Case Report

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# Severe Head Injury linked to Subsequent Development of Malignant Brain Tumour within a Short Period- A Case Report

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## Abstract

*There have been a few case reports of head injury leading to brain tumour development in the same region as the brain injury. Here we report a case where the patient suffered a severe head injury with contusion. He recovered clinically with conservative management. Follow up Computed Tomography scan of the brain a month later showed complete resolution of the lesion. He subsequently developed malignant brain tumour in the same region as the original contusion within a very short period of 15 months. Head injury patients need close follow up especially when severe. The link between severity of head injury and malignant brain tumour development needs further evaluation. Role of anti-inflammatory agents for prevention of post traumatic brain tumours needs further exploration.*

**Keywords:** Severe head injury, Inflammation, Brain tumour development, awake craniotomy

## Introduction

Head trauma can lead to a small increase in the overall risk of brain tumours like gliomas and meningiomas over a period of 15 years and may even increase incidence of vascular tumours [1]. The risk for benign tumours like meningioma development after brain trauma is shown to be high [2]. Neoplastic tumours have also been shown to occur within the traumatised brain regions over a period varying from 2 years to 20 years following the head injury [3-5]. There has been debate on the criteria for causal relationship between brain trauma and incidence of brain tumours. Zulch suggested the following criteria [6]:

1. The patient must have been in good health before suffering the head injury.
2. The blow must be severe enough to cause brain contusion and a secondary reparative process.
3. The location of the impact and the tumour should correspond exactly one to the other.
4. There should be a time interval between trauma and the appearance of the tumour of at least 1 year, a longer latent period increasing the likelihood of a causal relationship.
5. The presence of the tumour must be proved histologically.
6. Trauma should consist of an external force.
7. Manuelidis added the following three criteria [7]:
8. The traumatized brain must also be proved histologically.
9. Bleeding, scars and oedema secondary to the presence of the tumour must be clearly differentiated from that caused by trauma.
10. Tumour tissue should be in direct continuity with the traumatic scar, not merely in its vicinity or separated by a narrow zone of healthy or slightly altered brain tissue.

## Case Report

There have been a few case reports of tumours developing within the location of a previous brain injury. Here we present a 46 year old male who first presented to us in the emergency room with history of a road traffic accident associated withloss of consciousness and multiple abrasions over the body. He remained with altered sensorium and on examination was found to be drowsy. His Glasgow coma scale was E3V4M5, pupils were equal and reacting briskly to light. He had a left ear bleed and cerebrospinal fluid leak. He was moving all four limbs and his vitals were as follow: Blood pressure: 110/70 mmHg, PR: 60/minute; RR: 20/minute.

Computed tomography (CT) scan done at the time of presentation with head injury revealed a contusion with pericontusional oedema in the right posterior frontal region with mild midline shift of 3.3 mm towards the left(Fig 1). Also noted was a diffuse subarachnoid haemorrhage and a thin subdural hemorrhage over the right convexity with a left Parieto-temporal bone fracture extending to petrous bone. CT scan of chest revealed multiple rib fractures with bilateral pleural effusion with basal atelectasis and a fracture clavicle.

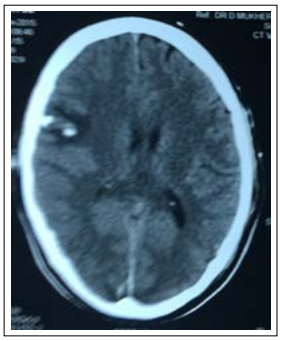

**Figure 1**: Plain CT scan Head 2 hours after head injury

Small Contusion with pericontusional hypodensity suggestive of edema seen in the right posterior frontal region. A midline shift to the left is seen measuring 3.3 mm. Thin extra-axial collection over the right occipital lobe seen. Subarachnoid hemorrhage noted along the posterior falx with small underlying contusion right occipital lobe.

He was admitted in intensive care unit and was managed conservatively with cerebral dehydrating agents, anticonvulsants, antibiotics and other supportive measures. He improved gradually and became more alert and was shifted to high dependency unitwithin 3-4 days. He was continued on medical management with close observation and he improved neurologically. A repeat plain CT brain, a week later, showed resolving hemorrhagic contusions. The midline shift persisted to the left. He was discharged a week later in a stable condition and maintained on anticonvulsants and antibiotics. He was followed up in the outpatientclinic with clinical examinations and a plain CT brain performed a month later revealed total resolution of haemorrhage and there was no midline shift(fig 2).He was able to resume his day to day activities and returned to his workplace.

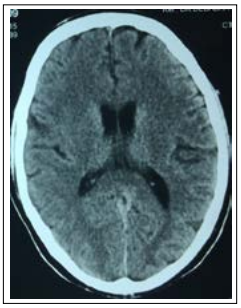

**Figure 2**: Plain CT scan Head 1 month after head injury

A repeat plain CT brain a month later showed resolution of hemorrhagic contusions with a small area of hypodensity in the left posterior frontal region. There was no midline shift.

Almost a year later (14 months later) following the head injury the patient presented in the emergency with an episode of tonic-clonic seizure. On examination he was found to have left hemiparesis grade 4/5.Radiological examination with head CT scan revealed a hypodense lesion in the right posterior frontal region with perilesional edema. There was no midline shift (fig 3).MRI brain with Godolinium revealed a right posterior frontal, suprasylvian region heterogeneously enhancing lesion with central necrosis and peripheral edema with mild mass effect (fig 4). As the lesion was located in the region of the eloquent cortex and since the patient was well preserved a functional MRI (fMRI) was planned. The patient was instructed to do simple tasks like moving his hand, and the areas of brain activation was captured. The location of the tumour was noted to be in close proximity to the central sulcus and the brain activation regions corresponding to the hand movements(fig 5).

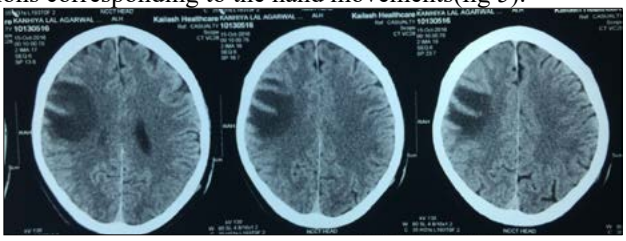

**Figure 3**: Contrast enhanced CT scan Head 14 months after head injury

A contrast enhanced CT brain done at the time of presentation with seizures more than a year after the head injury showed a large hypodense lesion in the right posterior frontal region with perilesional edema. No midline shift was noted.

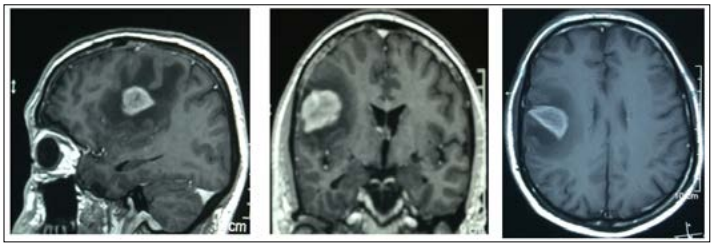

**Figure 4**: Contrast enhanced MRI scan brain 16 months after head injury

MRI brain with contrast enhancement revealed a right posterior frontal, supra sylvian region heterogeneously enhancing lesion with central necrosis and peripheral edema with mild mass effect.

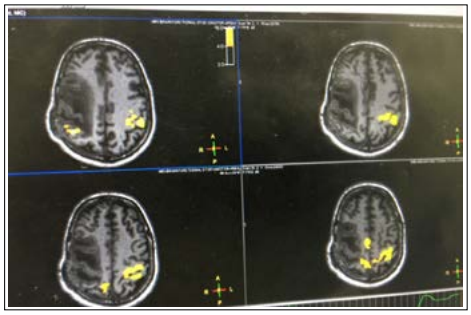

**Figure 5**: Functional MRI scan Brain 14 months after head injury

fMRI brain done to map the brain activity by asking the patient to perform simple tasks of hand movements. The tumor region was located in close proximity to the central sulcus engulfing the presulcal and postsulcal brain matter. The functional brain activity related to hand movements were located in the posterior region of the lesion.

There was minimal mass effect and no midline shift. He was taken up for surgery and planned for “awake craniotomy” as the lesion was in the eloquent cortex and he was still well preserved. The patient was sedated with mild sedation and a left frontal craniotomy was done under local anesthesia with scalp blocks.He recovered well postoperatively with no worsening of neurological deficit (fig 6). A postoperative CT scan of the brain done 2 days after surgery revealed evidence of craniotomy in the right frontal region with evidence of surgical changes in the right frontal lobe within the location of the hypodense lesion(fig 7). He was discharged in a stable condition.

**Figure 6**: Immediate post-operative clinical assessment after awake craniotomy for tumour decompression

Awake craniotomy was planned as the tumour was located in the eloquent cortex and patient was well preserved. Mild sedation with local scalp block was used and right posterior frontal craniotomy performed. Tumour decompression done with close monitoring of the patient's neurological function including performing simple tasks like moving the left hand, leg and answering a few simple questions. Surgical decompression was aborted when the delineation was unclear and the patient seemed to be a bit reluctant to perform the simple tasks. He recovered well postoperatively. Power remained grade 4/5 on the left side.

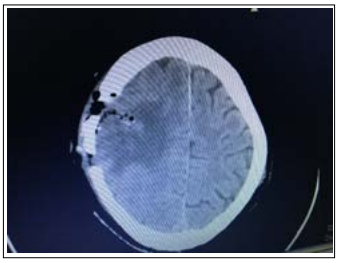

**Figure 7**: Plain CT scan head after 2 days following surgery for tumour decompression.

A plain CT brain done on the second post-operative day shows evidence of craniotomy. Surgical changes seen within the hypodense lesion. No increase in edema or midline shift seen.

Histopathological examination revealed neoplastic changes in the biopsied brain matter with bizarre nuclei and vascular proliferation and areas of pseudo-palisading neoplastic cells suggestive of WHO Kernohan grade IV glioma or glioblastoma multiforme(fig 8). Immunohistochemistry revealed positive staining for both glial tumour marker and cell proliferation markers like p53, s100, gfap and ki 67, proving high grade glioma (fig 9).HPE report).

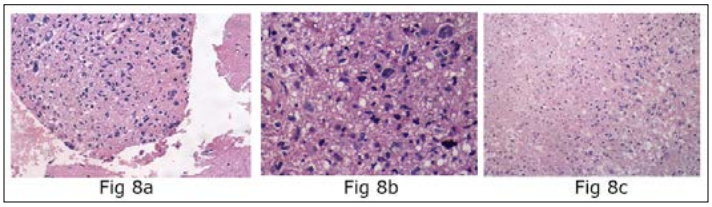


**Figure 8**: Histopathology indicating malignant glioma

Fig 8a: Histopathology showing the neoplastic region within normal brain tissue.
Fig 8b: Bizarre nuclei and vascular proliferation
Fig 8c; Necrosis with pseudo-palisading of necrotic cells.

He was followed up for a year in the outpatient clinic while he underwent radiotherapy and chemotherapy as per the WHO guidelines. However, unfortunately, he succumbed to sequelae of raised intracranial pressure within a year of brain tumour diagnosis.

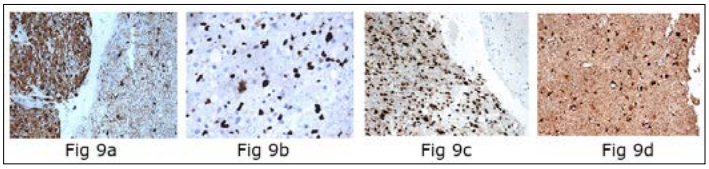


**Figure 9**: Immunohistochemistry indicating malignant glioma

Fig 9a: (H & E x 20) Tissue showing glial fibrillary acidic protein positivity, a marker for glial tumour.
Fig 9b: (H & E x 40) Tissue showing increased percentage of cells staining for Ki 67, a marker of cellular proliferation.
Fig 9c: (H & E x 20) Tissue showing excessive expression of p53, an oncogene protein.
Fig 9d: (H & E x 20) Tissue showing positive staining for s100, a marker for glial tumour.
H & E : Hematoxylin and Eosin

## Discussion

Trauma to different parts of the body causes local accumulation of inflammatory substances which can later on lead to neoplastic transformations. The famous pathologist, Rudolf Virchow hypothesized that chronic inflammation was the origin of cancer [8]. This was based on the hypothesis that some inflammatory chemicals and irritants, together with the tissue injury and ensuing inflammation can enhance cell proliferation. Inflammatory cells release growth and survival factors, promoting angiogenesis and lymphangiogenesis leading to precancerous DNA damage [9]. Lipomas have been known to occur in regions of large hematomas caused by massive trauma in different parts of the body especially in women [10].

Zhou et al proposed that trauma probably acts as a co-carcinogen in the presence of an initiating carcinogen, i.e. it may induce the proliferation of "initiated " cells [4]. They described the following criteria for causal relationship between trauma and tumour: (1) the patient had been in good health before suffering the head injury, and early brain CT was negative; (2) the blow was severe and caused brain contusion or intracranial hematoma with a secondary reparative process; (3) the location of the impact and the occurrence of the tumour corresponded exactly one to the other; and (4) there was a more than one year interval between trauma and the appearance of the tumour. In our case report, the findings corresponded to these criteria.

Some earlier studies have shown no significant increase in incidence of brain tumours in head injury patients [11]. Annegers et al reported that the occurrence of subsequent brain tumours in there long term follow up of 2,953 persons series was not associated with the severity or location of the head injury [11].

There have been conflicting reports on the causal relationship between brain trauma and tumours. Nygren et al. found no significant increase in the risk of brain tumour formation after traumatic brain injury while analyzing over 300,000 patients with traumatic brain injury and found 400 cases of brain tumours [12]. A similar cohort in Denmark showed a slightly elevated risk of brain tumour development following TBI [1]. A recent analysis of a very large cohort of over 400,000 patients in Denmark found no association between brain injury and risk of malignant glioma during the first 4 years after injury [13].

However, more recent studies have shown that in comparison, patients with traumatic brain injury were more likely to receive a diagnosis of malignant brain tumours within a 3-year period as comparedto those patients without traumatic brain injury [14]. Histopathology of the tumours developing in the injured lesions vary between glioblastoma multiforme andastrocytomas [3,4,15-18]. There has been more direct evidence of malignant transformation within the region of the injured brain. Zongli et al have actually shown a case where the 29 year old patient was operated for a right

frontal contusion and nine years later was operated for a malignant glioma underlying the cranioplasty in the region of the previous contusion [16]. Trapani et al have shown that serial CT scans for a patient presenting with headinjury were normal till four years later when a lesion was seen in the region of the contusion diagnosed as a glioblastoma multiforme following surgery for the same [17]. These favour a causal relationship between headinjury and brain tumour development. Neoplastic transformation have also been reported in other types of brain injury. Teresa et al have shown the development of a glioblastoma multiforme in the postgliotic scar of an MCA infarct 2 years following the incident [19].

Here we report a young 47 year old male patient who had multiple injuries with predominant contusion noted in the right frontal region following a road traffic accident with sufficient impact as demonstrated by the skull base fractures and rib fractures. He was managed conservatively and his scans showed resolutions of the contusions and oedema. He developed a malignant tumour the following year in the same right frontal region (which was the predominant contusion site at the time of injury). The time line for developing the tumour was short (14 months), and what appeared to be a diffusely infiltrative lesion suggestive of a low grade glioma radiologically was diagnosed histo-pathologically to be a malignant one, glioblastoma multiform.

The hypodensities seen in the posttraumatic scans were pericontusional and associated with moderate midline shift of upto 3 mm to the left. The hypodensity and hypointensities seen in the CT and MRI scans during the admission for surgery a year later appears to be more diffuse and honouring the anatomical boundaries of the sulci and gyri with minimal midline shift. It can be argued that the hypodense region in the right frontal region noticed in the CT scan done during his admission for headinjury is probably a neoplastic lesion. However, there is evidence of haemorrhage within the lesion, which could be explained with superadded headinjury. Resolution of the haemorrhage on followup scans as seen in this case is rare in malignant tumours.

The MRI study done a year later reveals a hypointense lesion in the right posterior frontal region which is suggestive of a low grade glioma. There is no midline shift and there is complete resolution of all other traumatic contusions. The right frontal regionhypodensity seen in the CT scan at the time of admission for surgery is more extensive, and not associated with a midline shift and is not the same as the one noted at the time of admission for the headinjury. Since the patient was well preserved and the lesion was in the eloquent area, we chose to do awake craniotomy in order to reduce incidence of postoperative deficits. The surgery was successful and the postoperative scans indicate the location of the tumour biopsy to be appropriate within the radiological location of the tumour. Both the histopathology and immunohistochemistry of the biopsied brain have shown malignant lesion. We observed that the head injury in our case report was severe and that the patient recovered radiologically and clinically to normal before developing the malignant tumour in the location within 15 months. This further proves that there seems to be an association for neoplastic transformation in injured areas of the brain subsequent to inflammatory changes which may have lead to mutations or accumulation of procarcinogens.

Chronic inflammation has been shown to be a major predisposing factor for development oftumours, including, but not limited to, hepatocellular carcinoma and colon cancer (Ref 9). Multiple brain injuries (a brain injury in infancy followed by another TBI later in life) may be much more likely to produce a primary tumour than a single injury [20]. This may indicate that the severity of the injury may correlate to the risk of developing a tumour as a result of post-traumatic inflammation, stem and progenitor cell transformation [21].Preston-Martin etalfound that head injury resulting in loss of consciousness or a permanent scar increased the risk for brain tumour especially meningiomas in men lending some credence to the connection between brain injury severity and subsequent tumour development [2].

In our case report the initial trauma was severe and caused not only contusions but pericontusionaledematous changes with mass effect and midline shift. The contusion induced inflammatory changes may have triggered a malignant transformation subsequently, though the post head injury (a month later) CT scan showed complete resolution of the contusion. The rapidity of the development of the tumour in the region of the head injury may be linked to the severity of the head injury and needs further evaluation.

The technique of using fMri and awake craniotomy for brain tumour located in the eloquent cortex reduces the morbidity of the disease. In our case report, the patient remained well preserved neurologically and underwent an early discharge following awake craniotomy for brain tumour surgery. We have demonstrated radiologically, that the location of the tumour was within the area of the previous head injury and that the histopathology correlated to the radiological site of the lesion as demonstrated in the post-operative CT scan of the brain.

The incidence of high grade glioma is usually higher in older age group, peaking in the 75-84 age group [22]. Oligodendrogliomas and oligoastrocytomas are most common in the 35-44 age group. In our case report, the patient was a 46 year old middle aged man who developed a malignant brain tumour in the region of the previous head injury. The role of the severity of the injury leading to malignancy needs to be explored with further studies. Road traffic accidents are common in the younger age group, and the improved infrastructure increases the risk of severe head injuries as compared to mild head injury. Modern aggressive intensive care reduces mortality and more patients with severe head injury are surviving. We recommend close and long term follow up of such patients for early diagnosis in case of subsequent brain tumour development.

## Conclusion

The development of a malignant tumour in the same location as the traumatic brain injury suggests that severity of brain injury can lead to neoplastic transformations within a short period. Patients with moderate to severe head injury need close followup post headinjury with regular clinical and radiological assessments. There may be a role for anti-inflammatory agents in reducing the risk of developing post traumatic brain tumours.

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