ACCSCIENCE PUBLISHING

Innovative Medicines & Omics

CASE REPORT

Rare subdural hematoma in a patient treated with avapritinib for gastrointestinal stromal tumor: A case report

Syed M. Imam[1], Faryal Haider[2], Rafiq J. Baksh[3], and Syed A. A. Rizvi[4,5]*

[1]HCA Northside Hospital, USF Morsani College of Medicine, St Petersburg, Florida, United States of America

[2]The Wright Center for Graduate Medical Education, Scranton, Pennsylvania, United States of America

[3]Maimonides Midwood Community Hospital, Brooklyn, New York, United States of America

[4]College of Biomedical Sciences, Larkin University, Miami, Florida, United States of America

[5]Division of Clinical and Translational Research, Larkin Community Hospital, Miami, Florida, United States of America

Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal malignancy of the digestive tract, accounting for 1% of all digestive tract malignancies. GISTs occur most frequently in the stomach, followed by the small intestine and colorectum, and rarely in the mesentery, omentum, and retroperitoneum. Avapritinib's approval for GISTs in 2020 marks a milestone in precision oncology, showing its significant antitumor activity against the resistant platelet-derived growth factor receptor-alpha D842V mutation. It has a manageable safety profile, with dose adjustments for mitigating side effects without reducing efficacy. Avapritinib-induced subdural hematomas are rare but potentially lethal complications. Our patient had a metastatic small bowel GIST and liver metastases and began avapritinib treatment in January 2024. He had a stable condition until early May. He presented with acute encephalopathy, altered mentation, and left subdural hematoma, which was suspected to be caused by avapritinib, resulting in its discontinuation. Despite receiving diligent care, the patient's condition did not improve, and he eventually died.

Keywords: Gastrointestinal stromal tumors; Chemotherapeutics; Novel targets; Side effects; Subdural hematomas

***Corresponding author:**
Syed A. A. Rizvi
(srizvi@larkin.edu; srizvi@larkinhospital.com)

Citation: Imam SM, Haider F, Baksh RJ, Rizvi SAA. Rare subdural hematoma in a patient treated with Avapritinib for gastrointestinal stromal tumor: A case report. *Innov Med Omics*. 2025;2(1):93-97.
doi: 10.36922/imo.7068

Received: October 8, 2024
Revised: December 5, 2024
Accepted: December 20, 2024
Published online: January 9, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Metastatic small bowel gastrointestinal stromal tumors (GISTs) are rare (5 – 20 cases/million) but highly aggressive malignancies originating from the soft tissues supporting the digestive system, particularly the small intestine. They originate from the interstitial cells of Cajal, which regulate gut peristalsis.[1] Until recently, metastatic small bowel GISTs were usually diagnosed at a very advanced disease stage, when the cancer had spread to other organs such as the liver, lungs, or peritoneum. Traditional treatments

for GISTs include surgery, radiation therapy, and targeted drug therapy with imatinib and sunitinib. Surgery might be performed to remove the primary tumor and any associated regional lymph nodes. Chemotherapy and targeted therapy aim to slow tumor growth and shrink the tumor by applying drugs targeting cancerous cells.[2] However, some patients are resistant to these treatments, whereas others experience severe side effects. This has led to the exploration of new treatment options, including a highly selective inhibitor of mutated forms of two proteins-receptor tyrosine kinase type III (KIT) and platelet-derived growth factor receptor-alpha (PDGFRA) commonly found in GISTs.[3]

A recent clinical trial showed promising results for avapritinib in treating GISTs (Figure 1).[4] Avapritinib demonstrated a high response rate and prolonged progression-free survival in a phase 1 trial involving patients with advanced GIST who had undergone unsuccessful treatments.[5] The drug revealed a good safety profile with manageable side effects. These findings have translated into the FDA approval of avapritinib to treat GISTs, presenting new hope for patients with minimal treatment options.[6] The overall prognosis for patients with metastatic small bowel GISTs is generally poor, with a 5-year survival rate of 15% – 20%. The emergence of various treatment modalities has thus far improved outcomes in selected subsets of patients and includes novel targeted therapies, immunotherapies, and combination therapies. Ongoing studies into new treatment strategies and methods for early detection are being pursued to improve the survival and quality of life of patients with metastatic small bowel GISTs.[7] A significant safety concern associated with avapritinib is the risk of intracranial hemorrhage (ICH), including subdural hematomas (SDH). Although these events are uncommon in clinical trials, they affect approximately 2.4% of patients receiving a starting dose of 300 mg. Patients with severe thrombocytopenia (platelet counts $<50 \times 10^9$/L) at baseline are at an increased risk of complications linked to mast cell infiltration in the bone marrow. This association was observed during clinical trials of avapritinib in individuals with advanced systemic mastocytosis.[8] All cases of intracranial bleeding (ICB) were directly attributed to the treatment; however, the risk is significant enough to warrant caution, particularly in patients predisposed to bleeding because of thrombocytopenia, anticoagulant use, or previous vascular events.[9] Thus, close monitoring of the platelet count is essential before and during treatment. ICH symptoms, such as headache, nausea, vision changes, or altered mental status, require immediate medical attention. Dose adjustments or treatment discontinuation may be necessary in patients with severe adverse effects.[10]

2. Case presentation

A 66-year-old man with a history of GIST presented (in early May 2024) to the emergency room along with his wife with complaints of worsening altered mental status, confusion, gait changes, and global weakness. They denied any occurrence of recent trauma or falls. However, the patient has had multiple "near falls." In early 2019, he was diagnosed with a small bowel GIST with metastases to the liver – grade 1, pT3 pNX pM1 (liver), stage IV. Imatinib was initiated at diagnosis in February 2019. Disease progression was monitored closely. In December 2020, next-generation sequencing revealed two KIT mutations, one in exon 17 and the other in exon 9, and <1% programmed death ligand 1 mutations. In February 2021, regorafenib was initiated as a second-line treatment. Unfortunately, the disease progressed further, and various therapies were used. Sutent was initiated in April 2021, ripretinib in January 2022, Y90 therapy to a part of the liver in July 2022, Cabometyx in November 2022, and Avapritinib at the end of January 2024. While being treated with avapritinib (300 mg), the patient presented with periorbital edema (known side effect of Avapritinib) and some new papules on his bilateral lower extremities, particularly along the feet. Thus, in April 2024, the avapritinib dose was reduced to 200 mg.

The wife reported that the patient had worsening altered mental status in the past few days and believed that it was caused by his medication, which the patient had weaned and subsequently stopped earlier this week. His mental status has still not improved, and he has had an unsteady gait. At present, although he is fully oriented, his wife reported episodes of the patient getting dressed at home and not knowing where he was going. The patient believed that the reason for the visit was abdominal pain (right upper quadrant). He had a fever and vomiting (non-bloody and non-bilious). The patient denied the presence of skin infections, acute changes in hearing or vision, unilateral weakness or paresthesia or vision loss, chest pain, shortness of breath, cough, falls, seizures, drug or alcohol use, dysuria, and changes in urinary frequency.

The patient reported imbalance and confusion. Differential diagnosis included medication side effects; however, even after stopping the drug, his symptoms persisted. He did not exhibit focal symptoms; however, given his history, the plan was to obtain a computed tomography (CT) of the head to detect ICH or mass. The laboratory results were inconsistent with toxic metabolic etiologies such as electrolyte disturbances, hypoglycemia, uremia, acidosis states, and infection (i.e., sepsis). History examinations were performed, and toxidromes of intoxication or withdrawal, hypoxemia or hypercarbia, liver disease or liver failure causing

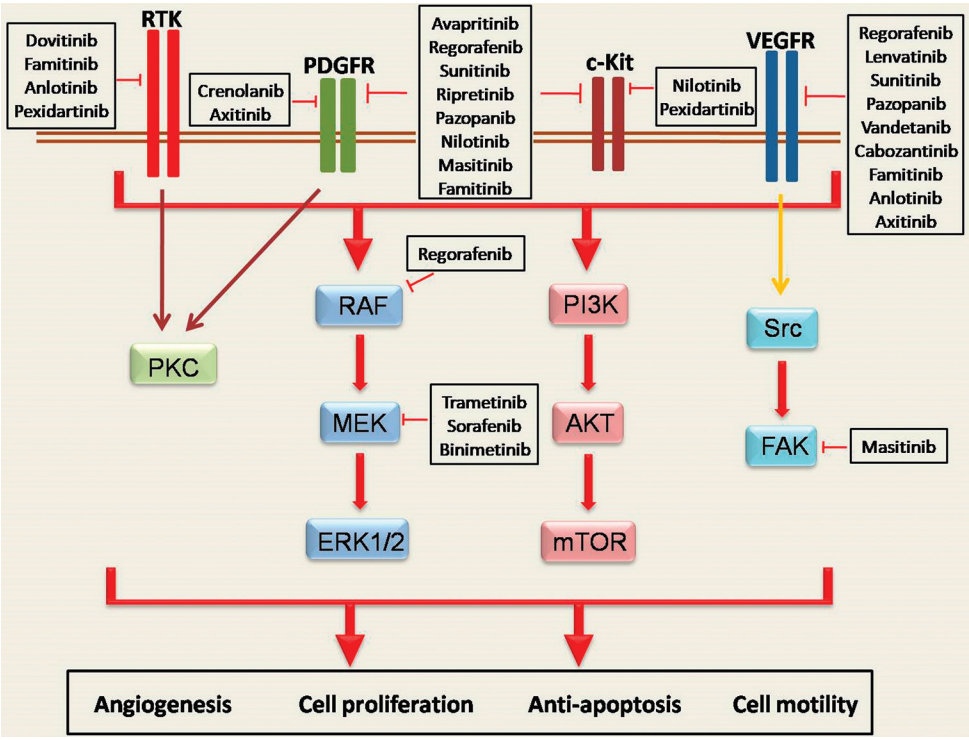

Figure 1. Role of receptors in the activation of signaling pathways in gastrointestinal stromal tumors. Reproduced from Vallilas *et al.*[4]
Abbreviations: RTK: Receptor tyrosine kinase; PDGFRA: Platelet-derived growth factor receptor a; c-Kit: Cellular Kit; VEGFR: Vascular endothelial growth factor receptor; RAF: Rapidly accelerated fibrosarcoma; MEK: Mitogen-activated protein kinase kinase; ERK ½: Extracellular signal-regulated kinase 1 and 2; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase b; mTOR: Mechanistic target of Rapamycin; Src: Sarcoma; FAK: Focal adhesion kinase.

hepatic encephalopathy, endocrine emergencies (hyper/hypothyroidism and adrenal insufficiency), seizures, and trauma were considered less likely.

Head CT (Figure 2) revealed a large SDH (up to 18 mm thick) overlying the left cerebral convexity, resulting in a 15-mm left-to-right shunt of midline structures and a trapped/dilated right lateral ventricle. Global sulcal effacement and uncal herniation with mild mass effect on the brainstem were noted. No evidence of a large transcortical infarct or acute bony abnormality was found. In the abdominal/pelvic examination, similar-appearing liver metastases and small nodules or lymph nodes in the lower mesentery were detected. No bowel obstruction, abscess, free gas, diverticulitis, or appendicitis was noted. Scattered sclerotic skeletal lesions indicated metastasis.

After CT, the neurosurgeon was consulted, and following a detailed discussion, the patient expressed verbal understanding, consented, and wished to proceed with a left burr hole washout (Figure 3). After the removal of the left scalp JP drain, the patient was cleared for discharge by neurosurgery to follow-up with them in 2 weeks with head CT. Acute metabolic encephalopathy secondary to SDH significantly improved, and the patient

Figure 2. Non-contrasted computed tomography of the head showing left subdural hematoma, with rightward midline shift and enlargement of the right ventricular system, and effacement of ambient cisterns with uncal herniation.

was discharged in a stable clinical condition. Oncology recommended discontinuing the current chemotherapy (Avapritinib) because of the recent SDH development. This is reported as a severe and infrequent side effect of avapritnib. Avapritinib was not resumed, and the patient

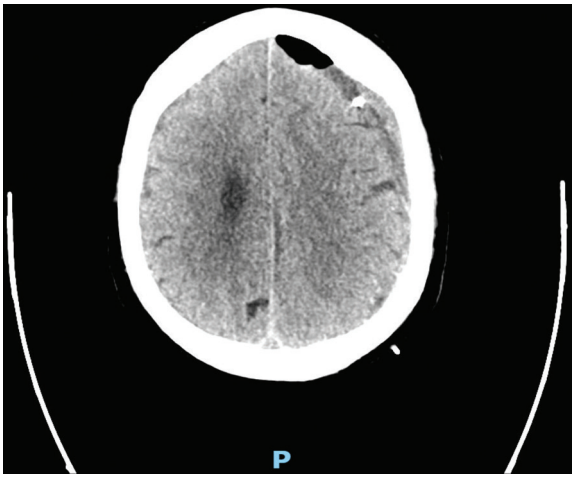

Figure 3. Repeat computed tomography post-surgery showing an overall decrease in the subdural collection volume, midline shift, and prominence of the ventricular system.

was planned for follow-up in the clinic in 2 – 4 weeks to discuss future management of metastatic GISTs.

The patient came back to the emergency department a few days later because he had not been eating and drinking and was progressively weak with a fever. A CT image of the head showed an increase in the low-attenuation component of the left SDH with an increase in sulcal effacement, left lateral ventricle effacement, and midline shift. The hyperdense hemorrhagic component appeared unchanged. The patient was admitted to the intensive care unit, with stable hemodynamics; however, he was increasingly somnolent. His encephalopathy continued to worsen. A component of metabolic encephalopathy was not suspected, although toxic encephalopathy/underlying bacterial infection could play a role. No hypoxia, uremia, or significant glucose abnormalities were noted. The patient's condition continued to decline despite repeat washout and antibiotic therapy. According to the patient and his wife's desire, the decision was to pursue comfort measures only. He was transferred to a palliative care unit and died a few days later.

3. Discussion

Avapritinib is a targeted therapy primarily used to treat GISTs. It is extremely effective for patients with PDGFRA exon 18 mutation, including D842V mutation, which is resistant to other treatments.[11] Avapritinib is also used to treat advanced systemic mastocytosis, a rare disorder that involves abnormal mast cell accumulation.[12] Avapritinib, a tyrosine kinase inhibitor, blocks proteins driving cancer growth, particularly in PDGFRA- and KIT-mutant tumors. Common side effects include fatigue, nausea, diarrhea, swelling around the eyes, cognitive impairment, and decreased appetite. ICH, anemia, liver toxicity, and memory issues are some of the rare but severe side effects. Avapritinib is a vital treatment option for patients with specific mutations but requires careful monitoring because of its potentially serious side effects.[13]

ICH is a severe side effect of avapritinib. ICH signs include severe headaches, dizziness, nausea, vomiting, neurological issues, and altered consciousness. Patients with hypertension and blood clotting disorders or those on anticoagulants may have a higher risk of ICH. Immediate interventions, including stopping avapritinib and providing emergency care, are necessary. Regular brain imaging and blood tests are recommended for patients on this treatment, especially if they have higher bleeding risks.[14]

4. Conclusion

This case highlights the rare but severe potential drug-related complication of SDH occurring in a patient treated with avapritnib for GISTs, without other known contributing factors. Such an adverse event underscores the importance of careful monitoring of neurological symptoms in patients receiving targeted therapies. Clinicians should remain vigilant regarding potential bleeding complications, particularly in patients with pre-existing risk factors. This case reinforces the need for further research to enhance the understanding of the relationship between avapritnib and hematological risks, improve patient outcomes, and determine the most optimal treatment protocols.

Acknowledgments

None.

Funding

None.

Conflict of interest

Syed A. A. Rizvi is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Syed M. Imam
Investigation: Syed M. Imam
Methodology: Syed M. Imam, Faryal Haider
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Patient gave consent to participate in this study.

Consent for publication

Verbal consent has been obtained from the patient to publish his data.

Availability of data

Not applicable.

References

1. Suresh Babu MC, Chaudhuri T, Babu KG, *et al*. Metastatic gastrointestinal stromal tumor: A regional cancer center experience of 44 cases. *South Asian J Cancer*. 2017;6(3):118-121.

   doi: 10.4103/sajc.sajc_290_16

2. Ahmed M. Recent advances in the management of gastrointestinal stromal tumor. *World J Clin Cases*. 2020;8(15):3142-3155.

   doi: 10.12998/wjcc.v8.i15.3142

3. Teuber A, Schulz T, Fletcher BS, *et al*. Avapritinib-based SAR studies unveil a binding pocket in KIT and PDGFRA. *Nat Commun*. 2024;15(1):63.

   doi: 10.1038/s41467-023-44376-8

4. Vallilas C, Sarantis P, Kyriazoglou A, *et al*. Gastrointestinal stromal tumors (GISTs): Novel therapeutic strategies with immunotherapy and small molecules. *Int J Mol Sci*. 2021;22(2):493.

   doi: 10.3390/ijms22020493

5. Cao L, Tian W, Zhao Y, *et al*. Gene mutations in gastrointestinal stromal tumors: Advances in treatment and mechanism research. *Glob Med Genet*. 2024;11(4):251-262.

   doi: 10.1055/s-0044-1789204

6. Jones RL, Serrano C, von Mehren M, *et al*. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial. *Eur J Cancer*. 2021;145:132-142.

   doi: 10.1016/j.ejca.2020.12.008

7. Zhang H, Liu Q. Prognostic indicators for gastrointestinal stromal tumors: A review. *Transl Oncol*. 2020;13(10):100812.

   doi: 10.1016/j.tranon.2020.100812

8. Reiter A, Schwaab J, DeAngelo DJ, *et al*. Efficacy and safety of Avapritinib in previously treated patients with advanced systemic mastocytosis. *Blood Adv*. 2022;6(21):5750-5762.

   doi: 10.1182/bloodadvances.2022007539

9. Joseph CP, Abaricia SN, Angelis MA, *et al*. Optimal avapritinib treatment strategies for patients with metastatic or unresectable gastrointestinal stromal tumors. *Oncologist*. 2021;26(4):e622-e631.

   doi: 10.1002/onco.13632

10. George S, Jones RL, Bauer S, *et al*. Avapritinib in patients with advanced gastrointestinal stromal tumors following at least three prior lines of therapy. *Oncologist*. 2021;26(4):e639-e649.

    doi: 10.1002/onco.13674

11. Li J, Zhang X, Deng Y, *et al*. Efficacy and safety of avapritinib in treating unresectable or metastatic gastrointestinal stromal tumors: A phase I/II, open-label, multicenter study. *Oncologist*. 2023;28(2):187-e114.

    doi: 10.1093/oncolo/oyac242

12. Gotlib J, Castells M, Elberink HO, *et al*. Avapritinib versus placebo in indolent systemic mastocytosis. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

    doi: 10.1056/EVIDoa2200339

13. Hossain M, Habib I, Singha K, Kumar A. FDA-approved heterocyclic molecules for cancer treatment: Synthesis, dosage, mechanism of action and their adverse effect. *Heliyon*. 2023;10(1):e23172.

    doi: 10.1016/j.heliyon.2023.e23172

14. Rong L, Xie M, Jiang M, Qiu H, Kong L. A post-marketing pharmacovigilance study of Avapritinib: Adverse event data mining and analysis based on the United States Food and drug administration adverse event reporting system database. *Br J Clin Pharmacol*. 2024;90(8):1816-1826.

    doi: 10.1111/bcp.15673