Gliomagenesis following chronic subdural hematoma: A case report

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Received September 20, 2024; Accepted April 9, 2025

DOI: 10.3892/etm.2025.12889

Abstract. The occurrence of subdural hematoma following brain tumor surgery is rare, with glioma-associated subdural hematoma only sporadically documented in the literature. However, to the best of our knowledge, reports of the occurrence of gliomagenesis following subdural hematoma have remained scarce. The present study delineates a case of left frontal gliomagenesis that developed within a brief period following the occurrence of a subdural hematoma in the left frontal and temporal lobes. Specifically, a 62-year-old male patient with a 7-month history of subdural hematoma presented with a large solid-occupying lesion centered in the left frontal lobe. Histological examination revealed the lesion to be a diffuse glioma. The patient exhibited a favorable recovery subsequent to the evacuation of the subdural hematoma and administration of routine medication. However, a neighboring brain tumor developed rapidly 5 months later, which was excised by surgical intervention and submitted for pathological examination. The results demonstrated that the tumor was a grade IV glioma. Conventional radiotherapy for glioma was then administered to the patient. Given the tumor's aggressive profile, the patient remains at elevated risk for recurrence and metastasis. At the 1-month postoperative evaluation, the patient was clinically stable with maintained independence in activities of daily living (ADLs), including household chores. The presented case report offers a potential indication of a causal relationship between subdural hematoma and gliomagenesis. It is plausible that subdural hematoma may be a contributing factor in the formation or rapid growth of glioma.

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Key words: subdural hematoma, glioma, gliomagenesis, astrocyte, neutrophil

Introduction

Chronic subdural hematoma (CSDH) represents a prevalent neurosurgical condition in the geriatric population, with annual incidence rates ranging from 1.0 to 13.1 per 100,000 individuals (1), exhibiting a predilection for patients over 65 years of age (2). Epidemiological studies document a rising global incidence trend, attributed to expanding indications for antithrombotic therapies and age-related traumatic mechanisms (3). Burr hole drainage (BHD) constitutes the standard neurosurgical intervention for uncomplicated CSDH, while craniotomy with membranectomy is reserved for cases with septated hematoma or recurrence after initial drainage (4). CSDH is a benign disease, but it frequently has an unfavorable prognosis due to its high recurrence rate. In adults, glioma is the most common brain malignancy, accounting for ~30% of all central nervous system tumors (5,6). Gliomas represent the most prevalent tumors of the central nervous system, constituting 80% of all malignant primary brain neoplasms (7). Among these, glioblastoma multiforme (GBM) is particularly notable, with a global incidence rate of 5 to 8 cases per 100,000 individuals (6). Despite significant advancements in the development of novel anti-tumor therapeutics, GBM persists as the most aggressive primary CNS malignancy, maintaining an exceptionally dismal prognosis characterized by a median overall survival duration of merely 12-15 months post-diagnosis (6,8). Chronic subdural hematomas and cerebral neoplasms constitute major intracranial pathologies in the geriatric population (6,9). Subdural hematoma following brain tumor surgery is an infrequent occurrence, where glioma-associated subdural hematoma has been sporadically documented (10-12). However, to the best of our knowledge, there is a paucity of literature on gliomagenesis following subdural hematoma. Therefore, in the present report, the case of a patient who developed a glioma subsequent to a subdural hematoma is documented. The anatomic colocalization and temporal proximity of these disease entities raise the hypothesis of a potential etiopathogenic link between chronic subdural hematomas and subsequent gliomagenesis.

Case report

A 62-year-old male with a history of lower extremity deep vein thrombosis underwent long-term anticoagulation therapy with

oral rivaroxaban at a maintenance dosage of 10 mg once daily over a 5-year period. However, the patient began experiencing symptoms of headaches in April 2023, which led to the cessation of rivaroxaban treatment. The patient presented to Beijing Tiantan Hospital, Capital Medical University (Beijing, China), for comprehensive diagnostic evaluation to assess disease progression and therapeutic efficacy in April 2023. A CT scan of the head revealed the presence of a chronic subdural hematoma on the left side of the head. Conservative management with the oral medication Lipitor (atorvastatin) 10 mg daily administered for one month was implemented, but proved ineffective, as the patient's intermittent headaches demonstrated progressive clinical deterioration. In June 2023, the patient exhibited gait instability and speech disfluency. A re-examination of the head CT scan at the same hospital revealed that the size of the left frontotemporal parietal subdural hematoma had increased in size, with the maximum thickness demonstrating an interval growth of 4-5 mm. Subsequently, a left parietal drilling and drainage procedure was performed at the Beijing Tiantan Hospital of Capital Medical University (Fig. 1A), postoperative imaging demonstrated resolution of subcranial abnormal density shadows and decreased midline deviation. A CT scan of the head conducted on day 4 following surgery revealed the presence of a left frontotemporal parietal subdural hematoma, in addition to evidence of drilling and drainage in the left parietal region. A cerebral herniation phenomenon was also observed (Fig. 1B). At 4 days after surgery, a subdural hematoma remained. The postoperative examination revealed no significant abnormality and the incision had healed to the expected standard (grade A). The sutures were removed at the conclusion of the healing process, and the patient was discharged from the hospital for observation, and a course of traditional Chinese medicine was initiated. The patient commenced treatment with a Chinese medicine practitioner at the same hospital from the day of discharge, who prescribed a course of Chinese medicinal remedies to facilitate the reduction in size of the subdural hematoma. The herbal remedies this patient was administered included the following: 20 g *Leonurus artemisia* Sweet, 9 g Semen persicae, 5 g Hirudo, 9 g Flos carthami and 20 g *Atractylodes macrocephala* Koidz. The duration of this prescription was 28 days, with a single dose administered in the morning and evening. The traditional Chinese medicine therapeutic drug combination utilized in the treatment of this patient is protected by a patent (designated patent no. ZL 2022 1 1276741.3). Following the completion of the initial prescription, the patient continued pharmacological therapy with the following formulation for 30 consecutive days via twice daily administration (morning and evening doses): 30 g *Leonurus artemisia* Sweet, 9 g Semen persicae, 5 g Hirudo, 9 g Flos carthami and 3 g *Notoginseng* Radix Et Rhizoma. Following 58 days of traditional Chinese medicine, a head CT scan at the same hospital revealed that the subdural hematoma had diminished in size, suggesting it had undergone slight absorption. Physical examination revealed no neurological deficits, and the patient reported complete resolution of cephalalgia symptoms.

In September 2023, the patient developed a hypertensive crisis manifesting as severe blood pressure elevation (systolic 208 mmHg/diastolic 116 mmHg). The CT scan revealed a notable reduction in the chronic subdural hematoma in the left frontotemporal parietal lobe, accompanied by a suspected slight increase in the density of the left frontal gyrus (Fig. 1C). Further observation was therefore conducted. In November 2023, the patient presented with symptoms suggestive of the recurrence of the subdural hematoma, including a 1-h headache. Consequently, the patient was promptly transferred to the Emergency Department Beijing Tiantan Hospital for a CT scan of the head. The scan revealed the presence of clumps and mixed high-density shadows in the left frontal lobe, accompanied by peripheral flaccid oedema, suspected hemorrhagic lesions and cerebral herniation (Fig. 2A). The following day, the patient underwent a routine examination and MRI of the head at the same hospital. The MRI results revealed a high-grade glioma in the left frontal lobe (Fig. 2B and C). Specifically, the patient exhibited left frontal lobe occupancy for a brief period, accompanied by compression and deformation of the ventricles, right deviation of the midline and substantial enhancement of the enhancement scans, manifesting as a wreath measuring ~50x55x48 mm. The necrotic areas were characterized by a mixture of solid portions and uneven signals. The presence of irregular thick ring-like enhancements (Fig. 2B and C), indicative of a necrotic core accompanied by a peripheral enhancement band, is a hallmark feature of high-grade glioma (5). These necrotic areas were intermingled with old hemorrhage, where the absence of a discernible cystic wall structure following enhancement was notable (Fig. 2B and C). MRI revealed an abnormal mass of signals in the left frontal lobe. The lesion exhibited marked enhancement on the subsequent enhancement scan and was surrounded by a substantial Fluid attenuated inversion recovery (FLAIR) high-signal shadow. This abnormality involved the left parietal lobe, basal ganglia and corpus callosum, accompanied by local narrowing of the sulcus fissure, deformation of the bilateral ventricles by compression and a rightward shift of the midline. Necrotic areas were characterized by a mixture of solid portions and uneven signals. The presence of irregular thick ring-like enhancements, indicative of a necrotic core accompanied by a peripheral enhancement band, is a hallmark feature of high-grade glioma. These necrotic areas are often intermingled with old hemorrhage and the absence of a discernible cystic wall structure following enhancement is notable. Therefore, it was highly suspected that the patient's disease was a high-grade glioma, due to the severe headaches and the rapid growth of the tumor.

The neurosurgeons from Beijing Tiantan Hospital of Capital Medical University then performed a left frontal hiatus resection in November 2023 to remove the intracranial occupancy. The resected tumor was then subjected to an immunohistochemistry test for protein markers, yielding the following results: Glial fibrillary acidic protein (GFAP) (+), Olig-2 (+), isocitrate dehydrogenase (IDH)1 R132H (-), IDH2 R172K (-), α-thalassemia/mental retardation X-linked (ATRX; +), p53(even +) and Ki-67 (30%). The diagnosis was left frontal glioblastoma, not otherwise specified, central nervous system and World Health Organization (WHO) grade 4 (5). This diagnosis was based on a number of key molecular markers, including IDH wild-type status, high proliferative index, p53 positivity and ATRX positivity. IDH mutations (such as IDH1 R132H or IDH2 R172) are key molecular markers for differentiating the subtypes of glioblastoma (5,13-15).

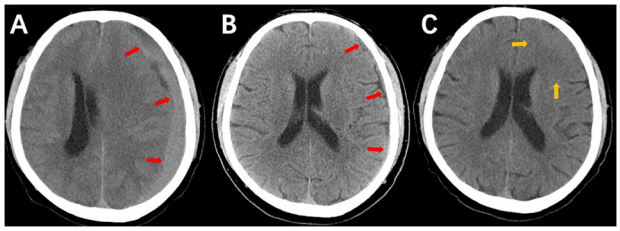

Figure 1. Images captured prior to the glioma's identification. (A) Left frontotemporal parietal subdural hematoma, accompanied by a cerebral hernia (red arrows), was observed in June 2023 (CT). (B) A left frontotemporal parietal subdural hematoma accompanied by cerebral hernia (red arrows) was observed in July 2023 (CT). (C) In September 2023 (CT), the density of the left frontal gyrus was observed to be slightly higher than normal brain tissue (yellow arrow, CT).

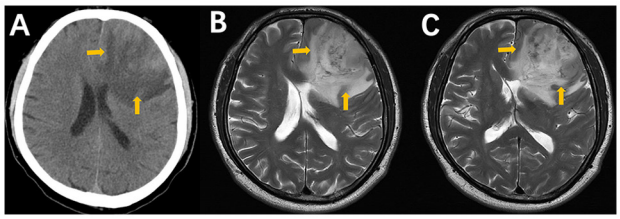

Figure 2. Images taken subsequent to the glioma's detection. (A) Hemorrhagic lesions in the left frontal lobe, exhibiting substantial abnormal density and space-occupying bleeding, as well as cerebral hernia (yellow arrows) on November 2023 (CT). Incisions with differing degrees of midline shift can be distinguished. (B) Left frontal space-occupying lesion compressing the lateral ventricle. Heterogeneous necrotic core with solid components and thick irregular rim enhancement, and absent cystic walls, pathognomonic of high-grade glioma. (C) The space-occupying lesion results in a more pronounced rightward midline shift, more severe compression and deformation of the lateral ventricle, and more prominent garland-like abnormal signal intensities on imaging. Left frontal occupation, which is identified as a high-grade glioma (yellow arrows) on November, 2023 (MRI).

IDH-wild-type glioblastomas account for ~90% of all glioblastomas and have a poor prognosis (13). Ki-67 is a marker of cell proliferative activity. In high-grade gliomas (WHO grade 4), Ki-67 positivity is frequently >10% and increases with increasing malignancy (16). A positivity rate of 30% strongly indicated the high proliferative activity of this tumor. p53, a tumor suppressor protein encoded by TP53, exhibits low basal expression and rapid degradation in normal cells, rendering it undetectable by standard immunohistochemistry (IHC) (17,18). In tumors, p53 positivity reflects aberrant stabilization of mutant or dysregulated protein. p53 expression is indicative of a TP53 gene missense mutation and is commonly observed during the progressive stages of glioblastoma (19). p53 positivity is associated with tumor invasiveness, resistance to therapy and a poor prognosis, where the rate of apparent p53 positivity is significantly higher in high-grade gliomas (50-70%) compared with that in its low-grade (approximately 10-30%) counterparts (13,20,21). The aforementioned findings aligned with the WHO grade 4 criteria for glioblastoma (5,22), thereby excluding low-grade gliomas. Mutation in the ATRX gene is typically associated with IDH mutant gliomas (such as in secondary glioblastoma). Conversely, ATRX(+) is an indication of an IDH wild-type (22,23), thereby supporting this diagnosis. Positivity for GFAP is a marker of astrocyte differentiation, whilst Olig-2 positivity not only suggested that the tumor may be characterized by mixed glial cell differentiation, but also helped to exclude metastatic tumors or neuronal malignancies (such as neuroblastoma).

In total, 7 days after brain surgery, the patient demonstrated a positive recovery trajectory and met the discharge criteria set by the hospital. In addition, the patient's condition was stable during the post-operative recovery, with no complications, such that the patient was largely able to care for themself. Therefore, the hospital considered arranging for discharge, in line with the wishes of the family of the patient. Subsequently, the patient was transferred to the Beijing Haidian Hospital (Beijing, China), a more convenient local hospital, for the administration of temozolomide chemotherapy (75 mg/m^2 daily during radiotherapy, followed by 150-200 mg/m^2 for 5 days/28-day cycle), combined with standard radiotherapy delivered as 2 Gy per fraction, five fractions weekly over six weeks (total dose 60 Gy in 30 fractions), aiming to reducing the risk of tumor recurrence.

At the subsequent follow-up visit 1 month after surgery, it was ascertained through a video call that the patient was capable of performing simple domestic tasks, such as sweeping and mopping the floor, while undergoing radiotherapy and chemotherapy. Thereafter, the patient was monitored on a monthly basis by Beijing Tiantan Hospital of Capital Medical University through telephone calls to ascertain their general condition. The patient exhibited consistent cooperation throughout the follow-up period, which continued until June 2024, when the patient condition was deemed stable. Thereafter, follow-up visits were conducted every two months. In September 2024, the patient began to experience speech disorders. An MRI review was conducted at Beijing Tiantan Hospital of Capital Medical University in September 2024, which indicated the suspicion of tumor recurrence (Fig. 3). Postoperative MRI revealed a well-demarcated surgical cavity in the left frontal lobe with peripheral irregular annular enhancement involving the frontobasal ganglia region. Adjacent dural linear enhancement was noted, radiologically consistent with recurrent neoplasm. However, neurosurgeons deemed the second operation to carry a high risk, leading to the decision to continue with radiotherapy treatment. The most recent follow-up in January 2025 revealed that the patient had undergone treatment for cholecystitis at Peking University International Hospital (Beijing, China) in December 2024.

At present, although the patient remains at high risk of glioma recurrence, treatment is still being administered for pre-squared glioma recurrence.

Discussion

Gliomas account for the majority (80%) of all primary malignant brain tumors. In particular, Glioblastoma multiforme is a type of glioma with the highest degree of malignancy and with a poor prognosis (6-8). Despite the use of advanced antitumor therapies, including anti-angiogenic agents (bevacizumab targeting VEGF-A), immune checkpoint blockade (anti-PD-1 monoclonal antibodies), tumor-treating fields and molecularly targeted therapies (EGFRvIII-specific CAR-T cells) (24-27), the median survival time of patients with glioblastoma is 14-15 months (28). By contrast, CSDH is one of the most

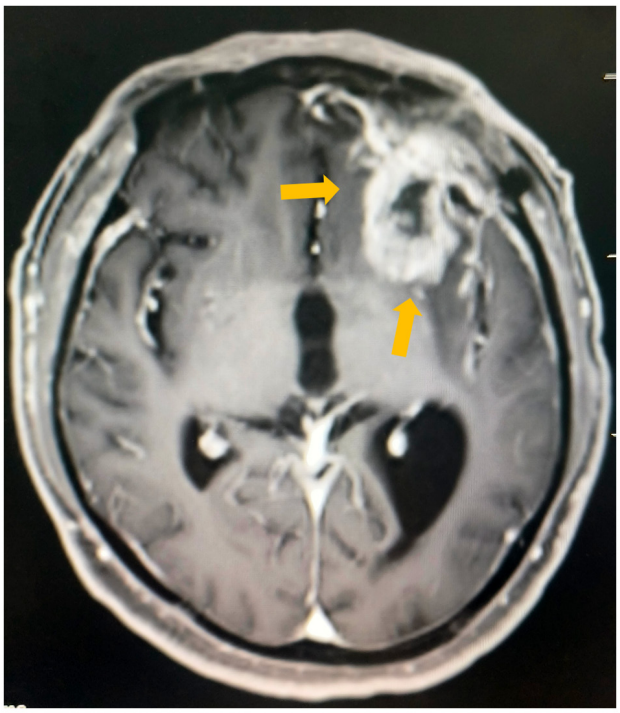

Figure 3. The postoperative review in September 2024 revealed an abnormal signal in the surgical area of the left frontal lobe, suggesting potential tumor recurrence. (yellow arrow) (MRI).

prevalent neurosurgical diseases necessitating surgical treatment in the elderly, with an annual incidence exceeding 100 per 100,000 individuals aged over 80 years (1,2,29), where a range of complications, including headache, emesis and epilepsy, can occur (8). To the best of our knowledge, there have been no reports of gliomagenesis following subdural hematoma (30). In the present case, a patient who developed a glioma following the development of subdural hematoma was documented.

The patient with a five-year history of rivaroxaban therapy for venous thrombosis (known to increase hemorrhage risk (31) demonstrated initial CT findings of mixed-density lesions suggestive of acute hemorrhage. These features were more likely be associated with nascent membrane formation and increased exudation and hemorrhage caused by long-term use of rivaroxaban (32-35). The patient subsequently developed an ipsilateral glioma following resolution of the subdural hematoma. There are several potential explanations for this causal relationship. CSDH is defined as the accumulation of hematoma fluid that is comprised of blood, body fluids and blood products, situated between the dural and arachnoid membranes (36). The accumulation of inflammatory cells has been reported to serve a role in the formation of the hematoma membrane and fluid (32,37). Vascular endothelial growth factor (VEGF) is of interest due to its elevated mRNA expression levels in CSDH hematoma fluid, membranes and neutrophils according to a previous study (38). VEGF also serves a key role in promoting angiogenesis. Hypoxia-inducible factor (HIF-α) represents a product of the cellular response to a hypoxic environment (39). The role of HIF-α and VEGF in tumor invasion and metastasis has been demonstrated, where there is a significant and positive association between VEGF expression and tumor invasive capacity (40). The formation of CSDH hematoma membranes and effusions is accompanied by elevated levels of proinflammatory factors such as TNF-α, IL-6, VEGF and MMP-9 (41-43), and the aggregation of inflammatory cells (32,41). Despite the absence of a direct experimental model that can conclusively demonstrate a causal relationship between CSDH-induced inflammation and glioma response, the existing literature provides support for the notion that these inflammatory factors serve a role in the glioma microenvironment. This role is considered to involve the regulation of tumor cell behavior through the activation of different signaling pathways such as IL-6/JAK/STAT3 Pathway, TNF-α/NF-κB Pathway and TGF-β/Smad Pathway (32,44-46). Further studies are required to elucidate the potential role of aforementioned cytokines. Abnormal activation of astrocytes can be another cause of this causal relationship, since astrocyte-specific alterations can increase the risk of glioma (47,48). The effects of local inflammation caused by CSDH can induce a reactive phenotype in astrocytes, including a phenotype that promotes glioblastoma, due to the release of IL-1β and TNF-α (49,50). The presence of extravasated blood leads to platelet activation, which results in the release of platelet-derived growth factor (PDGF) (51). PDGF serves a multifaceted role in tumor biology (52), as it can regulate angiogenesis and development, whilst inducing the proliferation and activation of astrocytes (47,51). Conversely, pathological alterations resulting from CSDH, including astrocyte swelling and a persistent increase in S-100β expression, have been observed in an acute subdural hematoma rat model (53,54). Additionally, S-100β and MMPs can indirectly activate microglia and astrocytes. Previous experimental studies have demonstrated that the S-100β protein can stimulate the overexpression of primary cortical astrocytes in rats by activating the NF-κB pathway (55-57) Activation of NF-κB has been demonstrated to inhibit p53-mediated apoptosis, primarily through the activation of NF-κB signaling by binding to RAGE (Receptor for Advanced Glycation End Products) (54,58,59). This process is associated with the inhibition of cell proliferation and the induction of apoptosis. Consequently, S-100β may be involved in the proliferation of reactive astrocytes in a synergistic manner. In the aftermath of parenchymal or structural brain injury, such as traumatic brain injury (60), astrocytes undergo reactive proliferation and migrate to the site of injury, thereby increasing the risk of malignancy (61-65). Neutrophils are another candidate for this potential causal relationship. Neutrophils have been identified to be key players in the development and recurrence of CSDH, as evidenced by numerous studies (32,66-68). It is therefore conceivable that the increased reactivity of neutrophils during CSDH may be involved in the pathogenesis and recurrence of gliomagenesis (69-71). Neutrophils exert their inflammatory functions through a number of mechanisms, including phagocytosis, degranulation and the release of neutrophil extracellular traps (NETs) (72,73). The oncogenic role of neutrophils and their NETs is manifested primarily through the induction of DNA damage, angiogenesis and immunosuppression, as evidenced by previous reports (74,75). Further evidence from the present patient for testing this hypothesis could not be obtained. This remains an important hypothesis for future studies due to the association between the

aforementioned factors and gliomagenesis. Furthermore, the immunohistochemistry results obtained from the tumor resection in the present case indicated the presence of astrocyte activation, along with potential activation of oligodendrocytes. Additionally, 30% of the tumor cells exhibited proliferative activity within the patient's glioma tissues, suggesting that the tumor was characterized by rapid growth and marked invasiveness. Since this phenomenon was only identified subsequent to the removal of the patient's glioma, it was not feasible to further refine the immunohistochemical results to confirm the relationship between CSDH and glioma.

To conclude, the pathological alterations resulting from CSDH may be linked to the emergence of gliomas. Although gliomagenesis following CSDH is a rare occurrence, it is nevertheless a phenomenon that should not be overlooked. Therefore, it is recommended that further mechanistic studies be conducted on this topic.

Acknowledgements

Not applicable.

Funding

The present report was supported by the National Natural Science Foundation of China (grant no. 82074350).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

WW was responsible for study design, case data collection, clinical analysis and writing of the first draft of the paper. YPF took the lead in constructing the study framework, analyzed data, and was responsible for multiple revisions of the manuscript and final academic control. YPF and WW confirm the authenticity of all the raw data. TY participated in the data interpretation. LL created diagnostic imaging charts, participated in case discussions and provided key clinical insights. XYL created diagnostic imaging charts and analyzed the results of pathology reports. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (Beijing, China) (approval no: HX-A-2023054) .

Patient consent for publication

Written informed consent was obtained from the patient, who agreed to the publication of data and images.

Competing interests

The authors declare that they have no competing interests.

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