Romanian Neurosurgery (2019) XXXIII (4): pp. 385-395
DOI: 10.33962/roneuro-2019-063
www.journals.lapub.co.uk/index.php/roneurosurgery

Secondary giant cell glioblastoma in a multiple drug abuser - simple association or ethiopathogenic correlation? Case presentation and literature review

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Keywords
multiple drug abuse, psychiatric symptoms, secondary giant cell glioblastoma, partial tumour resection

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ISSN online 2344-4959
© Romanian Society of Neurosurgery

First published
December 2019 by
London Academic Publishing
www.lapub.co.uk

ABSTRACT

Experimental investigations have shown that drug abuse initiates a cascade of pathophysiological events including toxic and hypoxic-ischemic injury on neurons, microglia and astrocytes, which finally lead to widespread disturbances in the brain. There are many reports about the psychiatric and neurologic effects of multiple drug abuse, but only a few clinical studies reporting possible correlation between recreational illicit drugs and gliomas.

In this paper we present the case of a 40 years-old male patient, with a long history (almost ten years) of multiple drug abuse, including cocaine, heroin, marijuana, ethnobotanical drugs and nicotine, who was diagnosed and surgically treated for a supratentorial secondary giant cell glioblastoma (sgcGB) developed in a diffuse astrocytoma NOS. Depending on the type of the illicit drug used by the patient and the moment of life he used them, the morphological features identified in the histological samples of our patient confirmed the gliomagenesis effect of chronic multiple drug abuse, but also its inhibitory effects on tumour cells growth. This was due to the fact that although the tumour was large in size and caused brain sub-falcine herniation, the patient reported the onset of seizures only late in the evolution.

In conclusion, the diagnosis of a brain tumour should take into consideration not only patient's clinical and imaging data, but also his lifestyle, especially his addiction to recreational drugs.

INTRODUCTION

The Psychostimulants (cocaine, methamphetamine, etc.), opiates and opioids (heroin, methadone, etc.), sedatives (benzodiazepines), and

some other drugs such as cannabis (marijuana) and nicotine are the most widely consumed recreational drugs in order to obtain a sense of well-being. Unfortunately, in the same time, these drugs of abuse have a significant negative impact on public health as they can induce pulmonary (1-4), cardiovascular (5, 6), renal diseases (7), gastrointestinal and endocrine diseases or infections (8).

However, psychiatric and neurologic symptoms are the most common manifestations of drug abuse toxicity. Along with the psychotic effects of recreational psychostimulants (9, 10), there are also reports of their neurological side effects, such as vasogenic edema formation (11), cerebral and spinal cord infarction, cerebral vasculitis associated with intraparenchymal or subarachnoid haemorrhage (12), hypoxic-ischemic leukoencephalopathy (13), ischemic optic neuropathy as well as partial and generalized seizures (14, 15).

Some researchers have made systematic histological, immunohistochemical and morphometric investigations in order to identify the morphological alterations in the brains of multiple abusers. There are reports of intramyelinic edema and mitochondrial dysfunction due to cocaine abuse, but also of neurovascular toxicity due to heroin (16). Other studies reported a toxic spongiform leukoencephalopathy after intravenous heroin injection or after inhaling heroin vapors (17-19). The morphological substrate of this disease is a spongiform demyelination that develops due to a dysfunction of the oligodendrocyte mitochondria (20, 21).

Neuropathological features encountered included neuronal loss, neurodegenerative alterations with significant widespread axonal damage (22), specific astroglial reaction patterns (23, 24), with a reduction of glial fibrillary acidic protein-immunopositive astrocytes, concomitant microglial activation as well as reactive and degenerative changes of the cerebral microvasculature (due to alterations of the endothelial cell and the basal lamina) (25). Fredericks et al. reported nonnecrotizing, nonleukocytoclastic small-vessel arteritis associated with cocaine use (26). On the molecular level, alterations in the expression of transcription factors and changes of brain neurotransmitter systems have been reported, too (27).

All these results have provided evidence that drugs of abuse initiate a cascade of pathophysiological events including toxic, hypoxic-ischemic injury, microglial and astrocytic - associated cytokine releases, which finally lead to widespread disturbances within the complex network of central nervous system cell-to-cell interactions (25, 28).

However, as far as we know, there is a scarcity of literature concerning the correlation of drug abuse with the development of a cerebral glioma. There is only one epidemiological study published in 2004 by Efird et al. that found a 2.8-fold increased risk for malignant primary adult-onset glioma for people who had smoked cannabis once or more per month (29).

In this paper we present the case of a 40 years male patient, a chronic multiple abuser for ten years, who was diagnosed and treated for a supratentorial secondary giant cell glioblastoma (sgcGB) developed in a diffuse astrocytoma NOS. We discuss the possible role of drug of abuse effects on tumour initiation, development and progression taken into consideration patient's history of multiple abuse.

Case presentation

A male patient, 40 years old, heavy smoker (about 20 cigarettes per day for 30 years), was brought by his family to the "Socola" Institute of Psychiatry, Iași, Romania, for strong headache and altered mental status over the last 24 hours. They considered that patient's status was the effect of his dependence on psychoactive substances as he had a long history (almost ten years) of multiple abuse, including cocaine, heroin, marijuana, and ethnobotanical drugs. Firstly, he used cocaine for five years, then he continued with heroin and marijuana for another two years and finally he only consumed ethnobotanical drugs over the most recent three years. The patient's relatives also declared that he had symptoms of anger or euphoria and changes in behaviour over the last twelve months, but also a state of sleepiness in the last month.

The patient complained of intermittent diffuse headaches, which developed during the preceding months and improved with the use of ethnobotanical drugs.

On physical examination the patient was apparently conscious, cooperative, and partially communicative. He had temporo-spatial orientation

and only presented a slight attention deficit. He denied any hallucinations and alcohol consumption, referring only to the chronic consumption of psychoactive substances.

The general medical examination was unremarkable. His blood pressure was 136/96 mmHg, pulse = 90 beats/minute, temperature = 36.3^0C, and glycemia = 113 mg/dl. There were no relevant family risk factors for neoplastic disease.

One day after his admission in the psychiatric unit, the patient's condition progressively worsened. The vomiting was triggered with a continuous frequency, even from the sitting position. Brain computer tomography (CT) scans, carried out in emergency, highlighted a large, irregularly shaped fronto-temporo-parietal expansive mass lesion, being hypo- and isointense on native examination, and with evidence of post-contrast heterogeneous enhancement; it was surrounded by an edema and induced an important mass effect. He was transferred to the 2nd Neurosurgery Clinic, "Prof. dr. N. Oblu" Emergency Clinical Hospital, Iasi, Romania, and a surgical intervention was performed the same day after admission with partial tumour resection.

The histopathological examination identified an astrocytic tumour of low cellularity, moderate nuclear atypia and focal microcystic degeneration (Figure 1, A and B). Some tumoural cells demonstrated apoptotic changes (smaller size, dark eosinophilic cytoplasm, condensed and hyperchromatic chromatin) (Figure 2, C and D). There were only few thin-wall vessels with near normal morphology (Figure 2,E and F). The diagnosis of a secondary anaplastic astrocytoma, WHO grade III (30), developed into a diffuse astrocytoma was established.

Approximately two weeks after his brain tumour surgery, the patient once again presented himself to our neurosurgical department with nausea, vomiting, diffuse headache, vertigo, and an episode of convulsive crisis. Blood pressure was 130/70 mmHg, pulse = 88 beats/minute, and temperature = $36,8^O$C. Neurological examination showed left facial paresis, muscular weakness and a slightly loss of sensibility of his left part of the body. Some minimal changes of the preoperative laboratory investigation due to previous surgery were identified. There were a slightly increased absolute number of WBC ($13.03x10^3$ /mm^3) and slightly elevated polymorphonuclear neutrophils (71.3%) on a differential count. In addition, a slightly fibrinogenemia (465 mg/dl) and slight hyperglycemia (120mg/dl) were recorded.

Brain CT scans revealed a right fronto-temporo-parietal enhancing tumour with a digitiform perilesional edema, with larger dimensions than the first tumour and with compression and dislocation of medial cerebral structures to the left (approximately 13.1 mm).

The patient underwent surgical therapy with partial resection of the tumour. The microscopical exam of hematoxylin-eosin (H&E) stained histological specimens revealed a highly malignant glial tumour made up of large, grotesque looking multinucleated giant cells, some containing up to 7 nuclei with abnormal shapes (Figure 4, A-D). Some of the nuclei contained prominent nucleoli and atypical mitotic figures. There were numerous blood vessels of various sizes and shapes, many of them presenting marked endothelial proliferation (Figure 4, E and F). Both large and small areas of ischemic necrosis were also observed. Histological reevaluation of all the available specimens highlighted the fact that the tumour was in fact a secondary giant cell glioblastoma (sgcGB), WHO grade IV (30), developed in a diffuse astrocytoma NOS.

One week after surgery the patient had a first check-up brain IRM scan that revealed an increase in the size of the lesion. The patient was referred to the Regional Institute of Oncology in order to be treated with adjuvant chemotherapy (with temozolomide) and radiotherapy. It should be mention that the patient didn't use any psychostimulants in all during this period.

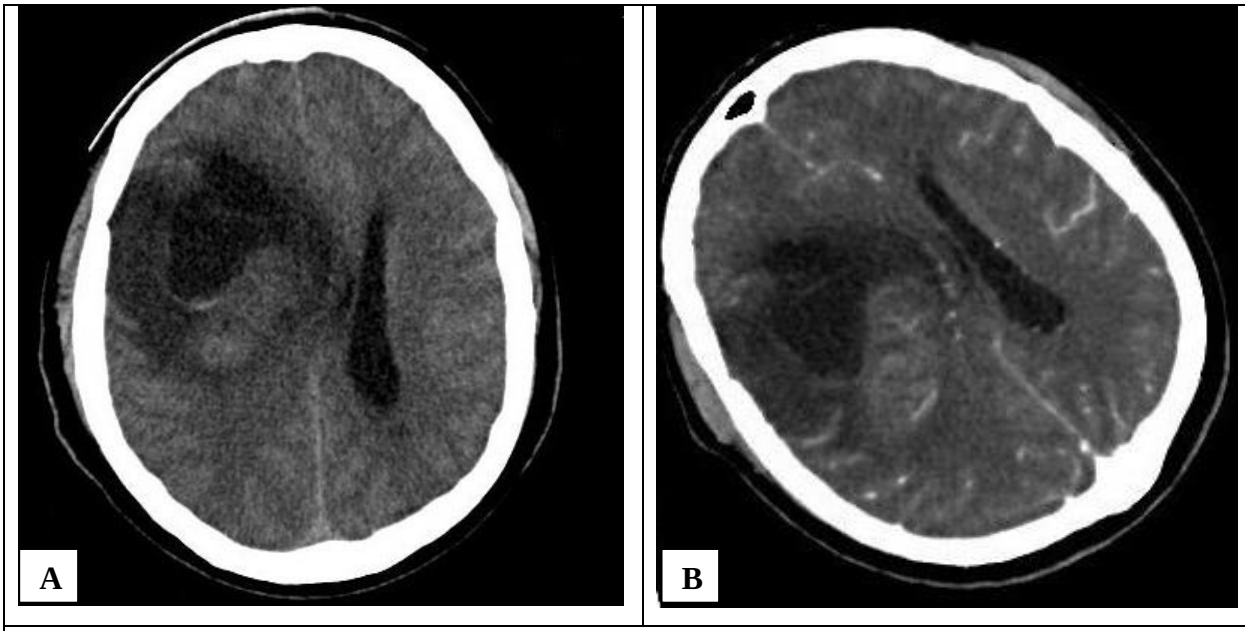
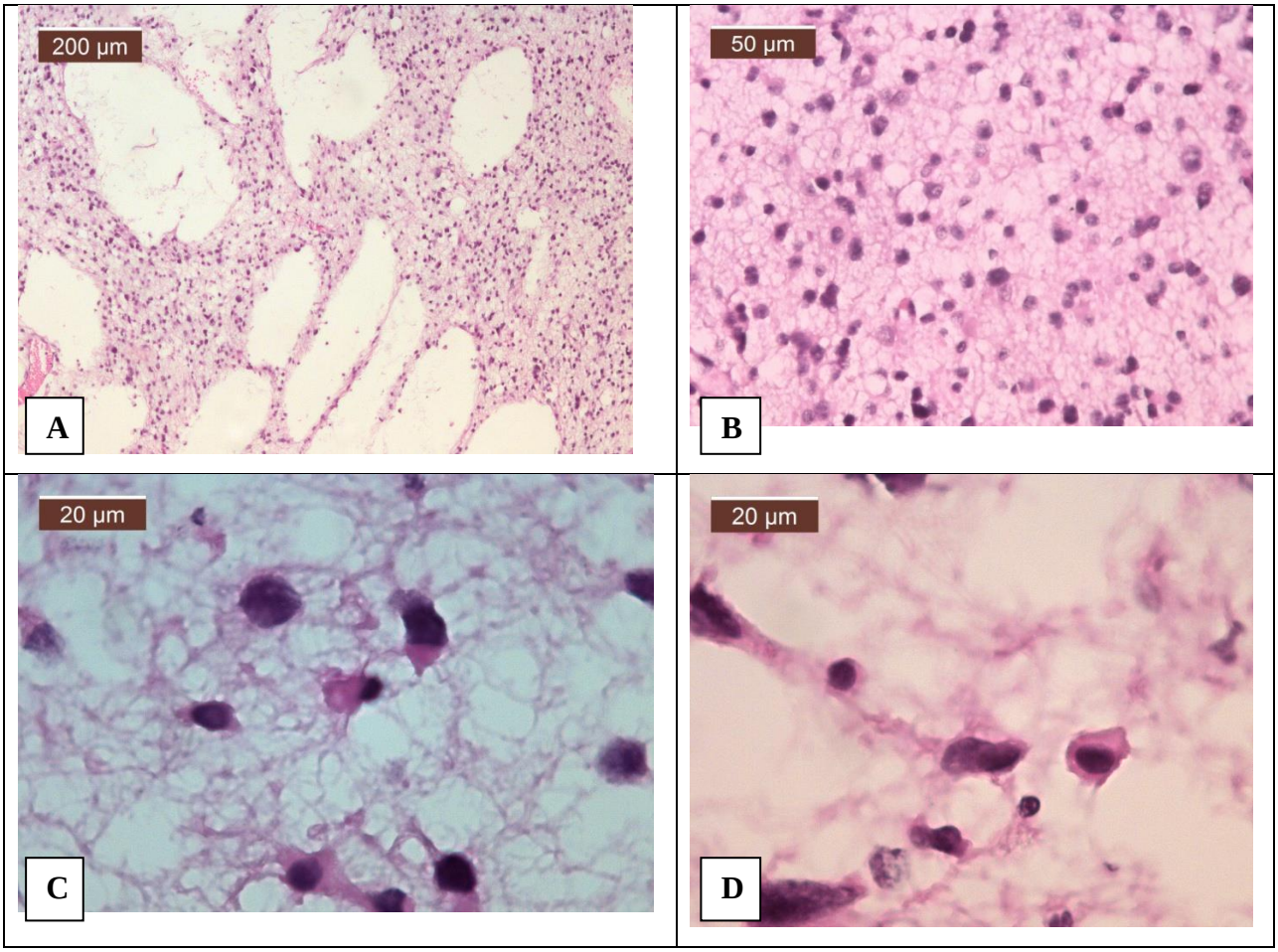


FIGURE 1. Preoperative axial head computed tomography scan (A. native; B. after contrast administration) performed on patient's first admission showed a large irregularly outlined cerebral lesion with central necrosis, peripheral contrast uptake, compression and dislocation of medial cerebral structures to the left.



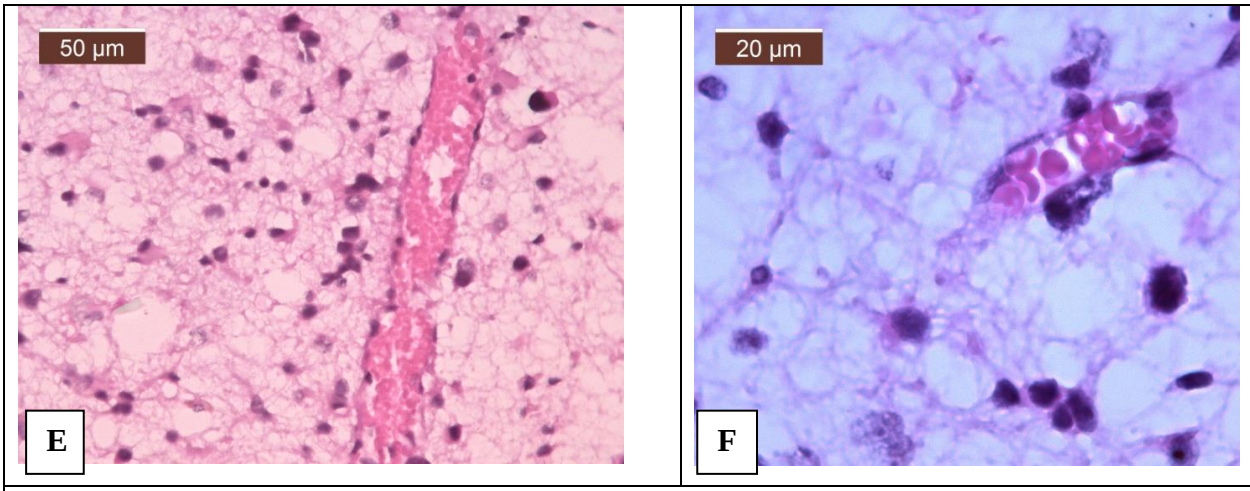


FIGURE 2. Histological sections of the first excised sample identified a glial tumor with focal microcystic degeneration and moderate cell density, made up of uniform cells resembling mature astrocytes, accompanied by dispersed anaplastic cells [A. (H&E, x10); B. (H&E, x40)]; at higher magnification, some tumoral cells revealed apoptotic changes (smaller size, dark eosinophilic cytoplasm, condensed and hyperchromatic chromatin) [C. (H&E, x40); D. (H&E, x100)]; there were also thin-wall vessels with near normal morphology, but surrounded by anaplastic astrocytic cells [E. (H&E, x100); F. (H&E, x100)].

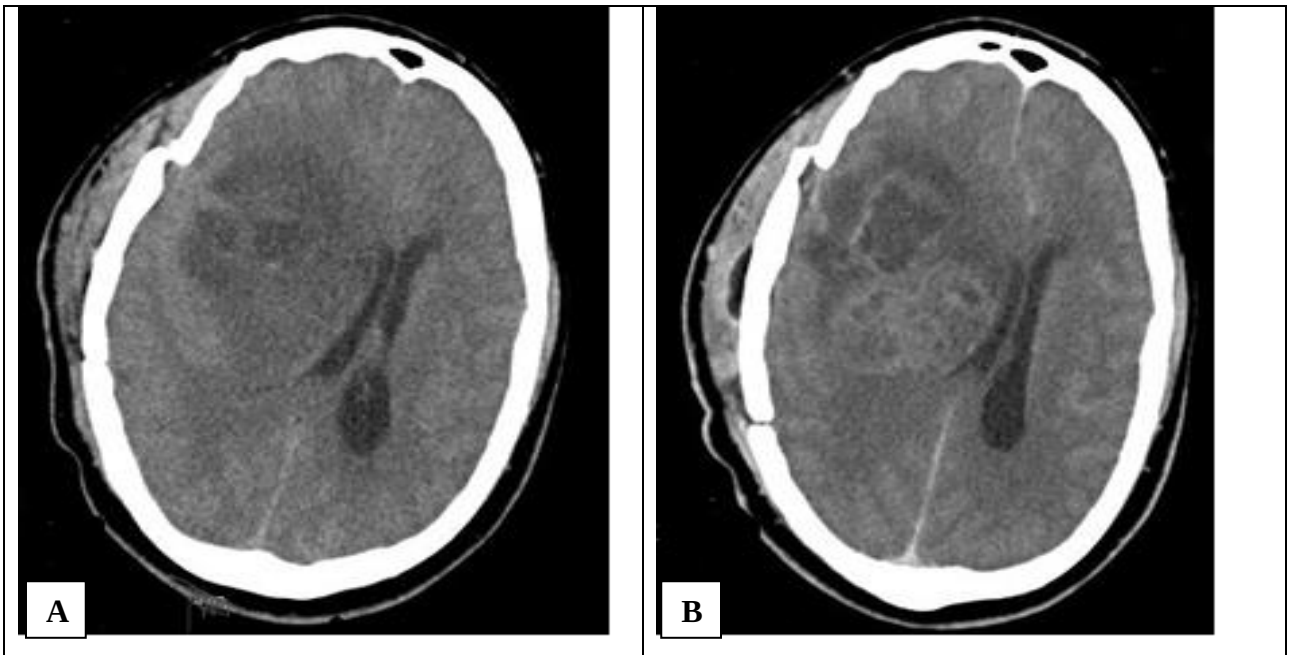


FIGURE 3. Axial head computed tomography scans (A. native, B. after contrast administration) performed on patient's second admission (at two weeks after first tumor resection) identified temporal scalp swelling, temporal craniotomy and increased lesion size with compression and dislocation of medial cerebral structures to the left.

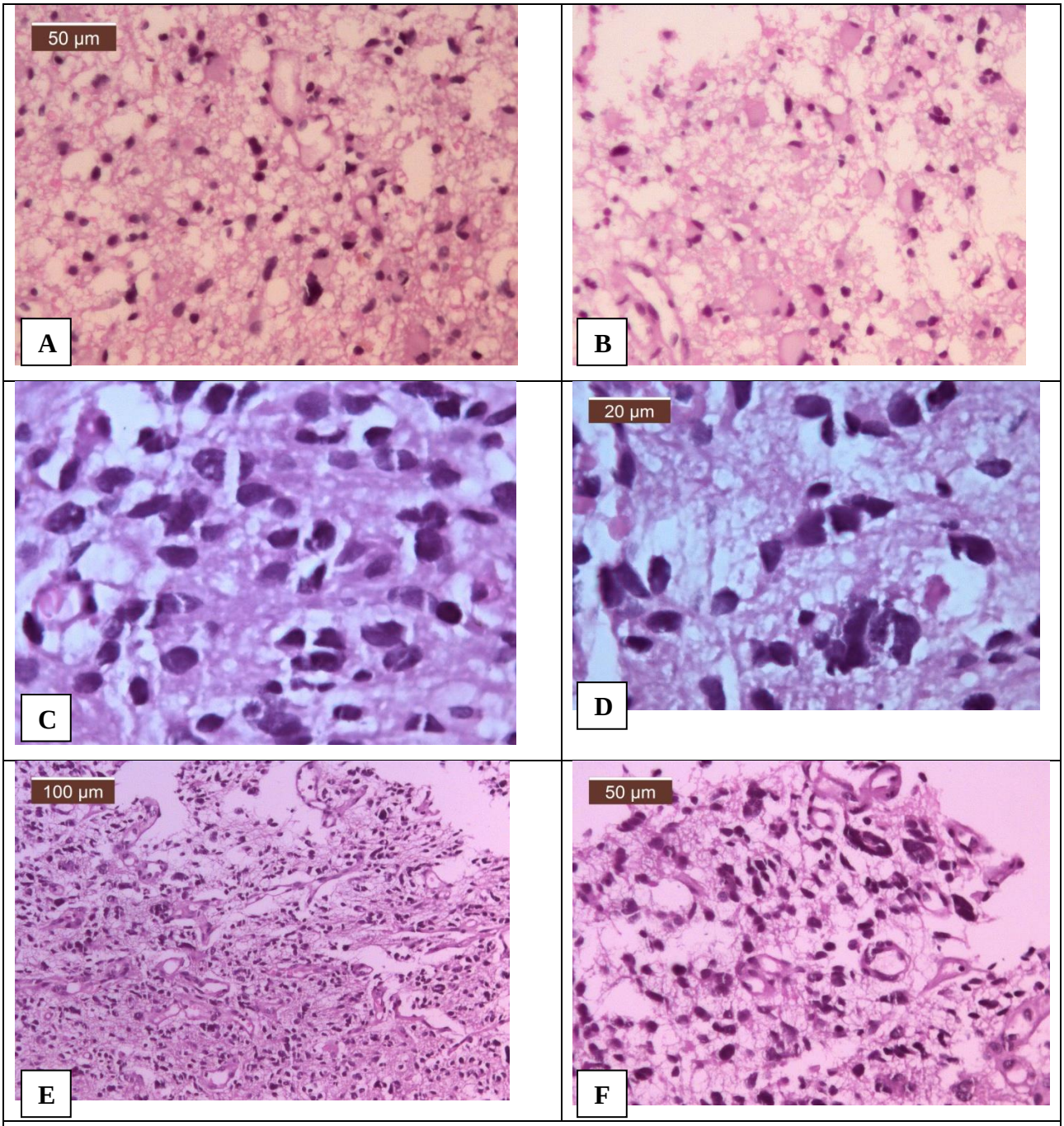


FIGURE. 4. Histological section of the second excised sample pointed out a glial tumor with moderate cell density, and cellular and nuclear pleomorphism [A. (H&E, x40); B. (H&E, x40); a higher magnification revealed in some other areas a highly cellular tumor tissue made up of bizarre looking, giant glial cells, with rich eosinophilic cytoplasm and one or many hyperchromatic irregular shaped nuclei [C. (H&E, x100); D. (H&E, x100)]; in areas close to the central part of the tumor there were many thick-wall vessels with disordered arrangement and moderate endothelial and pericytic proliferation [E. (H&E, x20); F. (H&E, x40)].

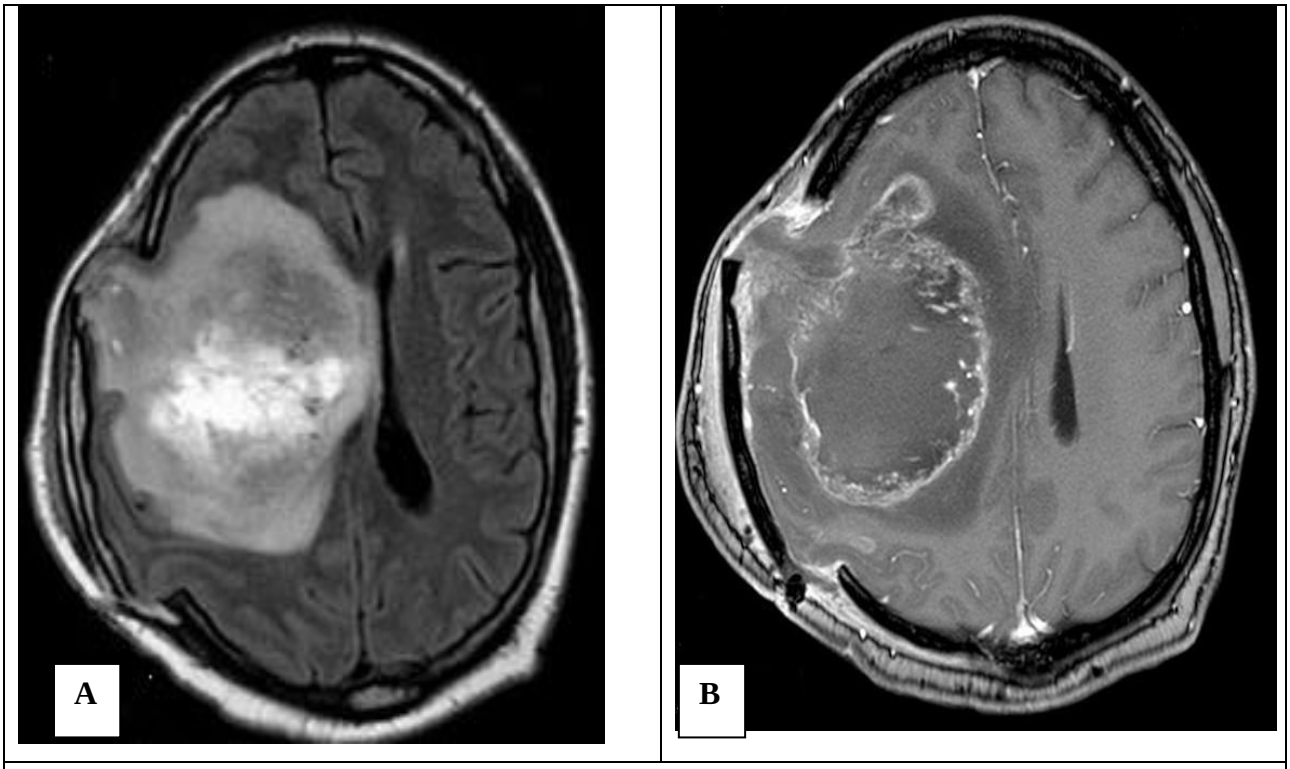


FIGURE 5. Axial MR images (A. FLAIR; B. T1 gadolinium-weighted) performed at one week after the second surgery highlighted a huge heterogeneous infiltrating mass that filled frontal, temporal and parietal lobes, with extensive peripheral edema and midline shift, all these features being indicative of rapid tumor progression.

DISCUSSION

The World Health Organization (WHO) defines multiple drug use "as the use of more than one drug or type of drug by an individual, often at the same time or sequentially, and usually with the intention of enhancing, potentiating, or counteracting the effects of another drug" (31). The most common association is with caffeine, nicotine and alcohol. However, the most important is the association of cocaine, with various combinations of heroin, barbiturates, and marijuana.

Our patient, a multiple drug abuser, who used at least four types of drugs (cocaine, heroin, marijuana, and nicotine) during a period of at least 10 years, presented a glioblastoma that developed in his right fronto-temporo-parietal area, which is known to be affected by alterations due to drug abuse (32).

Major neuropathological mechanisms underlying chronic abuse of recreational psychostimulants (such as cocaine) or nicotine consist of pronounced levels of oxidative stress and mitochondrial dysfunction in the blood-brain-barrier (BBB) endothelium and perivascular cells, i.e. astrocytes, due to an uncontrolled increase in cellular reactive oxygen and nitrogen species (33, 34). The abuse of drugs also induces neuroinflammatory signals and disrupts glutamate homeostasis through their interaction with microglia and astrocytes (35).

The German legist Andreas Büttner, who extensively investigated the neuropathological changes induced by chronic drug abuse, considered that the alterations of the intracellular messenger pathways, transcription factors and immediate early genes within the brain reward system are the most important factors for the development of addiction (25).

In 2016, some American researchers concluded that cocaine determines the proliferation of human astrocytes as this drug increased cyclin A2 (an essential regulator of the cell cycle) expression in human astrocytes. Lee et al. used cocaine with various concentrations and applied them to human astrocyte culture. They found that cocaine with increasing concentrations significantly increased human astrocyte proliferation using the JNK MAP kinase pathway as a driver of cell proliferation (36).

In the same year, certain other American researchers (37) reported the potential of the psychostimulant drugs such as cocaine in inducing astrogliosis through the sequential activation of endoplasmic reticulum stress and autophagy in human astrocytes.

It was possible to demonstrate that cocaine could also induce microglial activation via both the endoplasmic reticulum stress and autophagy pathways (38, 39). Cocaine potentially modulates the immune response in the CNS leading to an neuroinflammatory state that is characterized by enhanced activation of glial cells in the brains of addicts (40) as it seems that cocaine-mediated-increased upregulation of GFAP correlated with increased expression of proinflammatory mediators such as TNF, IL1B, and IL6 (37).

Reactive astrocytosis and microgliosis are classical features underlying neuroinflammation observed in drug abusers and in various neurodegenerative diseases. Astrogliosis is accompanied by the release of a wide range of neurotoxic mediators consisting of chemokines, complementary factors, cytokines, growth factors and reactive oxygen species (41), which remodel the cellular homeostasis in the CNS.

Recently, it has been reported that reactive astrocytes are prone to develop gliomas. Taken into consideration, the older Hansemann concept that tumours were derived by dedifferentiation of mature cells, it is possible to consider that astrocytes are able to dedifferentiate into a pluripotent precursor as a critical step in gliomagenesis (42, 43). In 2002, Bachoo et al. showed that combined loss of p16(INK4a) and p19(ARF), but not of p53, p16(INK4a), or p19(ARF), enables astrocyte dedifferentiation in response to EGFR activation (44) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3033226/ - R61) thus suggesting a possibility that an astrocyte, due to some extrinsic factors in its environment, could acquire some mutations necessary for its oncogenic transformation.

Based on all these scientific facts and the histopathological features of our patient's tumour that revealed a sgcGB developed in a diffuse astrocytoma, we can presume that during those five years of cocaine use, astrogliosis and then gliomagenesis have been triggered. Firstly, a low grade astrocytoma developed as we were able to see in the peripheral areas of the tumour. As he began to use heroin and marijuana, it is more likely that these substances had beneficial effects by reducing edemas, intra tumoural inflammation and the progression of the disease due to tumour cells apoptosis as some other reports have shown (45-46).

Because our patient wasn't able to buy cocaine, heroin or marijuana over the last three years (however only ethnobotanical drugs containing at least benzodiazepine) the tumour slowly progressed to an anaplastic astrocytoma and ultimately to secondary glioblastoma as the histopathological features of these two tumours can be seen in the middle portion and in the center of the tumour, respectively. Also, the absence of the symptoms induces by glioblastoma could correlate with the inhibitory role of benzodiazepine on glioblastoma proliferation (47). However, when the tumour had grown to considerable size, the patient presented periods of apathy alternating with periods of nervousness and ultimately somnolence, nausea and vomiting, that led him to the psychiatrist.

Many scientific studies have indicated the potential use of cannabinoids in the fight against cancer. Experiments carried out on cell lines *in vitro* and on animal models *in vivo* have shown that phytocannabinoids, endocannabinoids, synthetic cannabinoids and their analogues can lead to inhibition of the growth of many tumour types, exerting cytostatic and cytotoxic neoplastic effects on cells thereby negatively influencing neo-angiogenesis (48). Our patient's glioblastoma showed extensive necrotic areas, however intra tumoural microvasculature was reduced and there was only mild proliferation of the pericytes, demonstrating neoangiogenesis inhibition probably due to the toxic effect of multiple drugs abuse.

Pokrywka et al. have shown that the main molecular mechanism leading to inhibition of glioma cell by cannabinoids is apoptosis, being a consequence of induction of endoplasmic reticulum stress and autophagy (49). Indeed, a detailed examination of our patient's histological samples revealed many apoptotic tumour cells with cell shrinkage, dark eosinophilic cytoplasm, and condensed chromatin.

Forty years ago, White et al. (50) demonstrated the fact that cannabinoids inhibited tumour growth because delta9-tetrahydrocannabinol (delta9-THC) decreased DNA synthesis in transformed cell cultures. More recently, other studies have

investigated the molecular mechanism of anti-cancer effect of cannabinoids and have found that these substances inhibited tumour cell growth and induced apoptosis by modulating different cell signaling pathways e.g. via the upregulation of the endoplasmic reticulum stress-related genes ATF-4, CHOP, and TRB3 (51). Delta (9)-tetrahydrocannabinol (THC), the main active component of marijuana, induces human glioma cell death through stimulation of autophagy, a precursor event of apoptosis (52, 53).

The first clinical study with the aim to evaluate cannabinoid anti tumoural action was a pilot study conducted in 2006 in a cohort of terminal patients harbouring recurrent glioblastomas (54). All these patients were administered Δ^9-Tetrahydrocannabinol intra tumouraly. Inhibition of tumour-cell proliferation *in vitro* and decreased tumour-cell Ki67 immunostaining were observed.

Literature has shown that giant cell glioblastoma represented a distinct pattern of cytogenetic alterations when compared with small cell glioblastoma and suggested that multinuclear giant cells evolved from a non-giant tumour cell at an early tumour stage (51). Routine histological preparations of our patient's surgical specimens showed a variety of characteristic changes in tumour cell and nuclear morphology (prominent formation of giant monstrous cells, with bizarre, irregular, and hyperchromatic nuclei, a decrease in the number of mitoses, and severe cytoplasmic degeneration) indicating inhibition of tumour cell division. These morphological changes, quite similar with those induced by chemotherapy on glioma cells (56, 57), probably represent the effects of drug abuse on glial tumour cells.

Johnson and Weissman also reported an interference of cocaine with cell replication as it produced fine structural nuclear alterations in cultured neuroglioblastoma cells. (58). In 1993, Garg et al. exposed C6 glioma cells to cocaine and observed a reduced thymidine and uridine incorporation in these cells after four days of exposure (59). After almost ten years, other experimental studies have shown that various concentrations of cocaine caused a significant down-regulation of CYP2C8 and CYP2C9 genes and a decrease in the level of cellular protein in human U373 MG astrocytoma cells (60). More recently, Badisa et al. have demonstrated that the dual inhibition of cell cycle phases at G0/G1 and G2/M could appear in C6 glioma cells exposed to cocaine (61).

All these articles represent the evidence that cocaine exposure may be the cause for the appearance of monstrous, bizarre looking nuclei identified in our patient's tumoural astrocytes as their cell cycle was affected. The main molecular mechanism leading to inhibition of proliferation of cancer cells by cannabinoids is apoptosis (49) which was also identified in great number in our patient's histological sections.

Conclusion

The effects of illicit psychostimulant drugs exposure are not fully known. The morphological features identified in the histological samples of our patient revealed a sgcGB developed in a diffuse astrocytoma and in this respect, the case we presented in this paper was able to confirm the gliomagenesis effect of chronic multiple drug abuse. On the other hand, the drugs could have had inhibitory effects on tumour cells growth because, although the tumour was large in size and caused brain sub-falcine herniation, the patient only reported the onset of seizures late in the evolution.

Alongside the toxic effects on healthy organs and systems, these illicit drugs also have the effects of both inducing and inhibiting cancerogenesis, depending on the type of the drug. Therefore, the diagnosis of a brain tumour should take into consideration not only patient's clinical and imaging data, but also his lifestyle, especially his addiction to recreational drugs.

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