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Original Article

Historadiological correlations in high-grade glioma with the histone 3.3 G34R mutation

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ABSTRACT

Background and purpose. – Molecular alterations were recently added to the World Health Organization (WHO) 2016 classification of central nervous system (CNS) tumors. We correlated the histological and radiological features of G34R mutant high-grade gliomas, a recently described hemispheric and supratentorial glioma of children and young adults.
Materials and methods. – We performed a retrospective multicenter study on the histopathological and MRI results of 12 patients.
Results. – All tumors were supratentorial. Several radiological aspects were observed. Height over 12 were bulky and well delineated tumors, without visible peritumoral infiltration on MRI and pathologically characterized by highly cellular tissue associated with a moderate peritumoral infiltrative component. Two tumors were ill-defined and hyperintense on T2 sequences and pathologically characterized by diffuse tumoral infiltration. Two tumors were bulky and well delineated with an infiltrative component, both radiologically and histopathologically.
Conclusions. – These different patterns may correspond to different pathological mechanisms and a potential link with prognosis should be assessed in further studies.

Introduction

The 2016 World Health Organization (WHO) classification of central nervous system (CNS) tumors [1] incorporates specific molecular alterations into morphological diagnoses for the first time. This new concept fundamentally changes the classification of adult gliomas and a subset of pediatric gliomas. Pediatric and adult gliomas are biologically distinct [2]. For example, a predominantly pediatric glioma was added to the WHO classification as a new tumor entity, entitled diffuse midline glioma grade IV, H3K27M-mutant [1].

First described in 2012 [3], two types of heterozygous somatic histone H3 gene *H3F3A* mutations were discovered in pediatric high-grade gliomas (HGGs), leading to an amino acid exchange in key residues (K27M or G34R/G34V). For unknown reasons, H3K27M-mutant gliomas are almost exclusively located in the midline, even if a hemispheric H3K27M-mutant glioma was recently reported [4], whereas those with G34R mutations are hemispheric but both share a severe prognosis. The H3F3A G34 R/V mutant HGGs are associated with an overall survival between those of the IDH1 and H3K27M subgroups, with an estimated 37% 3-year overall survival [5,6]. Previous studies reported that the G34 mutant HGG subgroup is difficult to histologically diagnose due to pathological similarities with CNS embryonal tumors [7,8]. While several studies have described the radiological characteristics of the most

Abbreviations: WHO, World Health Organization; CNS, Central nervous system; HGG, High grade glioma; PWI, Perfusion weighted imaging; DWI, Diffusion weighted imaging.

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common molecular subgroups of adult HGG [9–11], none have focused on pathological-radiological correlations in H3F3A G34 R/V mutant HGG. To date, 141 G34R/V mutant HGGs have been reported in the literature [3,5–8,12–21] with detailed histological and molecular data, but without a precise radiological description.

Here, we aimed to correlate the histological and radiological features of G34R mutant HGGs in light of the major changes of the 2016 WHO classification of CNS tumors.

Materials and methods

Patients

We performed a retrospective analysis of tumor samples from three neurosurgical centers in blinded for review (blinded for review) between 2002 and 2015. The inclusion criteria were:

- HGG (WHO grade III or grade IV), HGG with a PNET component or PNET/CNS embryonal tumors with a confirmed H3F3A G34R mutation by direct genomic sequencing;
- available pre-operative T1-weighted images and T2-weighted or FLAIR images.

Histological review and immunohistochemistry

All histopathological specimens for this study were re-evaluated by an experienced neuropathologist (blinded for review, 15 years of experience) and the following histological features were assessed: tumoral differentiation, small cell component, tumoral cellularity, nuclear atypia, necrosis, endothelial proliferation and mitotic activity. Additional architectural patterns included the presence or absence of solid tumoral tissue, tumoral infiltration, subpial infiltration, leptomeningeal spread and Virchow Robin involvement. The presence or absence of microcalcifications (interstitial, vascular or necrosic) and hemorrhage were also analyzed.

Representative zinc formalin-fixed sections were deparaffinized and stained in a Ventana autostainer (BenchMark XT, Ventana Medical Systems or Discovery XT, Ventana Medical Systems) following the standard protocol. Immunological analyses were performed either at the time of the diagnosis or at the time of the study to completely establish the molecular status. The primary antibodies used were:

- OLIG2 (1:500, Polyclonal, Sigma-Aldrich, Saint-Quentin Fallavier, France);
- p53 (1:5000, DO-1, Santa Cruz Biotechnology, Heidelberg, Germany);
- ATRX (1:200, polyclonal, Sigma-Aldrich, Saint-Quentin Fallavier, France);
- BRAFV600E (1/100, VE1, Spring bioscience, Pleasanton, CA, USA);
- glial fibrillary acidic protein (GFAP) (1:200, 6F2, Dako, Les Ulis, France);
- INI (1:200, 25/BAF 47, BD Biosciences, San Jose, CA, USA);
- H3K27 me3 (1:1250, polyclonal, Diagenode, Liège, Belgium);
- H3K27M (1:1000, polyclonal, Millipore, Billerica, WA, USA);
- Ki-67 (1:200, MIB-1, DAKO, Les Ulis, France).

A standard pretreatment protocol included CC2 buffer and then affinity-purified rabbit polyclonal H3-G34R or H3-G34V antibodies (glycine elutes, diluted at 1:150 for G34R and 1:400 for G34V) incubation for 30 min at room temperature. Antibody binding was visualized with a ChromoMap detection kit (Ventana, Tucson, USA). Diaminobenzidine tetra hydrochloride (DAB, Ventana) was used as the chromogen. Scoring was performed by a neuropathologist, blinded to the tumor genotype. In case of the TMA, the genotypes were not known. A sample was considered as positive for G34R if tumor cells showed a nuclear staining associated with the negativity of the control endothelial cell nuclei.

Slide scanning was performed using NanoZoomer 2.ORS (Hamamatsu photonics, Hamamatsu, Japan).

Radiological data

Pre-operative radiological data were obtained from the respective hospital archives. Imaging was performed at the time of the diagnosis using either a 1.5 Tesla or a 3 Tesla MRI scanner. Images were acquired using a standard head coil. Inclusion criteria were: available MRI performed before surgery, with at least an axial T2-weighted or axial FLAIR sequence and a T1-weighted sequence. A 3D T1-weighted sequence after intravenous chelated gadolinium injection was available for 11 patients. Diffusion weighted imaging (DWI) was performed in four cases and perfusion weighted imaging (PWI) using pseudo-continuous arterial spin labelling was available for two cases.

The following image characteristics were evaluated:

- tumor location;
- corpus callosum and/or ventricular involvement defined as a protrusion of the tumor into the ventricles;
- median line crossing;
- basal ganglia invasion;
- leptomeningeal contact ± leptomeningeal spread, considered positive when dural or pial thickening was present at the point of contact with the tumor;
- ependymal contact;
- nodular aspect defined as a well delineated mass;
- infiltrative tumoral component, described as a poorly delimited T2 hypersignal associated with a mass effect;
- T2-weighted signal of the well-delineated component relative to the normal cortex signal;
- contrast enhancement, described as patchy, nodular, ring-like or serpiginous and graded as intense, moderate, or minimal;
- necrosis quantified as intense, moderate or minimal;
- T2* hyposignal when available;
- peritumoral edema quantified as intense, moderate or minimal and defined by a poorly delineated peritumoral T2 hypersignal;
- intrinsic T1 hyperdensity;
- PWI data when available;
- DWI data when available;
- tumoral density on CT relative to cortex density, when available.

The images were scored and analyzed by a radiology resident (blinded for review, 2 years of experience) and a senior neuroradiologist (blinded for review, 20 years of experience) and a consensus was reached for each case of nonconformity.

Results

Patients

Twelve patients met the inclusion criteria. Patients were initially diagnosed with glioblastoma with a primitive neuronal component in two cases, and HGG in 10 cases (4 grade IV, 4 grade III and 2 HGG NOS). There were nine males and three females (sex ratio = 3) with a mean age of 16 years at diagnosis (age range: 6–31 years). All initially presented with intracranial hypertension symptoms except the two grade III astrocytomas, which were revealed by inaugural epilepsy.

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