



Early stage glioblastoma: retrospective multicentric analysis of clinical and radiological features

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Abstract

Objectives The aim of this study was to report our experience with early stage glioblastoma (e-GB) and to investigate the possible clinical and imaging features that may be helpful to the radiologist to correctly diagnose this entity.

Methods We performed a retrospective research of patients diagnosed with glioblastoma at two hospitals during a 10-year period. We reviewed all pre-operative MR and included only patients with early stage GB lesions, characterized by hyperintense on T2-weighted signal, with or without contrast-enhancement at post-contrast T1-weighted images, without “classic” imaging appearance of GB (necrosis, haemorrhage, oedema). All preoperative MR were evaluated by an experienced neuroradiologist and information on patients’ demographics, clinical presentation, follow-up, and histopathology results study were collected. When available, preoperative CT examination was also evaluated.

Results We found 14 e-GBs in 13 patients (9 males, 4 females, median age 63 years) among 660 patients diagnosed with GB between 2010 and 2020. In 10 lesions, serial imaging revealed the transformation of e-GB in classic glioblastoma in a median time of 3 months. Clinical presentation included stroke-like symptoms, vertigo, seizures and confusion. Preoperative plain CT was performed in 8/13 cases and in 7 e-GBs presented as a hyperdense lesion. Ten out of 14 lesions transformed in classic GB before surgical intervention or biopsy. All lesions revealed typical immunohistochemical pattern of primary glioblastoma.

Conclusions E-GB is a rare entity that can often lead to misdiagnosis. However, the radiologist should be aware of its imaging appearance to suggest the diagnosis and to request close imaging follow-up, hopefully improving the prognosis of this very aggressive disease.

Keywords Glioblastoma · Magnetic resonance imaging · Stroke · Seizures

Abbreviations

e-GB Early stage glioblastoma
GB Glioblastoma
T1w T1-weighted

T2w T2-weighted
MPRAGE Magnetization Prepared Rapid Acquisition Gradient Echo

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GM Grey matter
WM White matter

Introduction

Glioblastoma (GB) corresponds to grade IV astrocytoma in 2016 World Health Organization Classification of Tumors of the Central Nervous System (2016 CNS WHO) and represents the most common malignant brain tumour [1]. Identification and diagnosis of brain tumours has been subjected to a renovation, switching from the traditional principle of neuropathological diagnosis to a molecularly oriented diagnosis. Thus, according to 2016 CNS WHO, GB is now categorized in IDH wild type and IDH mutant, with IDH gene status being the major criterion for classification [2]. GB IDH wild type corresponds with *de novo* or primary GB, while GB IDH mutant corresponds to the secondary glioblastoma, deriving from a prior lower grade diffuse glioma. GB IDH wild type is the most common GB (nearly 90%), and it has the most aggressive behaviour, with a mean length of clinical history of 4 months and a median overall survival of 9.9–15 months when surgery, radiotherapy and chemotherapy are administered [2].

In addition to IDH status, other genetic aberrations have been searched and catalogued by The Cancer Genome Atlas (TCGA) Research Network [3], in order to find the ones that may be associated with higher malignant potential, better response to treatment, and targeted therapies.

Immunohistochemistry tests are routinely performed, in addition to IDH status, to research the most common alterations, such as loss of heterozygosity (LOH) on chromosome 10q, epidermal growth factor receptor (EGFR) amplification, platelet-derived growth factor receptor (PDGFR) amplification, tumour protein 53 (TP53) mutation, cyclin-dependent kinase inhibitor 2 A/B (CDKN2A/B) deletion, phosphatase and tensin homolog (PTEN) mutation or deletion, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation [4].

Despite the wide variety of genetic profiles, at imaging and particularly on MRI, GB typically reveals a heterogeneous lesion with ring-like enhancement around necrotic central components, with surrounding T2 fluid-attenuated inversion recovery (FLAIR) signal abnormality, corresponding to infiltrating tumour and oedema [5].

Besides this classic imaging presentation, there is a subset of GB that is found before it develops central necrosis and mass effect. It presents mostly as an ill-defined T2 weighted (T2w) hyperintense lesion, with or without focal/nodular enhancement and can be misdiagnosed as non-neoplastic lesions such as encephalitis, seizure changes, infarction, venous thrombosis and demyelinating process [6–10]. These GBs with unusual characteristics were defined as early

stage glioblastomas (e-GB) [10]. At present, our knowledge about e-GB imaging findings derives mostly by its description in case reports and case series with a modest number of patients. Among them, one of the most comprehensive analysis, by Toh et al. [11], was based on 26 cases. In their work, they proposed a classification for e-GB and described the pattern of growth of these atypical cortical lesions.

We believe that further research about e-GB is necessary, firstly to raise awareness about this entity, because it may be encountered during routine emergency practice by the radiologist and neuroradiologist, as happened in our case series; secondly to help building a comprehensive and more coherent picture about this topic, considering that the rarity of e-GB makes the literature fragmentary.

The aim of this case series is to share our experience, through the retrospective analysis of e-GBs that underwent serial MR examinations and to investigate the possible clinical and imaging red flags that may be helpful to the radiologist to give these patients the correct diagnosis.

Materials and methods

Patient population

We performed a retrospective analysis at two reference centres for neurological surgery. The study was approved by our institutional review board and the need for informed consent was waived.

We searched for patients diagnosed with GB from a prospectively maintained database of the Pathology department of both hospitals between January 2010 and January 2020. We excluded patients with GBs arising from histology-proved low-grade gliomas or relapsing GBs. For all selected patients we performed a research in the Picture Archiving and Communication System (PACS) of both institutions, and we excluded all patients without a preoperative imaging available. All preoperative studies (MR and CT) were reviewed by a neuroradiologist with more than 15 years of experience, who selected only patients with e-GB findings at preoperative study. We considered as e-GB circumscribed hyperintense areas on T2-weighted and FLAIR imaging, with or without enhancement at T1-weighted (T1w) images, without “classic” imaging appearance of GB (necrosis, haemorrhage, oedema, heterogeneous enhancement). We collected information on patients’ demographics, clinical presentation, imaging follow-up, clinical management and histologic and immunohistochemistry study.

Histology and immunohistochemistry

All cases were confirmed by histopathology according to 2016 CNS WHO [2]. Immunohistochemistry was performed

with specific antibodies (Ab) against GFAP, R132H mutation in isocitrate dehydrogenase 1 (IDH1-R132H) and EGFR. The status of MGMT promoter was also evaluated.

Imaging analysis and clinical management

All preoperative examinations were evaluated for lesion size, location, involvement of grey matter (GM) and/or white matter (WM), presence of restricted diffusion, enhancement pattern and CT appearance, if available. All lesions were categorized following the Toh et al. classification that divides lesions in three groups: type I, lesion involving predominantly GM without any enhancement; type II, lesions involving the cortex and subcortical WM, without enhancement, and type III, lesions involving both cortex and subcortical WM with small focal areas of enhancement at GM/WM junction [11].

MR imaging protocol differs from the two medical centres; however, there are basic sequences that were acquired in all examinations and were used for the evaluation. MR scanner used were a 3 T and 1.5 T. The sequences analysed acquired at 3 T scanner included T1w and T2w turbo-spin-echo (TSE) images, FLAIR, DWI sequence ($b=0$ and $b=1000$), contrast-enhanced (CE) SE T1w and T1w 3D MPRAGE. All sequences were acquired on axial or coronal plane with 3 mm of slice thickness, and T1w 3D MPRAGE sequence acquired with 1 mm slice thickness.

The sequences acquired at 1.5 T scanner included T1w spin-echo (SE) images, FLAIR, T2w TSE images, DWI sequence ($b=0$, $b=1000$) and CE SE T1w sequence. All sequences were acquired on axial or coronal plane with 5 mm of slice thickness.

A standard dose of 0.1 mmol/kg of gadoterate meglumine (Dotarem) or gadobutrol (Gadovist) was injected intravenously for CE sequences.

MR studies were also classified as incomplete if CE T1w sequences were lacking. Emergency or elective setting of imaging was also evaluated.

We collected data about morphologic changes, lesion enlargement and time to transformation in classic GB by revising follow-up imaging. Information about initial diagnosis and clinical management were also recorded.

Statistical analysis

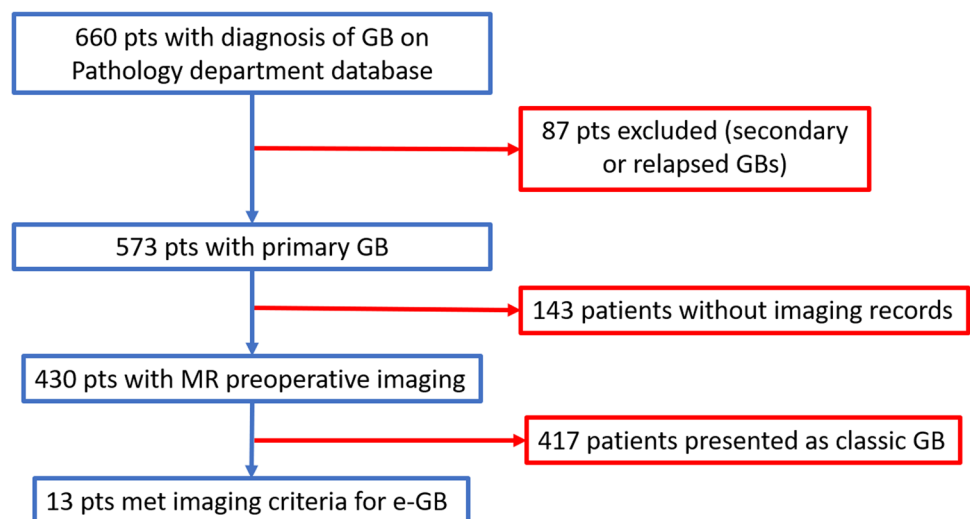
Given the small number of patients enrolled in the study, we performed only descriptive statistics. Continuous variables were presented as mean or median and categorical values as absolute values and percentages. All statistical analysis was performed by using software MedCalc (version 15.6.1; MedCalc Software bvba, Ostend, Belgium).

Results

Patient population

We found 660 patients diagnosed with GB between 2010 and 2020. Among these, 87 were excluded because they were secondary or relapsed GBs treated at other institutions. Among the 573 patients enrolled, 430 had an available preoperative MRI on PACS. After revision of all preoperative MRI examinations, 13 patients (9 males, 4 females) fulfilled the imaging criteria for e-GB (Fig. 1). Median age was 63 years, age range 48–86. One patient presented at preoperative imaging study with two lesions, with a final of 14 e-GBs in our case series. In 10/14 lesions, serial imaging revealed the transformation of e-GB in classic GB. Ten patients presented to the emergency department and underwent the first MR examinations in an emergency setting.

Fig. 1 Algorithm of retrospective analysis and patient selection. pts = patients; GB = glioblastoma



Among the preoperative MR examinations, 8/13 were performed with a complete protocol.

As for clinical presentation, three patients presented with unilateral hemiparesis/hemiplegia/hyposthenia, two with aphasia, two with dysarthria and two with seizures (one in combination with speech disturbances, one with right facial hypoesthesia). Other presenting symptoms were vertigo, confusion and disorientation. Clinical onset was not available in three cases. Table 1 summarizes patients' demographic and clinical information, management and immunohistochemistry results of each lesion.

Immunohistochemistry and histopathology

All lesions revealed typical findings of pseudopalisading necrosis and microvascular proliferation.

All cases resulted IDH wild type, consistent with a diagnosis of de novo type glioblastoma. Seven patients presented EGFR amplification, and two resulted positive for glial fibrillary acidic protein (GFAP). MGMT promoter was methylated in 9 patients (Table 1).

Preoperative imaging analysis

Twelve lesions were localized in the left hemisphere (4 frontal, 3 parietal and 4 temporal lobe, 1 insula) and 2/14 lesions in the right hemisphere (1 frontal and 1 temporal lobe). All lesions were hyperintense at FLAIR images and had a mean maximal diameter of 16 mm (range 4–40 mm). Six lesions involved predominantly GM, seven lesions involved both GM/WM, and one lesion involved only WM. E-GBs were classified into three types using the Toh classification [11]: one lesion resulted type I, two lesions type II and five lesions type III.

In five cases, it was not possible to classify the lesion, because of incomplete MR protocol. One lesion did not match the classification criteria as it involved only WM (Fig. 2).

Seven lesions showed restriction of diffusion with low ADC values. Preoperative plain CT was performed in 8/13 patients and 7 e-GBs presented as a hyperdense lesion (Fig. 3). Table 2 shows findings on preoperative imaging studies and MR findings at diagnosis.

Follow-up imaging analysis and clinical management

In the initial MR report diagnosis was subacute ischemic lesion for 5 patients, venous thrombosis for one patient, non-specific gliotic lesions suggestive for chronic vascular leukoencephalopathy for 2 patients, neoplastic lesion for 2 patients and encephalitis for 2 patients. In one patient no diagnosis was mentioned in the report. Ten lesions

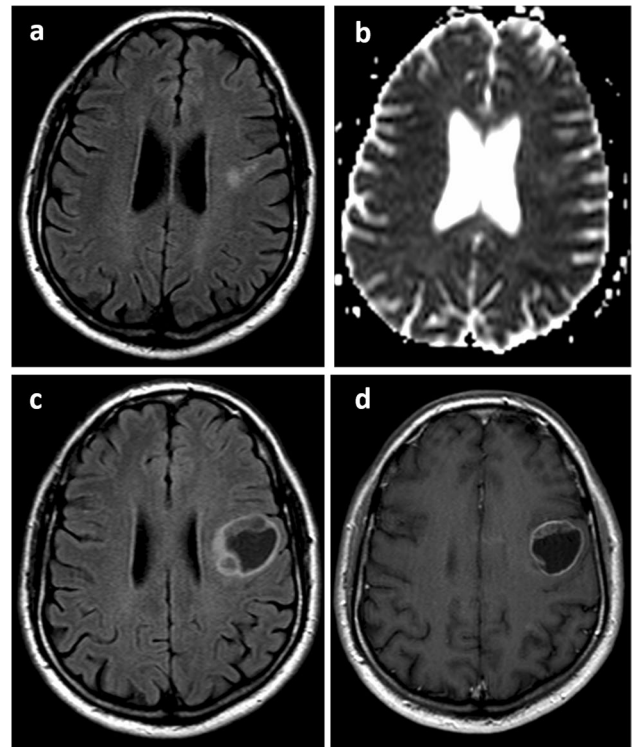


Fig. 2 Case 2, a 60-year male presenting with vertigo. Pre-operative MR shows a hyperintense lesion on FLAIR image (a), involving white matter in the left frontal lobe, without any clear extension to the cortex neither diffusion restriction on ADC map (c). He comes back to emergency department 6 months later for apraxia of speech, and MR examination shows a heterogeneous lesion with necrotic centre on FLAIR image (b) and post-contrast T1 weighted image (d)

transformed in classic GB before surgical intervention or biopsy. Median time of transformation from e-GB to classic GB at MR serial imaging was 3 months, with a maximum of 12 months and a minimum of 4 days (Fig. 4). One lesion transformed from type II to type III, one lesion transformed from not classifiable to a type III lesion and five not classifiable lesions transformed into classic GBs. Mean maximal diameter at diagnosis was 30 mm (range 13–51 mm) with a mean increase of 11 mm [95% confidence interval (C.I.): 7–15] corresponding to a mean increase of 80% (95% C.I.: 39–122) of the original maximal dimension.

Discussion

In our retrospective analysis, we found 13 patients with 14 e-GBs that underwent serial imaging revealing the transformation from early stage to classic GB appearance.

In our case series, we had predominant involvement of left hemisphere (12/14 lesions), with prevalence of frontal

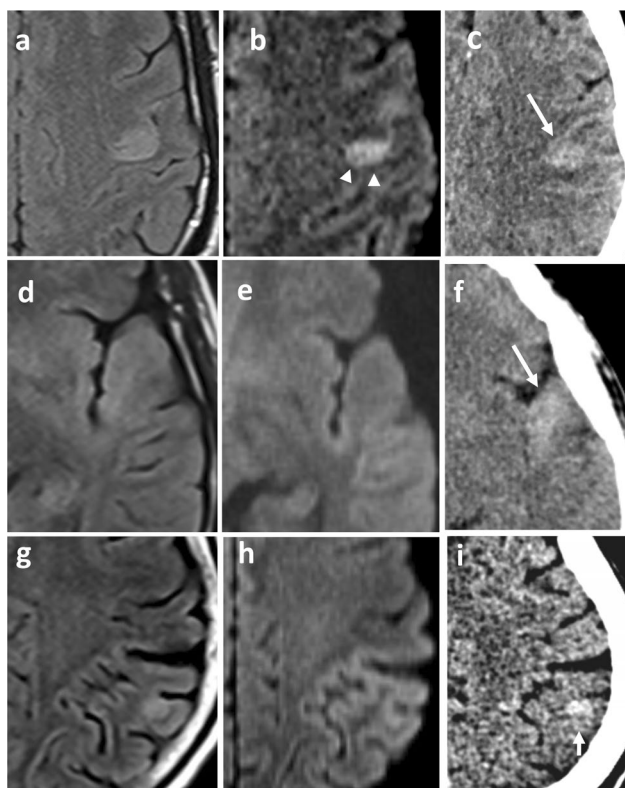


Fig. 3 FLAIR images (a, d, g) DWI images (b, e, h) and plain CT (c, f, i) of case 13 (a-c) and case 6 (d-i). All lesions showed hyperdensity on plain CT (c, f, i, white arrows). Lesion 13 demonstrates hyperintense signal on both FLAIR and DWI sequences, while lesions 6a (d-f) and 6b (g-i) do not present restricted diffusion on DWI (e, h)

(5/14) and temporal lobe (5/14, 2 of them in the hippocampus), while parietal (3/14), and insula regions were less affected.

Even if it has not been demonstrated that early clinical presentation of cerebral tumours corresponds to specific brain localisations, in our experience 11 out of 14 e-GBs were in eloquent areas, such as motor and language control cortex; accordingly, patients presented with acute onset of aphasia, dysarthria, hemiparesis, seizures. Given the variety of presenting symptoms, the first proposed diagnosis ranged from ischemic stroke to encephalitis to venous thrombosis, when malignancy was not considered.

Our data are consistent with other studies, describing frontal lobe as the first most common location of e-GB [12] and a first radiologic diagnosis that was often wrong or at least very challenging [10]. However, literature on this topic is mostly composed by several case reports [6, 9, 13–15], with only a few studies attempting at characterizing this atypical entity and discussing its best management [10, 11, 16].

The immunohistochemistry findings of our case series raised few considerations. Nine lesions out of 14 e-GB

demonstrated MGMT promoter methylation, seven lesions presented EGFR amplification and two GFAP expression. EGFR amplification is associated with high-grade malignancy and a good response for EGFR-targeted therapies and MGMT promoter methylation is a marker of favourable prognosis linked to better response to Tamizolide therapy [4].

Unfortunately, most of e-GB case reports lack of information about molecular profile [6, 14, 17–19]. When described, it presents some similarities to our results as for IDH status, EGFR amplification and GFAP overexpression [9–11, 13].

There have been several attempts at correlating genomics to imaging findings such as radiogenomics studies trying to correlate semiquantitative (i.e. enhancement or T2 flair hyperintensity) and quantitative (i.e. cerebral blood volume or MR intensity texture) attributes to genetic profiles [20–22]. However, this topic is beyond the scope of the article, and the population is too small to find significant correlations.

In our analysis, we tried to categorize lesions according to the classification proposed by Toh et al. [11], which includes 26 patients and represents one of the most comprehensive description of e-GB available at present. This classification is based on the epicentre of the lesion (grey matter, or grey/white matter junction) and its contrast enhancement. In our study, most of the lesions had epicentre in GM/WM junction (6 out of 14), while seven lesions showed a predominant involvement of the cortex, and one lesion involved only white matter without any clear spread to cortical ribbon on preoperative MR.

However, apart from the epicentre, we could not fit 6 out of 14 lesions in any category. The first most important hurdle was the lack of CE sequences in MR protocol performed in the emergency setting that made impossible to classify five lesions. Besides the incomplete imaging protocol, one lesion (case 2) did not match any criteria for Toh et al. classifications, because the lesion involved WM without a clear extension to grey matter or GM/WM junction [11]. To our knowledge, e-GBs with exclusive involvement of white matter with intact cortex at imaging were not previously described [6, 9, 13–15]. With such atypical epicentre, the lesion was considered as part of the mild leukoencephalopathy that affected the patient and he was discharged without scheduling any follow-up.

Overall, our results suggest that in a in a real-world setting, especially in an emergency one, the Toh et al. classification [11], based on the largest number of e-GB collected in a case series, may be difficult to apply because of the need of contrast administration.

Secondly, we found one case with imaging findings not consistent with the pattern of a small cortical lesion that is the most widely accepted description of e-GB. Therefore, we cannot exclude that there is a subset of e-GB with different

Table 1 Patient population

Case	Age, sex	Symptoms	Location	Preoperative MR	Interval to transformation	Histology IV stage GB
1	86, M	Left facio-brachial hemiparesis	Frontal right	Incomplete	4 Days	IDH-; Methylated
2	60, M	Vertigo	Frontal left	Incomplete	6 Months	IDH-; EGFR +; Methylated
3	51, F	Dysarthria, vertigo	Temporal left	Incomplete	4 Days	GFAP +; IDH-; EGFR +; Methylated
4	84, M	Hyposthenia left arm	Frontal Left	Incomplete	6 Days	IDH-; Methylated
5	78, F	NA	Frontal left	Complete	12 Months	IDH-; Non Methylated
6	68, F	Global aphasia, seizures	Temporal left, parietal left	Complete	2 Months	IDH-; Methylated
7	49, M	NA	Parietal left	Complete	2 Months	IDH-; Methylated
8	63, F	NA	Insula left	Complete	2 Months	IDH-; Non Methylated
9	54, M	Confusion	Temporal left	Complete	20 Days	IDH-; Methylated; EGFR +
10	66, M	Global aphasia	Temporal left	Incomplete	21 Days	IDH-; Methylated; EGFR +
11	48, M	Confusion, dysarthria	Parietal left	Complete	3 Days	IDH-; Methylated; EGFR +
12	79, M	Vertigo, disorientation, hemiplegia right lower limb	Temporal right	Complete	4 Months	IDH-; Non Methylated; EGFR +
13	48, M	Partial seizures, right facial hypoesthesia	Frontal left	Complete	NA	IDH-; Non Methylated; EGFR +; GFAP +

Summary of patients' demographic, clinical presentation and immunohistochemistry pattern for each patient. NA=not available; Methylated=MGMT promoter methylated; IDH-=IDH1-R132H negative (IDH wild type); EGFR=epidermal growth factor receptor, GFAP=Glial fibrillary acidic protein

imaging characteristics that may be considered in order to build a more comprehensive vision.

Reviewing all preoperative imaging studies, we believe there are some clinical and imaging red flags that may help the neuroradiologist to propose the early the correct diagnosis.

As regards imaging red flags, plain CT may add some useful clues to the neuroradiologist.

In our case series, 7/8 CT demonstrated regions of hyperattenuation corresponding to the lesion. As described by Wang et al. [16] in the analysis of 8 cases of e-GBs, a combination of DWI and unenhanced CT findings may improve diagnostic accuracy. In fact, even if lesions as encephalitis, infarction, demyelinating or degenerative disease may be associated to hypoattenuation, they do not show hyperattenuation. The interpretation of the hyperdense appearance of the gliomas may be explained by an increased cellularity and vascularisation of the tumoural lesion [18].

In our experience, DWI was not such a discriminating sequence to characterize e-GB, as 10 out of 14 lesions presented hyperintense signal in DWI images, and only seven lesions corresponded to restriction of apparent diffusion coefficient, the other corresponding to T2 'shine-through' effect. This discordance between DWI and ADC map in the diagnosis of glioblastomas has been described [23] as the result of several signal changes, deriving from tumour vasogenic oedema, tumour cellularity, degenerative changes and compression of normal structures. Moreover, diffusion

restriction may also be present in other neoplastic pathologies, such as lymphoma or metastasis, or in non-neoplastic diseases, such as brain abscess, encephalitis, and stroke.

Concerning CE T1w sequences, in literature several lesions are described as non-enhancing [6, 11, 14, 24], so the neuroradiologist may suggest the right diagnosis even with a MR study performed without contrast injection in the emergency setting.

Interestingly, three lesions (case 1, case 3 and case 4) changed MR appearance from e-GB to classic GB in few days. This short time MR follow-up was demanded by clinical worsening, and it demonstrated an increase in dimension of the lesion, and heterogeneous signal due to a central higher signal intensity in FLAIR/T2w sequence, representing necrosis, and an increase in mass effect on the near cortical tissue and oedema (as showed on Fig. 4). In all these cases, contrast media was not administered in the first examination, but in the follow-up examination, CE T1w sequence confirmed the central initial necrosis, with blood-barrier damage and ring-enhancement. Unfortunately, there is no possibility to know if contrast-media administration at the first examination would have shown blood barrier at the beginning, however, necrotic fluid-filled areas appeared on T2w images at the second examination. The change from ill-defined small cortical/subcortical lesion, to heterogeneous lesion with oedema, central necrosis and haemorrhage, helped to suggest the right diagnosis in short time. In literature, it is described

Table 2 Imaging findings

Lesion	Max diameter (mm)	Preop. MR GM/WM	Preop. MR Restriction ADC	Preop. MR CE	Preop. CT	Initial diagnosis	Type	Max diameter at diagnosis (mm)	MR at diagnosis type
1	11	GM+ /WM	–	NA	Negative	Subacute ischaemia	NA	18	III
2	10	WM	–	NA	NA	Aspecific gliosis	NA	25	Classic GB
3	10	GM/WM	–	NA	Hyperdense	Venous thrombosis	NA	27	Classic GB
4	12	GM+ /WM	+	NA	Hyperdense	Neoplastic lesion	NA	19	Classic GB
5	8	GM+ /WM	–	NA	NA	Vascular gliosis	NA	26	Classic GB
6a	26	GM/WM	–	–	Hyperdense	Subacute ischaemia/peri-ictal changes	III	33	III
6b	6	GM+ /WM	–	–	Hyperdense	NA	I	13	Classic GB
7	25	GM/WM	+	+	NA	Subacute ischaemia	III	51	Classic GB
8	26	GM/WM	–	–	NA	NA	II	42	Classic GB
9	35	GM/WM	+	+	Hyperdense	Encephalitis	III	45	Classic GB
10	40	GM/WM	+	NA	NA	Subacute ischaemia	NA	48	Classic GB
11	13	GM+ /WM	+	+	Hyperdense	Subacute ischaemia	III	13	III
12	30	GM/WM	+	+	NA	Encephalitis	III	37	Classic GB
13	12	GM+ /WM	+	+	hyperdense	Metastasis/neoplastic lesion	III	NA	NA

Summary of imaging findings in pre and post-operative MR and CT and imaging classification of all lesions. preop. = preoperative; Type = Type of lesion corresponding to Toh et al. classification [11] GM+ /WM = predominantly grey matter; GM/WM = grey/white matter; WM = white matter; CE = contrast-enhancement; + = present; – = absent; NA = not available

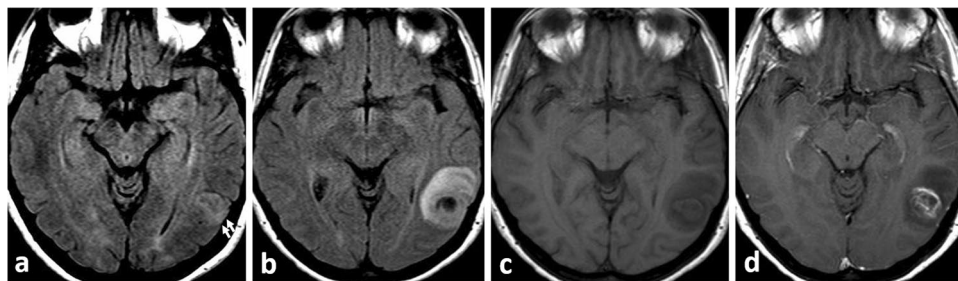


Fig. 4 (Case 3) a 45-year-old woman with dysarthria and vertigo, at first MR showed GM/WM hyperintensity on FLAIR image in left temporal lobe (a, white arrows); 4 days later MR was repeated for

worsening of symptoms, showing a necrotic lesion (b, c) with blood barrier damage and contrast enhancement at T1w image acquired after contrast injection (d)

the short interval of time between e-GB and classic GB appearance [6, 9–11, 13–15, 17–19]; however, these three cases suggest the possibility to shorten the time of follow-up MR examination, especially when new symptoms are present.

Other important red flags concern the discordance between imaging and clinical setting.

Two of our cases (case 6 and 13) presented with seizures. The association between seizures and e-GB has been reported: infiltration of the cortex may result in earlier onset of symptoms and possibly focal neurologic deficits, if the malignancy develops in eloquent areas of the brain [25]. MR signal changes are usually present after prolonged seizure activity, or status epilepticus [26]. Transient seizure-induced

signal changes on MR in patients with first seizures has been described by Kim et al. [27] as peri-ictal changes involving both cortex and thalamus or hippocampus, rather than only unilateral cortex. Seizures combined to with ill-defined hyperintensities on MR or hyperattenuating CT lesions in adult patients are red flags and require close follow-up because of the possibility of high-grade glioma.

As for the differential diagnosis between subacute stroke and e-GB at preoperative imaging, neuroradiologists should consider both onset of symptoms and imaging findings. T2-FLAIR images are positive 6–12 h after onset of symptoms, and ADC require at least 10 days to normalize [28]. It is not uncommon for e-GB to mimic ischemia, as reported by Nishi et al. [15]. In our case reports, reviewing the five cases misdiagnosed as stroke (cases 1, 6, 7, 10, 11), we noticed they presented with cortical ribbon “blurring” of GM/WM junction, and only three cases presented heterogeneous diffusion restriction. On plain CT, both case 6 and 11 showed hyperattenuation. Neurologic deficits with ill-defined prevalent cortical lesions, with no correct correlation between the onset of symptoms and the imaging findings on MR, or hyperattenuation on CT are red flags, and early stage GB should be considered as possible diagnosis.

In this context, the neuroradiologist has the chance to report the lesion at its very early stage, as acute symptoms like seizures or focal neurological deficits are often approached with imaging. Unfortunately, early appearance of glioblastoma is rare. In our research, only 13 patients out of 430 with preoperative imaging in our databases presented as e-GB at imaging. This give us a partial idea of how rare the possibility is to catch the disease in advance. As described in other reports [9, 14, 29], we also observed a rapid growth of the lesions from nodular to the development of central necrosis.

However, it is uncertain if an earlier diagnosis of GB has a true impact on patients’ prognosis. GB is characterized by poor prognosis, with medial survival of about 15 months if surgery, radiotherapy and chemotherapy are all performed [2]. To this aggressive behaviour, correspond an aggressive surgical treatment that aims at performing a maximal and safe resection of the tumour. It was shown that maximal resection prolongs overall survival [30–34]. It was also observed that preoperative MR showing little or no necrosis, little tumour enhancement and a lesser degree of peritumoral oedema are associated to a better prognosis [35]. Reporting glioblastoma at its early stage, when the lesion is still small, especially in young patients, may therefore provide a survival prolongation thanks to a more radical resection.

Limitation of our study is the impossibility to assess the true prevalence of e-GB in our cohort, because not all patients with a definite diagnosis of GB had imaging records available in our PACS. In addition, a proportion of patients presenting with imaging findings consistent with e-GB does

not receive a pathologically confirmed diagnosis, because of the advanced age and/or comorbidities. For these reasons, further studies that combine pathologic data with clinical and imaging data are required.

Conclusions

Awareness of the early presentation of GB is growing; however, we are still far from a comprehensive imaging description of the e-GB. Given the rarity of the condition, case reports and case series will help to give a more detailed picture of this entity, and to catch characteristic imaging findings.

In our case series, we found a combination of clinical settings and relevant imaging findings that enables the radiologist to suggest e-GB as a possible diagnosis and to request close imaging follow-up to exclude the presence of a neoplastic lesion, hopefully improving the prognosis of this very aggressive disease.

Authors contributions All authors whose names appear on the submissions made a substantial contribution to the conception or design of the work, the acquisition analysis and interpretation of data. All authors revised it critically for important intellectual content. All author approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Conflict of Interest The authors of this manuscript declare that they have no competing interests.

Ethics approval Institutional review board approval was obtained.

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