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Pitfalls in the diagnosis of glioblastoma

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ABSTRACT

Glioblastoma (GBM) is one of the most dreadful human cancers having a literature-reported median of life of 14 months with maximal treatment. The correct diagnosis is of crucial importance for the best chances of treatment. Misdiagnosis is uncommon, but seen in daily practice, and leads to important delays for patients. This paper will discuss the delays found in glioblastoma diagnosis in a series of 60 newly diagnosed patients. Four out of 60 patients had a delay of more than 6 weeks of treatment initiation, as at first imaging, GBM was not suspected as a diagnosis.

Keywords
glioblastoma misdiagnosis, glioblastoma diagnosis pitfalls, glioblastoma treatment delay

INTRODUCTION

Glioblastoma is one of the most dreadful human cancers having a literature reported median of life of 14 months with maximal treatment[6]. The natural history of the disease is a median of two to three months from diagnosis. Hence the correct diagnosis is of crucial importance so that these patients have the best chances to treatment. The clinical manifestations of glioblastoma vary from headaches to neurological deficits, epilepsy or, in some instances, psychiatric manifestations are seen[21]. Imaging is normally done for neurological manifestations or persistent symptomatology, starting with MRI or CT scan. Resection surgery or biopsy is usually the next step in diagnosing and treating a glioblastoma patient. At surgery tumour tissue is taken and analysed in the pathology laboratory. During all these steps, from first symptoms to diagnosis, due to the complexity of cases, difficulties can arise, and these could lead sometimes to misdiagnosis. This paper will discuss the delays found in glioblastoma diagnosis in a series of 60 newly diagnosed patients.

CLINICAL MATERIAL AND METHODS

From January 2015 to October 2022, 60 newly diagnosed patients with glioblastoma have been operated by the first author either by resection or stereotactic biopsy. Of these patients we have analysed the cases in which the time from first imaging to surgery was more than six weeks. Six weeks is an arbitrary number chosen to sort out only the patients where an important delay has been observed. Usually, in our clinic it takes a maximum of ten days to schedule a patient with

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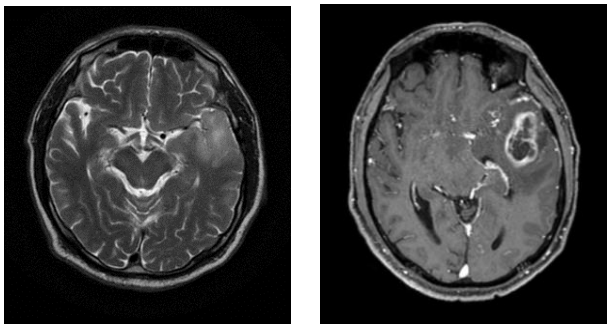
glioblastoma for surgery, so definitely six weeks sorts out only a patient where GBM was missed as diagnosis. In our standard procedure follow up is not an option when GBM is a suspicion.

Medical records were reviewed, including all imaging. Patient data included age, gender, diagnosis, symptoms, past medical history, Karnofsky score, imaging, time from first to secondary imaging, symptoms that led to secondary imaging and then to surgery.

Results

We found five patients out of 60 that had surgery more than 6 weeks after first cerebral imaging was done. Of these five patients 1 had an initial image highly suggesting GBM, but the patient refused any form of treatment for 3 months. She showed up to the hospital eventually with a state of confusion and hemiplegia and surgery was done. This patient is excluded from the discussions as the diagnosis was suspected from the first imaging.

The other four patients had initial imaging 7, 6, 4 and 2 months respectively after first imaging to surgery for GBM and the considered diagnosis was ischaemia for two patients, haemorrhage, and low-grade glioma respectively for the other two (Table 1). The first patient is a 61-year-old male who presents an episode of intermittent paraesthesia on the right side of the body followed by slurred speech, and simple motor Jackson contractions on the right side. A non-contrast MRI scanning is done showing left temporal pole T1 hypointensity, and T2 hyperintensity (Fig. 1).

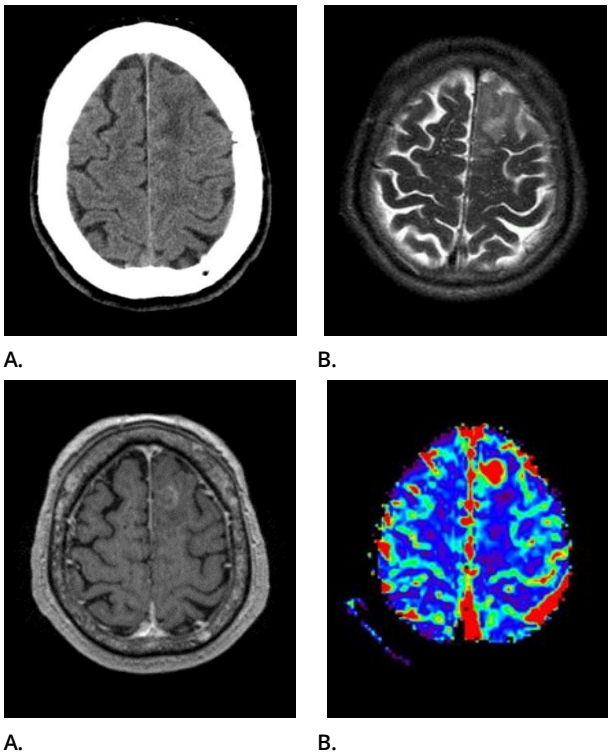


A. B.

Figure 1. (Case No. 1): **A.** MRI T2 hyperintensity at first imaging; **B.** Contrast enhancing T1 MRI showing tumour 7 months later.

The past medical history shows hypertension and dyslipidaemia. Ischaemia is considered as diagnosis and the patient is sent home with antiepileptics and follow up indication. Seven months later the patient presents to hospital with fatigue, headaches and a follow up MRI shows a contrast enhancing lesion. Stereotactic biopsy is done in the first instance in another clinic confirming the diagnosis of GBM, followed by resection surgery in our clinic one month later.

The second patient is a 69-year-old male who presents to the emergency room with an episode of confusion and memory disturbances. An initial CT scan is done, and the patient is considered to have had a stroke. Low resolution MRI is done during the same hospitalisation, and it does not raise the suspicion of tumour. Initial evolution is favourable, and the patient is discharged home. Few months later progressive confusion is observed, situation which culminates with a grand-mal convulsion. He is referred to the emergency room where new scanning is done including enhanced MRI that shows left frontal enhancing intra axial tumour (Fig. 2). The patient is referred to surgery and the glioblastoma diagnosis is confirmed. Six months have passed between first head scan and surgery.



A. B.

A. B.

Figure 2. (Case No. 2): **A, B.** CT scan and MRI scan at first symptoms; **C, D.** Contrast enhanced MRI and perfusion MRI 6 months later.

The third patient is a 47-year-old lady that is referred to our clinic with confusion, aphasia, right side

hemiparesis, having hypertension and epilepsy as past medical history. Four months in advance the patient presents to the emergency room with right side hemiplegia. A CT enhanced and non-enhanced scanning shows a left frontoparietal profound ICH (Fig 3). She is considered to have haemorrhage after hypertensive bleed, and she is discharged to rehabilitation. There is initial good evolution but 3 months later the patient slowly deteriorates presenting again to the emergency room with confusion, aphasia and deteriorated right sided hemiparesis. MRI shows a contrast enhancing tumour. The patient is referred to surgery and GBM is confirmed by the pathology report.

Table 1. Medical record details of patients. LGG – low grade glioma

No	Gender	Age	Initial imaging	Initial diagnosis	Time to surgery	Initial symptoms	Karnofsky score before surgery
1	Male	61	MRI	ischemia	8 months	epilepsy	90
2	Male	69	CT/MRI	ischemia	6 months	confusion	70
3	Female	47	CT	hemorrhage	4 months	hemiplegia	40
4	Female	61	MRI	LGG	2 months	slurred speech	90

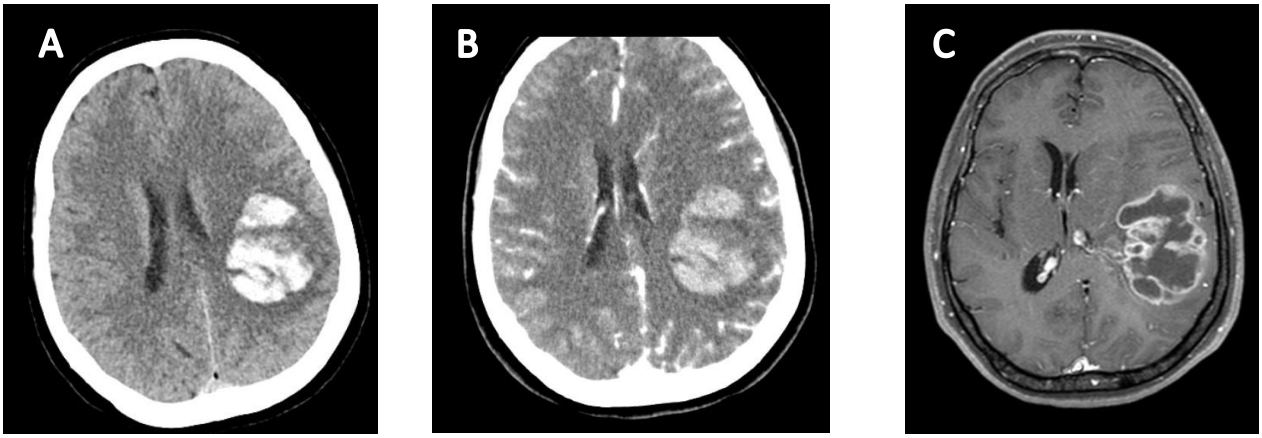


Figure 3. (Case No. 3): **A.** Non enhanced CT scan showing ICH at first symptoms; **B.** Contrast enhanced CT scan with no obvious tumour; **C.** Contrast enhanced MRI 3 months later showing tumor, highly suggestive for GBM.

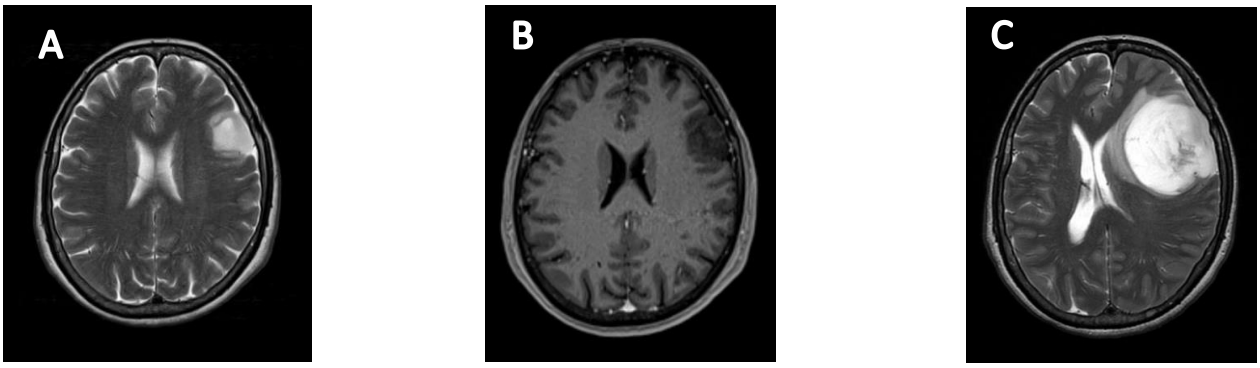


Figure 4. (Case No. 4): **A.** T2 hyperintensity 1 at first symptoms; **B.** Contrast enhanced T1 at first symptoms; **C.** T2 hyperintensity 6 weeks later. Very fast growing is to be observed.

The fourth patient is a 61-year-old lady that is referred to the neurology department for slurred speech. Initial contrast enhanced MRI is done showing a left frontal tumour in the vicinity of Broca area which is considered as low-grade glioma (Fig 4). Initial evolution is favourable under corticosteroids and the patient is sent home with MRI follow up indication. Six weeks later after initial good clinical evolution the slurred speech reappears, and the patient complains also of headaches and fatigue.

Imaging studies show an important augmentation of the tumour which is highly suggestive for glioblastoma at this point. The patient is referred to surgery confirming diagnosis.

Discussions

Misdiagnosis can be seen in different phases of the GBM diagnosis. Misdiagnosis can be of different sources: symptomatic/clinical origin[12,13, 14, 19], of radiological origin, of surgical origin or of pathology origin [5, 9]. When considering the radiological origin of misdiagnosis in glioblastomas, the initial image can be interpreted as other diagnostics like lymphoma[4], metastasis, meningioma[10], ischemia[7,17], haemorrhage[11], parasites[23], abscess[1], inflammatory diseases and degenerative processes[13]. It can even be misdiagnosed as contusion[15]. Other sources of errors can be seen but the discussion is beyond the scope of this article.

In this cohort of patients three of the 60 patients have been considered on initial scanning of having other diagnosis than tumour. A fourth one has been diagnosed with tumour, but it has been considered to be a lower grade, whose treatment implied only follow up if the diagnosis were to be correct.

The survival of patients with glioblastoma is dismal. With treatment, most of the teams report a 14 months median survival. Without treatment the median survival is two to three months[6]. Sometimes patients present as emergency cases and surgical treatment needs to be instituted immediately. This is usually the case of high-volume tumours that have mass effect. In such cases the survival of the patient can be even of days without surgery[14]. Very fast evolution can be seen[23] confirming in vitro studies[8]. In our current practice we have all met patients, in whom despite maximal treatment with surgery, very fast recurrence of tumour is observed. Case number four in this article seems to have such an evolution (Fig 4).

The importance of a correct diagnosis is crucial for patients with glioblastoma because of the speed of evolution of this disease. The longer the delay to diagnosis, the more difficult the surgery. The delay allows the spread of the tumour, by infiltrating farther into the brain. There are several prognostic factors for patients with GBM and one of them is the extent of resection. There are multiple studies showing that the extent of resection is important on the survival of these patients[16]. The sooner the diagnosis, the better for the patient in terms of surgery complexity and initiation of treatment. The delay makes surgery more complex, resection complexity usually being proportional with the size and location of the tumour. An important part of GBM patients is sent directly to palliative care, in part probably due to the operability of the tumour[18], meaning that a late diagnosis can even prevent any initiation of active treatment.

Two of our patients were considered to have an ischemic stroke. They were discharged home with prophylactic antithrombotic therapy, but with no clear follow up indication of MRI, as tumour was not considered as differential diagnosis. There are other case reports in literature with an almost identical trajectory with a percentage of misdiagnosis up to 10% in different series[3]. In our patients, presentation at the hospital did not imply thrombolysis or thrombectomy, but should they have arrived at the hospital inside the thrombolysis window, the stroke treatment could have harmed them as thrombolytic therapy should not be given to patients with brain tumours[17]. For the third patient, hypertensive bleed was the diagnosis on the initial enhanced CT scan. The diagnosis of tumour was not suspected. Hence, the patient presented three months later with deteriorated symptomatology. A contrast enhanced MRI showed tumour (Fig 3). Other teams report delay of diagnosis in case of haemorrhage[20].

In the case of the fourth patient, on the initial MRI the diagnosis was low grade glioma.

Four out of 60 patients, 6,66% of patients, in this cohort of GBM patients, have been misdiagnosed in a way or another. As this is a devastating disease time is crucial for these patients. Certain teams relate that in the case of misdiagnosis, only initial CT scanning was done[3]. In our cohort three of the patients had initial MRI scanning, situation that could suggest that standard MRI scanning or low-resolution MRI is not always enough in depicting differential diagnosis between ischemic stroke and GBM or between LGG and GBM. Diffusion MRI, including DWI and ADC, should be standard procedure for every brain pathology.

New advanced MRI techniques like spectroscopy, perfusion MRI, DTI should be used in diagnosing and making the differential diagnosis between other brain diseases and GBM[22]. Obviously, advanced MRI techniques cannot be made for every ischemic stroke even in highly developed societies because of

cost-effectiveness issues[11], as for developing societies advanced MRI techniques for every patient is prohibitive. In difficult cases where there is doubt over the diagnosis SPECT[1] and PET CT[2] have been proposed as imaging techniques to be able to sort out the diagnosis.

There are several possible reasons for fallacies in our cases, as retrospectively, few things could have been done better: better communication between clinician and radiologist, closer follow up, better communication with the rehabilitation clinic, advanced MRI techniques when in doubt. These cases leave the impression that the scanning was done at the very beginning of the developing of the tumor. Unfortunately, no genetic profile of the tumor has been done to further understand the evolution of these cases.

GBM could be misdiagnosed as other pathologies like lymphoma, metastasis, or abscess. In these cases, immediate surgery is the standard treatment so at least there is no harm done by any delay. The correct diagnosis is the target for every single case, the diagnosing methods should be properly used, but this discussion is beyond the aim of this study.

Conclusions

Literature suggests that a non-negligible percentage of patients with 'stroke' are actually misdiagnosis for an even more devastating disease. Other brain pathologies have been rarely considered instead of GBM, so it should be kept in mind that GBM is part of the differential diagnosis in other types of diseases of the brain. The conclusion of our study is in concordance with the reports of other teams. There are permanently updated guidelines for the diagnosis of GBM, but the pattern observed in all our cases is that the diagnosis has not been considered in the first instance. Yet, the multitude of teams reporting misdiagnosis shows that this problem is not yet solved. Improvements can be done in decreasing the number of misdiagnoses in GBM patients, but the diagnosis is not always straight forward, nor advanced technology is readily available.

List of Abbreviations

ICH: intracerebral haematoma;
GBM: glioblastoma;
MRI: magnetic resonance imaging;
CT: computed tomography;
LGG: low grade glioma.

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