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A manifestation of the malignant progression of glioma following initial intracerebral hemorrhage: a case report

glioma following initial intracerebral hemorrhage

Enxi Xu, Siyuan Lu, Bo Chen, xiaodong ma, Er-Yi Sun

Abstract

BACKGROUND

Intracranial hemorrhage is extremely rare during the initial stages of glioma. We hereby report a case of glioma with an unclassified pathology and intracranial bleeding.

CASE SUMMARY

After the second surgery for intracerebral hemorrhage, the patient experienced weakness in the left limbs but could walk unassisted. One month after being discharged, the weakness in the left limb had exacerbated, and the patient suffered from headaches and dizziness. The third surgery was ineffective against the rapidly growing tumor. Intracerebral hemorrhage may be the initial symptom of glioma in some rare cases, and atypical perihematomal edema can be used for diagnosis during an emergency. Certain histological and molecular features of our case were similar to that of glioblastoma with a primitive neuronal component, which is termed as diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC). The patient underwent three surgeries for tumor removal. The first tumor resection was performed when the patient was 14 years old. Hemorrhage resection and bone disc decompression were preformed when the patient was 39 years old. One

month after the last discharge, the patient underwent neuronavigation-assisted resection of the right frontotemporal parietal lesion plus extended flap decompression. On the 50th day after the third operation, computed tomography (CT) imaging showed rapid tumor growth accompanied by brain hernia. The patient was discharged and died 3 days later.

CONCLUSION

Glioma may present as hemorrhage at the initial stage, and should be considered in such a setting. We have reported a case of DGONC, which is a rare molecular subtype with a unique methylation profile.

Key Words: Intracranial hemorrhage, glioma, glioneuronal tumour , case report

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Core Tip: Core tip: Intracranial hemorrhage is extremely rare during the initial stages of glioma. We hereby report a case of glioma with an unclassified pathology and intracranial hemorahage at the intial stage twicely, and atypical perihematomal edema may help in its diagnosis. Certain histological and molecular features in this case are reminiscent of the newly defined DGONC, a glioblastoma subtype with a primitive neuronal component, which however is not currently recognized by the WHO.

INTRODUCTION

Around 6% of the cases of intracerebral hemorrhages are associated with brain tumors, and most are the result of cerebral metastases and glioblastoma multiform[1]. The incidence of intracerebral hemorrhage in glioma ranges from 3.7 to 7.2% [2], and the majority of these cases are high grade gliomas with abnormal vascular alignment and

immature growth, which result in bleeding. On the other hand, low grade gliomas rarely bleed.

Gliomas hemorrhage infrequently during the initial stages[3, 4], which may lead to misdiagnosis during CT imaging since the products of hemorrhage can completely obscure the tumor. This in turn can cause the brain edema to grow out of proportion with the hemorrhage or present at an early time point[5]. Therefore, follow-up neuroimaging is necessary to ensure that a malignancy is not missed, and whether the hemorrhage requires emergency surgery or not. The risk of hemorrhage in pilocytic astrocytoma, a low grade glioma based on WHO classification,[6] is extremely rare, especially decades after tumor onset. In fact, only one case of bleeding that occurred 18 years post-onset has been reported[7]. Pilocytic astrocytomas bleed as a result of abnormal vessels, or endothelial proliferation in parts of the tumor that have features of oligodendrogliomas, which lead to the rupture of an encased aneurysm or bleeding from retiform capillaries.

In this report, we have presented a case of glioma progression following initial intracerebral hemorrhage.

Case presentation

The 14-year-old female patient underwent the first tumor resection surgery in Shanghai in 1996, following frequent complaints of headache. She was not prescribed any drugs, had no history of psycho-social symptoms and her parents were healthy. The postoperative pathological results indicated pilocytic astrocytoma. Only the summary report at discharge is currently available. The patient was followed-up every year and imaging results (Figure 1) showed that the patient had recovered well without the need for radiotherapy or chemotherapy. The patient participated in daily life, got married and gave birth to a son.

When she was 39 years old, she had a sudden onset of aphasia and left limb hemiplegia, and was admitted to our hospital 3 h later. CT imaging showed right basal ganglia

hemorrhage and cerebral hernia formation (Figure 2A). Initial surgery was performed to remove the hematoma and bone disc decompression (Fig 2B). CT imaging showed the softening of the frontal lobe and basal ganglia (Figure 2C), while cranial magnetic resonance imaging (MRI) showed right frontal lobe and basal ganglia residual cavity with marginal enhancement (Figure 2D-F) 11 days post-operation. The patient was discharged from the hospital on the 13th day after the operation. At the time of discharge, the patient was alert and could walk unassisted. In addition, the head incision had healed well, bone window tension was not high, and the left muscle strength was at level IV.

One month after being discharged, the patient suffered from headaches and dizziness, and exacerbation of left limbs weakness. CT imaging showed a new cerebral hemorrhage in the right craniocerebral operation area and frontal lobe (Figure 3A). Therefore, MRI imaging was performed and the results indicated the presence of a residual cavity in the right fronto-parietal lobe and basal ganglia area with marginal enhancement (Fig 3E-G). To obtain the SWI of the hemorrhage of frontal lobe and craniocerebral operation area (Figure 3H), we performed neuronavigation-assisted resection of the right frontotemporal parietal lesion plus extended flap decompression. As shown in Figure 3B, the patient had obvious swelling of the right frontotemporal parietal lobe. During the operation, a neoplasm was detected under the meninges of the right inferior frontal gyrus and parietal lobe, which appeared gray and yellow with a brittle texture. A hematoma with a complete capsule and a thick and tough texture was present in the right temporo-parietal frontal lobe. After surgery, the patient was continuously conscious but the scalp in the bone window of the right surgical area gradually bulged due to high tension, and the scalp was invaded by the tumor and presented multiple ruptures. On the 23rd day after surgery, the tumor was observed again in the intracranial surgical area and had enlarged (Figure 3C). Due to the failed surgery, the patient's family refused consent for another operation. On the 50th day after the operation, CT imaging showed rapid tumor growth accompanied by brain

hernia (Figure 3D). The patient was discharged and died 3 days later. The patient's husband has provided informed consent for the publication of this case.

The right temporo-parietal frontal lobe was removed, and the tumor mass was suspected to be glioblastoma (WHO IV) with extensive necrosis and hemorrhage, and sent for pathological confirmation. The tumor cells were round and diffusely arranged with perinuclear haloes, akin to that seen in oligodendrogliomas (Figure 4A-C). Immunohistochemical staining showed that 70% of the tumor cells were positive for Ki67 (Figure 4D). The tests for GFAP, S-100, p53, IDH1/2, OLig-2, CK, CD3, CD5 CD10, CD20, Bcl-6, C-MYC, EMA, Mum-1, EBER, Syn, CD99 and CgA were negative. The samples were sent to Jiangsu Shihe Gene, Nanjing for high-throughput sequencing (reference genome: GRCh37/ HG19). The results indicated that the tumor was negative for 1P/19Q co-deletion, ATRX mutation, BRAF mutation/fusion, IDH1, 2 mutation, MGMT methylation, TERT promoter mutation and TP53 mutation/copy number variation, and positive for MYCN amplification and CDKN2A deletion.

CASE PRESENTATION

Chief complaints

a sudden onset of aphasia and left limb hemiplegia 3 h.

History of present illness

When the patient was 39 years old, she had a sudden onset of aphasia and left limb hemiplegia, and was admitted to our hospital 3 h later. CT imaging showed right basal ganglia hemorrhage and cerebral hernia formation (Figure 2A). Initial surgery was performed to remove the hematoma and bone disc decompression (Fig 2B). 11 days post-operation. The patient was discharged from the hospital on the 13th day after the operation. At the time of discharge, the patient was alert and could walk unassisted. In addition, the head incision had healed well, bone window tension was not high, and the left muscle strength was at level IV.

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History of past illness

The 14-year-old female patient underwent the first tumor resection surgery in Shanghai in 1996, following frequent complaints of headache.The postoperative pathological results indicated pilocytic astrocytoma.

Only the summary report at discharge is currently available. The patient was followed-up every year and imaging results (Figure 1) showed that the patient had recovered

well without the need for radiotherapy or chemotherapy. The patient participated in daily life, got married and gave birth to a son.

Personal and family history

She was not prescribed any drugs, had no history of psycho-social symptoms and her parents were healthy.

Physical examination

aphasia and left limb hemiplegia at the first admission.

the patient suffered from headaches and dizziness, and exacerbation of left limbs weakness at the second admission.

Laboratory examinations

The right temporo-parietal frontal lobe was removed, and the tumor mass was suspected to be glioblastoma (WHO IV) with extensive necrosis and hemorrhage, and sent for pathological confirmation. The tumor cells were round and diffusely arranged with perinuclear haloes, akin to that seen in oligodendrogliomas (Figure 4A-C). Immunohistochemical staining showed that 70% of the tumor cells were positive for Ki67 (Figure 4D). The tests for GFAP, S-100, p53, IDH1/2, OLig-2, CK, CD3, CD5 CD10, CD20, Bcl-6, C-MYC, EMA, Mum-1, EBER, Syn, CD99 and CgA were negative. The samples were sent to Jiangsu Shihe Gene, Nanjing for high-throughput sequencing (reference genome: GRCh37/ HG19). The results indicated that the tumor was negative for 1P/19Q co-deletion, ATRX mutation, BRAF mutation/fusion, IDH1, 2 mutation, MGMT methylation, TERT promoter mutation and TP53 mutation/copy number variation, and positive for MYCN amplification and CDKN2A deletion.

Imaging examinations

CT imaging showed right basal ganglia hemorrhage and cerebral hernia formation at the first admission (Figure 2A). Initial surgery was performed to remove the hematoma

and bone disc decompression (Fig 2B). CT imaging showed the softening of the frontal lobe and basal ganglia (Figure 2C), while cranial magnetic resonance imaging (MRI) showed right frontal lobe and basal ganglia residual cavity with marginal enhancement (Figure 2D-F) 11 days post-operation.

CT imaging showed a new cerebral hemorrhage in the right craniocerebral operation area and frontal lobe at the second admission (Figure 3A). Therefore, MRI imaging was performed and the results indicated the presence of a residual cavity in the right fronto-parietal lobe and basal ganglia area with marginal enhancement (Fig 3E-G).

On the 23rd day after surgery, the tumor was observed again in the intracranial surgical area and had enlarged (Figure 3C). Due to the failed surgery, the patient's family refused consent for another operation. On the 50th day after the operation, CT imaging showed rapid tumor growth accompanied by brain hernia (Figure 3D).

FINAL DIAGNOSIS

glioblastoma (WHO IV)

TREATMENT

Initial surgery was performed to remove the hematoma and bone disc decompression.

we performed neuronavigation-assisted resection of the right frontotemporal parietal lesion plus extended flap decompression at the second time.

OUTCOME AND FOLLOW-UP

The patient was discharged and died 3 days later. The patient's husband has provided informed consent for the publication of this case.

DISCUSSION

We have presented a case of glioma that initially manifested as spontaneous intracranial hemorrhage (ICH), which at separately the same cerebral region of lesion before. The patient showed spontaneous hemorrhage in the same region prior to the second and

third hospital admission at basal ganglia. On the third admission, we detected hemorrhage in the frontal lobe, corresponding to a pilocytic astrocytoma resected 25 years before. Spontaneous ICH is a rare initial clinical presentation of intracranial tumors, and has been reported in only 0.5%–3.4% of the published cases[3, 4].

Bleeding of gliomas may be the result of the direct pressure of the brain tumor cells on blood vessels, or proliferation of malformed vasculature due to hypoxia, tumor necrosis and tumor coagulopathy[8]. One study on 23 patients with gliomas that initially presented as intracerebral hemorrhage[3, 9] did not report presence of intracranial tumors or intracranial transformed tumors. Therefore, intra-tumoral hemorrhage and abnormal coagulation may increase the risk of spontaneous ICH[3], while hypertension is responsible for 8% of the cases of parenchymal hemorrhages in cancer patients[10].
It is challenging to diagnose tumors that initially present with hemorrhage. One study showed that diagnostic delay is common in up to 2/3rd of such cases, and is made after a median duration of 60 days from presentation (range 0–280 days)[4]. In our case, the patient had ICH and hernia, which require emergency care, which left no time to finish the MRI. In addition, the hematoma was large and covered the tumor, making it impossible to identify the tumor using CT imaging. MRI can also be ineffective for the diagnosis of tumor or metastatic ICH lesion in such cases[5], although it has the highest diagnostic efficiency for glioma and other malignancies that present with spontaneous ICH, especially in adult patients[4]. However, MRI imaging could not identify the tumor in our patient after the operation. We hypothesized that the hemorrhage was related with the glioma as the perihematomal edema was larger than normal during 3 h of intracerebral hemorrhage. Edema associated with brain tumors is vasogenic, which frequently leads to the loss of brain blood barrier (BBB) integrity prior to a secondary ICH incidence. Due to the accumulation of serum proteins and thrombin as well as inflammatory processes, the BB may be increasingly disrupted, resulting in an extensive perihematomal edema. However, perihematomal edema formation in ICH is caused mainly by hematoma-induced direct tissue injury in the absence of a pre-existing

edema. In addition, thrombin and iron from hemoglobin breakdown cause inflammation and neurotoxicity, which exacerbates the perihematomal edema[5]. In our case, the perihematomal edema volume was larger than that of normal hemorrhage for 3 h. Therefore, we doubt that the tumor was formed and presented as ICH at the second admission. MRI was performed 11 days after the 2nd surgery, and showed marginal enhancement of the right frontal lobe and basal ganglia residual cavity, which may have indicated a tumor but we misdiagnosed it as gliocyte hyperplasia.

One and a half month after the operation, the patient was admitted for the third time. She had developed another hematoma in the basal ganglia, which had been operated. The hematoma in frontal lobe was verified by SWI. The patient had developed a pilocytic astrocytoma (PA) in the frontal lobe 25 years before, which had been surgically removed and did not re-bleed for 25 years. Spontaneous hemorrhage has been observed in 8%–24% of pilocytic astrocytoma cases[11]. PAs primarily occur in the pediatric population, and only 59 cases of hemorrhagic pilocytic astrocytoma have been reported in adults so far,[7] of which only 20 cases include supportive radiological data[12]. Delayed hemorrhage of PA is very rare, and only one case of hemorrhage has been reported that occurred 18 years after operation[12].

The degree of tumor malignancy is highly correlated with the risk of hemorrhage. The majority of ICH cases occur in high grade gliomas, which are characterized by rapid growth that induces formation of abnormal blood vessels[13]. In our case however, the PA was classified as WHO Grade 1 rather than a benign, slow-growing type[6]. Therefore, our patient showed good recovery, and gave birth to a son several years later. Spontaneous hemorrhage is a rare clinical event in patients with LGG, including PA, but can be lethal despite a benign tumor pathology.

Most LGG patients presenting with hemorrhage do not undergo genetic testing. One study reported 2 cases of cerebellar PA that were tested for BRAF V600E mutation and K-B fusion[14]. In addition, FGFR1 mutations are frequent in pediatric and young adult LGG patients with spontaneous hemorrhage, and FGFR1-mutated PAs are mainly located in the midline, including the diencephalon[11]. However, no significant

differences have been reported between hemorrhagic and non-hemorrhagic glioma patients in terms of age, gender, location, Ki-67 expression and microvascular proliferation[15]. None of the above mutations were detected in our patient.

PA hemorrhage is likely associated with the vascular changes due to thick-walled densely hyalinized vessels, vascular endothelial hyperplasia, and thin-walled ectasic vessels[16]. A stretched vessel may be disrupted by a large cystic component after a trivial trauma[17]. Another hypothesis is that vascular alterations determine the alteration of flow-dynamics with the consequent formation of micro-aneurysms, which eventually rupture. Rapid tumor growth may lead to local hypoxia due to overexpression of VEGF, alterations of the flow dynamics and hydrostatic pressure, resulting in micro-hemorrhages during Valsalva-like maneuvers, eventually lead to extensive hemorrhage[14]. However, some studies suggest that microvascular proliferation does differ significantly different between hemorrhagic and non-hemorrhagic cases of PA[15]. There are also reports of hemorrhage occurring years after radiation therapy and chemotherapy[18]. Radio-induced intra-tumoral hemorrhage may be the result of repeated micro-bleeds in regressive alterations[19]. However, none of the PAs treated with radiation therapy have presented with re-bleeding during follow-up[7]. In our case, the patient did not accept irradiation or chemotherapy, which excluded them as risk factors of hemorrhage. Therefore, it can be presumed that PA may portend a slightly worse prognosis resulting in a higher rate of bleeding, in spite of its benign nature[20].

The patient had tumor recurrence or progression in the right craniocerebral operation area and frontal lobe, which we misdiagnosed as gliocyte hyperplasia. MRI showed a complete capsule and residual cavity in the operated area, which we identified as abscess or just rebleeding. Glioma diagnosis was confirmed only after pathological examination, which also revealed oligodendroglioma-like features. The tumor mass was negative for GFAP, S-100, p53, IDH1/2, OLig-2, CK, CD3, CD5 CD10, CD20, Bcl-6, C-MYC, EMA, Mum-1, EBER, Syn, CD99 and CgA, and positive for the proliferation

marker Ki-67[21]. The high degree of proliferation coincided with rapid tumor growth and formation of brain hernia within 50 days after resection.

Genetic analysis identified MYCN amplification and CDKN2A deletion in the tumor samples, whereas 1P/19Q co-deletion, ATRX mutation, BRAF mutation/fusion, IDH1, 2 mutation, MGMT methylation, TERT promoter mutation and TP53 mutation/copy number variation were not detected. Gliomas with 1P/19Q co-deletion as well as mutations in isocitrate dehydrogenase (IDH) 1 are typically characterized as oligodendrogliomas, and respond well to radiation and chemotherapy[6]. IDH1 mutation is an early event in glioma, and appears before TP53 mutation or 1p/19q deletion. IDH mutations have been detected in 80% of LGGs and in 76% of secondary GBM[22]. Accordingly, our case was diagnosed as glioblastoma with oligodendroglial features and atypical molecular structure.

A population-based study showed that the mean duration of progression from LGG to GBM was 5.3 years, and that from anaplastic astrocytoma to GBM was 1.4 years[23]. Although LGG progresses slowly during the early period of the disease, its growth accelerates once it advances to a higher grade. Furthermore, its progression pattern may change following therapy, particularly after surgical resection[23]. Patient prognosis is substantially worse during tumor recurrence or progression, and LGG may be fatal once it undergoes malignant progression. An average of 44 LGG patients experience 3.15 somatic gene alterations during recurrence or progression but not in the primary tumor. The most frequently mutated genes in LGG include NF1, CDKN2A, BAX, CCND2, EGFR, CREB3L2, GNAS, MYCN, PLAG1, PTK6, RIM2, RNF213 and WNK2[24]. Furthermore, the CDKN2A-CDKN2B tumor suppressor locus is deleted in 44% of the gliomas. However, neither MYC amplification nor CDKN2A-CDKN2B deletion are frequent in the oligodendroglial or astrocytic subtypes[25]. In our case, both alterations may have been involved in tumor recurrence or progression. There is evidence that MYCN amplification and homozygous deletion of CDKN2A/B are significantly associated with worse overall survival[26].

Some histological and molecular features of this case were consistent of glioblastoma with a primitive neuronal component, although not entirely typical. Glioblastoma with primitive neuronal component is a newly recognized pattern in the WHO 2016 classification that includes otherwise classical high-grade diffuse gliomas with one or more foci of sharply demarcated primitive nodules showing neuronal differentiation[27]. Similar to primitive neuronal cells that constitute CNS embryonal neoplasms, these foci show immunoreactivity for synaptophysin, loss of GFAP expression, and a high Ki-67 proliferation index, which were also noted in our case. Two particularly distinctive features of this pattern are its high rate of CSF dissemination and frequent MYCN or MYC gene amplification[28]. However, we did not observe CSF dissemination or syn positivity, which contradicts a primitive neuronal component.

Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)[29] is a newly defined CNS tumor characterized by DNA methylation-defined class of low-grade glioneuronal tumors with recurrent monosomy 14, oligodendroglioma-like features and nuclear clusters. The histological profile of the DGONC tumor class overlap substantially with other CNS tumor entities, including the presence of a clear cell morphology, vascular proliferation and GFAP-negativity, which are commonly observed in (anaplastic) oligodendroglioma, 'pediatric oligodendroglioma', or neurocytic tumors[30]. The histological and molecular features of these tumors are similar to that of our case, but are currently not recognized by WHO classification.

CONCLUSION

We report a case of glioma initially presenting as intracerebral hemorrhage, which was misdiagnosed and not verified histologically. The patient underwent hemorrhage repeatedly at the same place again, and bled spontaneously at the frontal lobe which was the site of pilocytic astrocytoma that was resected 25 years before. The hemorrhage was verified as the malignant progression of glioma.

There were several limitations in our case. The patient underwent tumor resection in other hospital, and we had received only a summary of the postoperative pathological results at discharge. The hemorrhage that occurred at the second admission was an emergency situation, which we did not recognize as a tumor and therefore did not verify it histologically.

Intracerebral hemorrhage may be the initial manifestation of glioma, and atypical perihematomal edema may help in its diagnosis. Certain histological and molecular features in this case are reminiscent of the newly defined DGONC, a glioblastoma subtype with a primitive neuronal component, which however is not currently recognized by the WHO.

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