcinoma (HCC). Although generally well tolerated, anti-angiogenic therapy may predispose to hemorrhagic complications. Intracranial hemorrhage is an uncommon but potentially life-threatening adverse event.

Case Summary: A 61 year-old male with hepatocellular carcinoma receiving lenvatinib presented with altered mental status and confusion. Initial evaluation revealed hyponatremia and the patient was managed as metabolic encephalopathy. However, persistent neurological symptoms prompted MRI brain which demonstrated an acute intraparenchymal hemorrhage in the left frontoparietal region with surrounding edema. No alternative cause of coagulopathy or bleeding was identified.
Lenvatinib therapy was discontinued and the patient was managed conservatively with anti edema measures and supportive care.

Conclusion: Drug induced intracranial hemorrhage should be considered in patients receiving antiangiogenic therapy who present with unexplained neurological symptoms.

Keywords: Hepatocellular carcinoma, Lenvatinib, Intracranial hemorrhage, VEGF inhibitors, Targeted therapy complication

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer related mortality worldwide. For patients with unresectable disease, systemic targeted therapies have significantly improved survival outcomes. Lenvatinib is a multikinase inhibitor that suppresses tumor angiogenesis by blocking vascular endothelial growth factor receptors and fibroblast growth factor receptors. By inhibiting angiogenesis, lenvatinib limits tumor vascularization and proliferation.

However, antiangiogenic therapy may impair vascular integrity and increase the risk of bleeding complications. Hemorrhagic events have been reported with VEGF inhibitors, though intracranial hemorrhage remains rare. Early recognition is essential as delayed diagnosis can result in severe neurological complications.

Case Presentation

A 61 year old male presented with acute onset altered mental status characterized by confusion and disorientation. He was a known case of hepatocellular carcinoma receiving systemic therapy with lenvatinib. His medical history included type 2 diabetes mellitus and coronary artery disease status post coronary artery bypass grafting. He was on single antiplatelet therapy and had reduced left ventricular ejection fraction.

On examination, the patient was drowsy but arousable with a Glasgow Coma Scale score of 12/15 (E3V4M5). He was disoriented to time and place. Vital parameters were stable and pupils were equal and reactive to light. No focal neurological deficit was detected initially.

Laboratory investigations showed hyponatremia while other parameters including complete blood count, renal function, liver function tests and coagulation profile were within normal limits. The patient was initially managed as metabolic encephalopathy with sodium correction and antiepileptic therapy. Despite adequate correction, the patient continued to remain confused and disoriented.

Imaging Findings

Neurology consultation was obtained and MRI brain with contrast was performed to exclude intracranial metastasis. Imaging revealed an acute intraparenchymal hemorrhage in the left frontoparietal region with surrounding edema on T2/FLAIR sequences. No evidence of metastatic lesions or vascular malformations was seen.

Figure 1: DWI sequence showing intraparenchymal hemorrhage in the left frontoparietal region.
Figure 2: FLAIR sequence showing intraparenchymal hemorrhage with surrounding edema.

Management

Considering the absence of other identifiable causes and the temporal relationship with lenvatinib therapy, the intracranial hemorrhage was suspected to be drug related. Lenvatinib was discontinued and the patient was managed conservatively with anti edema therapy, neurological monitoring and supportive measures.

Discussion

Antiangiogenic agents such as lenvatinib inhibit VEGF signaling pathways and reduce tumor vascularization. However, inhibition of angiogenesis can compromise vascular stability and predispose to bleeding complications. Intracranial hemorrhage remains an uncommon adverse effect but may occur particularly in patients with underlying vascular risk factors.

This case highlights the importance of maintaining a high index of suspicion for drug induced hemorrhage in patients receiving targeted therapy who present with unexplained neurological symptoms. Early neuroimaging and prompt discontinuation of the offending agent are critical for optimal outcomes.

Discussion

Lenvatinib is an oral multikinase inhibitor that targets several receptor tyrosine kinases involved in tumor angiogenesis and proliferation, including vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), fibroblast growth factor receptors (FGFR-1–4), platelet-derived growth factor receptor-α (PDGFR-α), RET, and KIT. By inhibiting these pathways, lenvatinib suppresses tumor angiogenesis and has demonstrated significant clinical efficacy in patients with unresectable hepatocellular carcinoma (HCC) (**1,2**).

The pivotal REFLECT trial established lenvatinib as a first-line systemic therapy for advanced HCC, demonstrating non-inferiority to sorafenib with improved progression- free survival and objective response rates (**1**). However, anti-angiogenic therapies including lenvatinib are associated with several vascular adverse effects such as hypertension, thromboembolic events, and hemorrhagic complications (**3**).

Hemorrhagic events associated with VEGF inhibition occur primarily due to disruption of vascular endothelial integrity. VEGF signaling plays a crucial role in maintaining endothelial cell survival, vascular stability, and repair mechanisms. Inhibition of VEGF pathways can result in endothelial dysfunction, increased vascular fragility, and impaired repair of microvascular injury, thereby predisposing patients to bleeding complications (**3**). Additionally, inhibition of FGFR signaling may contribute to impaired vascular remodeling and endothelial repair processes.

Clinical trials evaluating lenvatinib have reported hemorrhagic events in approximately 5–10% of patients, although most events are minor mucocutaneous bleeds such as epistaxis or gingival bleeding (**1,2**). Major hemorrhagic complications are less frequent but have been reported, including gastrointestinal bleeding, tumor-associated hemorrhage, and rarely intracranial hemorrhage (**4**). Intracranial hemorrhage represents a particularly serious complication because of its association with high morbidity and mortality.

Several mechanisms may contribute to intracranial hemorrhage in patients receiving lenvatinib. Chronic inhibition of VEGF signaling may lead to endothelial injury and weakening of cerebral microvasculature. Furthermore, anti-angiogenic therapy may impair vascular autoregulation and induce systemic hypertension, which is a recognized risk factor for spontaneous intracerebral hemorrhage (**3**). In addition, cancer-related factors such as underlying liver dysfunction in HCC, thrombocytopenia, coagulopathy, and concomitant medications including antiplatelet agents may further increase bleeding risk.

Discussion

In the present case, the patient had multiple comorbidities including diabetes mellitus, ischemic heart disease with prior coronary artery bypass grafting, and was receiving single antiplatelet therapy. However, detailed evaluation did not reveal any evidence of coagulopathy, vascular malformation, or intracranial metastatic lesion. The temporal relationship between lenvatinib therapy and the development of intracerebral hemorrhage, combined with the absence of alternative etiologies, suggests a probable association with lenvatinib-induced vascular injury.

Another important aspect of this case was the diagnostic challenge posed by concomitant hyponatremia at presentation, which initially led to management as metabolic encephalopathy. Persistent neurological symptoms despite adequate electrolyte correction prompted further evaluation with neuroimaging, which ultimately revealed the intracerebral hemorrhage. This emphasizes the importance of maintaining a broad differential diagnosis in patients with malignancy presenting with altered mental status, particularly those receiving targeted therapies.

Management of lenvatinib-associated hemorrhage primarily involves prompt discontinuation of the offending drug along with supportive care. In cases of intracranial hemorrhage without significant mass effect or neurological deterioration, conservative management with anti-edema measures, blood pressure control, and close neurological monitoring may be sufficient (**4**). Early neuroimaging plays a crucial role in timely diagnosis and appropriate management.

This case highlights a rare but clinically significant complication of lenvatinib therapy. Clinicians should maintain a high index of suspicion for intracranial hemorrhage in patients receiving anti-angiogenic therapy who present with persistent altered sensorium or new neurological symptoms. Early recognition, prompt neuroimaging, and multidisciplinary management are essential to improve patient outcomes

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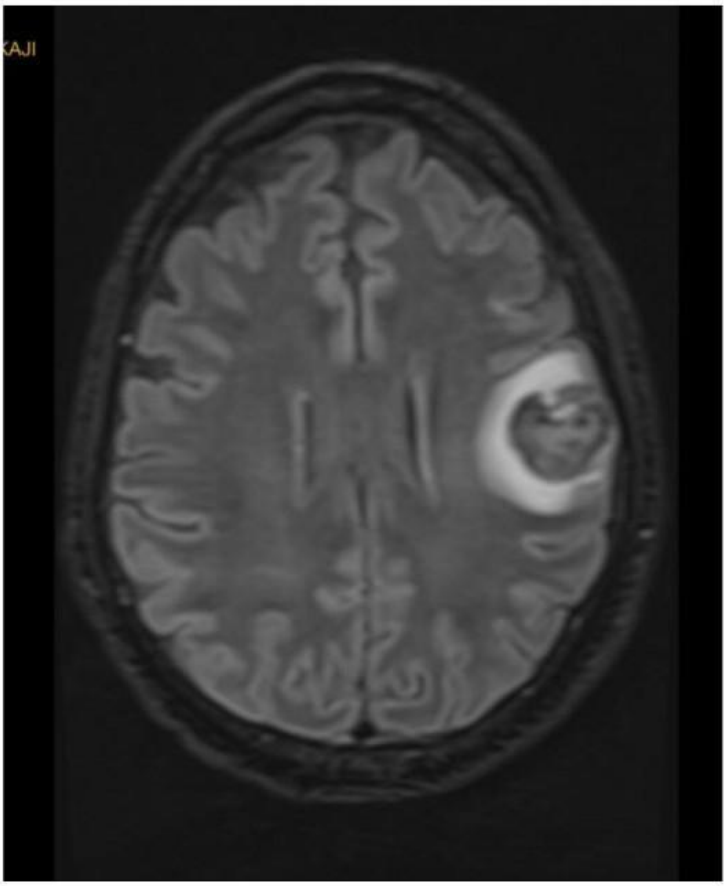
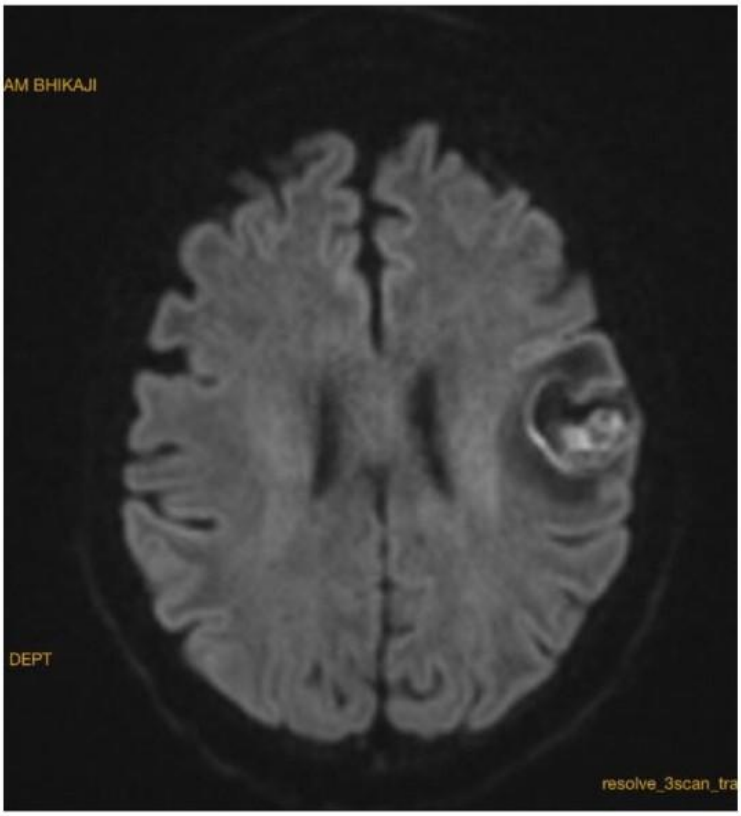


FLAIR sequence showing intraparenchymal hemorrhage with surrounding edema.



DWI sequence showing intraparenchymal hemorrhage in the left frontoparietal region.

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