Neurochirurgie xxx (2014) xxx–xxx

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Clinical case

Early presentation of primary glioblastoma

Présentation précoce des glioblastomes primaires

R. Faguer[a], J.-Y. Tanguy[b], A. Rousseau[c], A. Clavreul[a], P. Menei[a,*]

[a] *Department of neurosurgery, university hospital, 4, rue Larrey, 49933 Angers cedex 9, France*
[b] *Department of radiology, university hospital, 4, rue Larrey, 49933 Angers cedex 9, France*
[c] *Department of pathology, university hospital, 4, rue Larrey, 49933 Angers cedex 9, France*

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Glioblastoma
Occult tumor
Early diagnosis
Immunohistochemistry
Molecular biology

ABSTRACT

Background. – Clinical and neuroimaging findings of glioblastomas (GBM) at an early stage have rarely been described and those tumors are most probably under-diagnosed. Furthermore, their genetic alterations, to our knowledge, have never been previously reported.
Methods. – We report the clinical as well as neuroimaging findings of four early cases of patients with GBM.
Results. – In our series, early stage GBM occurred at a mean age of 57 years. All patients had seizures as their first symptom. In all early stages, MRI showed a hyperintense signal on T2-weighted sequences and an enhancement on GdE-T1WI sequences. A hyperintense signal on diffusion sequences with a low ADC value was also found. These early observed occurrences of GBM developed rapidly and presented the MRI characteristics of classic GBM within a few weeks. The GBM size was multiplied by 32 in one month. Immunohistochemical analysis indicated the de novo nature of these tumors, i.e. absence of mutant IDH1 R132H protein expression, which is a diagnostic marker of low-grade diffuse glioma and secondary GBM.
Conclusions. – A better knowledge of early GBM presentation would allow a more suitable management of the patients and may improve their prognosis.

Mots clés :
Glioblastome
Tumeurs occultes
Diagnostic précoce
Immunohistochimie
Biologie moléculaire

RÉSUMÉ

Introduction. – Les signes cliniques et radiologiques des glioblastomes (GBM) au stade précoce ont été rarement décrit et ces tumeurs sont probablement sous-diagnostiquées. De plus, leurs anomalies génétiques n'ont jamais été rapportées.
Méthodes. – Nous rapportons les données cliniques et radiologiques de quatre cas de GBM au stade précoce.
Résultats. – Dans notre série, les formes précoces de GBM sont survenues à un âge moyen de 57 ans. La crise d'épilepsie a été le premier symptôme pour tous les patients. Dans tous les cas, un hypersignal sur les séquences T2 et une prise de contraste sur les séquences T1 avec injection de gadolinium ont été observés sur l'IRM. Un hypersignal sur les séquences de diffusion ainsi qu'une baisse de l'ADC ont été également retrouvé. Ces observations de formes précoces de GBM se sont rapidement développées en des formes classiques de GBM à l'IRM en quelques semaines. Les GBM ont multiplié leur taille par 32 en un mois. L'absence de mutation R132H d'IDH1 sur les analyses immunohistochimiques, marqueur des tumeurs gliales de bas grade et des GBM secondaires, confirment leur caractère de novo.
Conclusion. – Une meilleure connaissance des présentations précoces de GBM pourrait permettre une meilleure prise en charge de ces tumeurs et en améliorer le pronostic.

* Corresponding author. Service de neurochirurgie, centre hospitalier universitaire, 4, rue Larrey, 49933 Angers cedex 9, France.
E-mail address: phmenei@chu-angers.fr (P. Menei).

http://dx.doi.org/10.1016/j.neuchi.2014.02.008
0028-3770/

1. Introduction

Glioblastoma (GBM) is the most common malignant primary tumor of the central nervous system [1]. Most patients with GBM present tumor-related symptoms, such as progressive focal neurologic deficit(s) or increased intracranial pressure. On MRI, typical characteristics of GBM are seen including irregular rim contrast enhancement, central necrosis, and perilesional edema. Despite optimal management combining surgery, radiotherapy, and chemotherapy, the prognosis is poor with a median survival time of 14.6 months [2].

In some patients GBM appears early in the course of the disease, before harboring typical clinical and radiological findings. Presentation at an early stage seems to be associated with seizures, as well as small cortical signal abnormalities [3].

The development of a multimodal MRI including diffusion weighted imaging (DWI), perfusion imaging (PWI) and magnetic resonance spectroscopy (MRS) appears to be useful in distinguishing between an early presentation of GBM and other brain abnormalities [4].

Few studies have reported early clinical and neuroimaging features of high-grade glioma [3–10]. A recent study has reviewed the 15 articles previously published in the literature concerning these occult brain tumors [11].

Nevertheless, although the de novo nature of these early presentations has been hypothesized, their molecular characteristics have still not been defined and their growth is unknown.

We report the clinical, neuroimaging and molecular characteristics of four cases of GBM with an early presentation. We also evaluated the early volumetric evolution without treatments. We discuss which imaging techniques are helpful to identify these early stages of GBM and to distinguish them from other brain diseases. Finally, we propose a management scheme for patients with new-onset epileptic seizures in order not to miss a GBM at a very early stage in the tumor growth process.

2. Methods

2.1. Patients and imaging

Four patients with an early presentation of GBM were treated in our neurosurgery department between May 2011 and January 2012. We reviewed the clinical, neuroimaging and histopathological findings of these cases (Table 1).

All patients first underwent a brain CT scan with and without a contrast agent. An initial cerebral (MRI 1) was performed in all cases with T1-weighted (T1WI) and gadolinium-enhanced T1 (GdE-T1WI) sequences. For three of the four cases, T2-weighted imaging (T2WI) or fluid attenuated inversion recovery imaging (FLAIR), and DWI with attenuated coefficient diffusion (ADC) were obtained. A subsequent MRI (MRI 2) with the same sequences was performed during the second admission. In all cases, the second MRI showed typical findings of GBM leading to surgery for two patients and to a frameless stereotactic biopsy for the other two.

2.2. Tumor volume

For each patient we measured, the three axes of the tumor on the GdE-T1WI. Enhanced areas and central necrosis were considered as the volume of the tumor. In cases of bifocal lesions the larger lesion was utilized for the comparison.

Tumor volume (Vol) was calculated using the validated ellipsoid model [12] defining as:

Vol = (1/6) pi ABC.

A, B, and C correspond to the maximal diameter of the tumor in the three axes (x, y, z). The two volumes were calculated on the MRI 1 and called Vol-1 and on the MRI 2 and called Vol-2. Volume augmentation corresponded to the difference between the two MRI and was expressed in a percentage and in coefficient of multiplication.

2.3. Immunohistochemical analysis and array Comparative Genomic Hybridization (aCGH)

The tumors were classified according to the 2007 World Health Organization (WHO) classification of tumors of the nervous system. Immunohistochemistry was carried-out using antibodies directed against the following antigens: p53, internexin alpha (INA), mutant IDH1 R132H protein, and MIB1/Ki-67.

Three tumors were analyzed by whole genome aCGH. In one case, the analysis could not be performed because of the small sample size (case 2, stereotactic biopsy). Genomic DNA was extracted from formalin-fixed paraffin-embedded tumor samples.

3. Results

3.1. Clinical picture

Patients' age ranged between 45 and 69 years with a mean age of 57 years at the time of first admission. They represented 5.5% (4/72) of the newly diagnosed GBM cases in our department over a nine month period. Patients were admitted for a focal clonic seizure (cases 2 and 4) or a generalized seizure (cases 1 and 3). None had a previous history of seizures.

Diagnosis of GBM was not obtained from the first MRI, thus leading to a misdiagnosis (cavernous malformation, herpetic encephalitis). The patients were discharged from our institution with anti-epileptic drugs and no recurrence of seizures occurred. A second MRI was scheduled at three months follow-up. However, all patients were admitted for raised intracranial pressure one to two months after their first admission.

After the second MRI, all patients underwent surgery. In cases 1 and 3 gross total resection was achieved and in the other two cases, a frameless stereotactic biopsy was performed because of its bifocal localization (case 2) and low KPS (case 4).

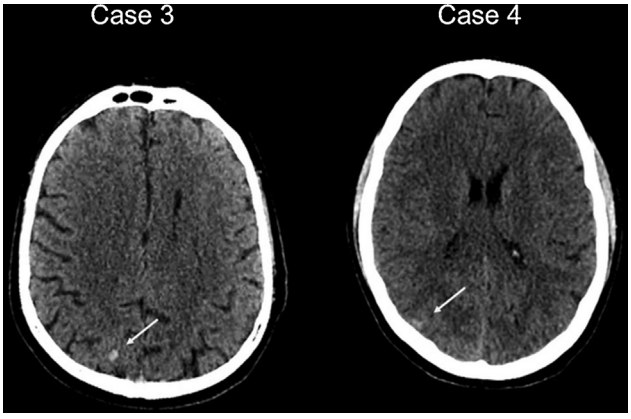

Fig. 1. Early stage GBM on CT. Axial CT scan shows a spontaneously hyperdense cortical lesion mimicking a hemorrhagic infarct in the right parietal lobe (cases 3 and 4).
Stade précoce de GBM au TDM. Coupe axiale de scanner montrant une hyperdensité corticale spontanée mimant une hémorragie au sein du lobe pariétal droit (cas 3 et 4).

Please cite this article in press as: Faguer R, et al. Early presentation of primary glioblastoma. Neurochirurgie (2014), http://dx.doi.org/10.1016/j.neuchi.2014.02.008