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Neuropathological diagnosis of brain tumours

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Abstract With recent progress in radiological, pathological, immunohistochemical, molecular and genetic diagnoses, the characterisation of brain tumours has improved. The last World Health Organization (WHO) Classification of Tumours of the Central Nervous System was done in 2007, based on morphological features, growth pattern and molecular profile of neoplastic cells, defined malignancy grade. The neuropathological diagnosis and the grading of each histotype are based on identification of histopathological criteria and immunohistochemical data. Molecular and genetic profiles may identify different tumour subtypes varying in biological and clinical behaviour, indicating prognostic and predictive factors. In order to investigate new therapeutic approaches, it is important to study the molecular pathways responsible for proliferation, invasion, angiogenesis, and anaplastic transformation. Different prognostic and predictive factors for glioma patients were identified by genetic studies, such as the loss of heterozygosis on chromosome 1p and 19q for oligodendrogliomas, proangiogenic factors such as Vascular Endothelial Growth Factor for glioblastomas and the methylation status of gene promoter of MethylGuanine–MethylTransferase. In conclusion, the prognostic evaluation and the therapeutic strategies for patients depend on the synthesis of histological diagnosis, malignancy grade, gene-molecular profile, radiological images, surgical resection and clinical findings (age, tumour location, and "performance status").

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Introduction

The tumours of the central nervous system are classified according to the criteria defined in the international classification published by the World Health Organisation (WHO) in 2007 [1, 2]. A classification of human brain tumours that is accepted and used worldwide, with clearly defined histopathological diagnostic criteria, is very important in the clinical management of patients in order to carry out internationally comparable epidemiological studies and clinical trials.

The classification of brain tumours is based on the histopathological diagnosis, including morphological evaluation of neoplastic cells by defined criteria such as cell density, nuclear polymorphism, mitoses, infiltrative pattern, vascular proliferation and necrosis. These criteria concur in identifying the malignancy grade based on biological features and growth pattern.

The histological grading of tumours of the central nervous system may be added to the WHO classification as a "malignancy scale" suggesting the biological behaviour and the outcome. Tumour grade is widely used as a prognostic factor influencing the therapeutic options.

Within different types of tumours histologically classified, the molecular profiles identify tumour subtypes with chromosomal, genetic and molecular changes related to biological behaviour, therapeutic response and prognosis.

The aim of neuro-oncological research is to discover alterations in the molecular and genetic pathways involved in the development of tumours, as diagnostic, prognostic, predictive markers and therapeutic targets.

Neuropathological diagnosis

The application of advanced molecular biology techniques in brain tumour studies enables in identifying genetic and molecular alterations specific to some histotypes, suggesting tumour biological behaviour. To this end, the clinical management of patients and therapeutic strategies have changed; thus it is essential to implement some biomarkers during routine laboratory. At present, the neuropathological diagnosis of brain tumours, particularly gliomas, based on defined histological morphological criteria, growth parameters (such as cell density, nuclear polymorphism, mitoses, infiltrative pattern, vascular proliferations and necrosis) and immunohistochemistry, also requires molecular profiles by different tools (PCR, RT-PCR, FISH, microsatellite analysis, CGH, and genomic arrays).

Neoplastic transformation is related to an alteration of the balance between oncogenes and onco-suppressor genes expression that may occur for mutations or amplification of these genes; different genetic profiles correspond to different biological and clinical behaviour. Tumourigenesis is a complex process involving different genetic pathways implicated in mechanisms of differentiation, proliferation, angiogenesis and apoptosis. Every processes itself involves a combination of molecules and receptors with their interactions and regulations.

The aim of modern neuropathology is to utilise data from molecular biology in routine histopathological diagnosis, which enables the oncologist to receive early information about expression of molecular markers and thus reduces the waiting period for therapeutic planning. For this purpose, the tool most used in histological diagnosis is immunohistochemistry, which reveals the expression of an antigen related to a specific histotype and indicates the proliferative potential of neoplastic cells, whilst detecting prognostic and predictive markers. Hence, immunohistochemistry could represent a useful, easy, fast and not so expensive method for pathologists in routine practice, and also for supporting oncologists to make treatment decisions. The data obtained with an immunohistochemical panel of molecular marker may be the first step to select patients for specific advanced molecular studies.

In conclusion, the modern neuropathological diagnosis of brain tumours require to introduce in routine diagnosis, a panel of prognostic and predictive biomarkers to achieve molecular information identifying different subgroups of patients.

Glial tumours

Gliomas, the most common primary brain tumours, are often highly malignant and invariably recur because of the regrowth of invasive cells that are immune to standard treatment modalities.

Gliomas develop as a result of genetic alterations that accumulate with tumour progression and therefore show a great morphological and genetic heterogeneity. Primary and secondary glioblastomas represent distinct entities evolving through different genetic pathways, molecular profile and response to therapy.

Histopathology is the gold standard for the typing and grading of gliomas. However, additional markers are needed for a refined and more objective glioma classification, a better prediction of prognosis and a tailored therapeutic decision making [3].

The deletions of chromosomal arms 1p and 19q are associated with markedly improved clinical courses in patients with oligodendroglial tumours, playing a role as prognostic or predictive marker. 1p/19q status can be assessed by: loss of heterozygosity (LOH) assays, FISH, array comparative genomic hybridization (aCGH) [4].

Recently, many studies on molecular profiles of gliomas, in particular *The Cancer Genome Atlas (TCGA)* project, allow the possibility to recognise genome abnormalities recurrent in tumour subtypes with different clinical–biological features, like a "gene signature" [5, 6, 7].

Glioblastoma multiforme, the most aggressive glioma, has a poor prognosis due to its aptitude to infiltrate the normal brain tissue as single cells and this feature makes complete surgical resection almost impossible.

For the routine diagnosis of glioblastoma, it is possible to introduce an immunohistochemical panel of molecular markers to select patients undergoing specific molecular investigations, identifying subgroups of patients with different biological behaviour. Well-known alterations with prognostic and therapeutic implications are methylguanine–methyltransferase (MGMT), IDH1, p53, EGFR, PTEN, vascular endothelial growth factor (VEGF) and PDGFR.

The primary mechanism of action of alkylating agents is the addition of methyl groups to the O6 position of guanine to produce methylguanine adducts. The DNA repair enzyme MGMT reverses this process by repairing methylguanine adducts. In 2005, a multinational collaborative trial reported that MGMT gene silencing predicts enhanced benefits in glioblastoma patients treated concurrently with radiotherapy and temozolomide [8]. In gliomas and other tumours, epigenetic silencing of MGMT gene transcription secondary to promoter hypermethylation, rather than gene mutation or deletion, has been observed as the major mechanism for MGMT inactivation. MGMT promoter methylation assay by methylation-specific-PCR is now currently used in routine clinical practice, playing an important predictive role.

Mutation of isocitrate dehydrogenase 1 (IDH1) has been reported in astrocytic and oligodendrocytic tumour and

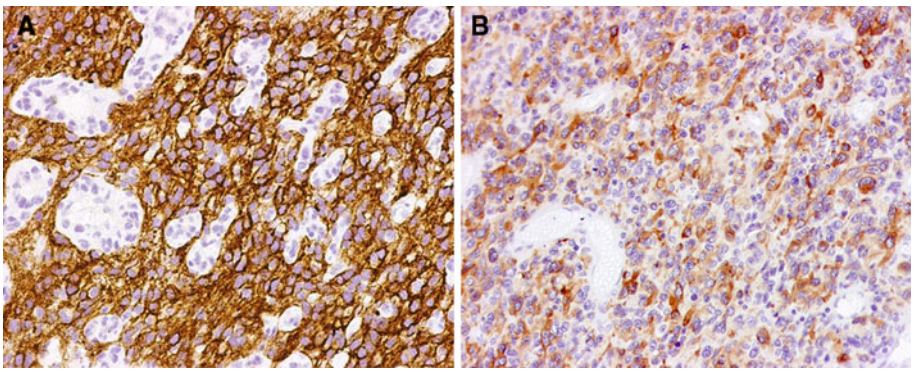

Fig. 1 Immunohistochemical analysis showing expression of EGFR (**a**) and EGFRvIII (**b**) in the same glioblastoma

many of those with IDH1 mutation had features of secondary glioblastoma, younger age, longer survival and TP53 mutation. IDH1 mutations are early events in low-grade gliomas. The R132H is the most frequent mutation, present on 90% of secondary glioblastomas. Primary glioblastoma occur in older patients, showing epidermal growth factor receptor (EGFR) amplification, mutation of IDH1 gene rare or absent.

TP53 mutations represent an early event on the pathogenesis of gliomas, frequent on secondary glioblastomas. There are different mutations and polymorphisms of p53; recurrent glioblastomas usually retain the same molecular profile.

Amplification and overexpression of the EGFR were observed on 35–45% of glioblastomas. Increased activity of EGFR pathway promotes proliferation, motility and invasion of neoplastic cells. Mutations of EGFR could be present, out of these EGFRvIII is the most common, suggesting a worse prognosis (Fig. 1).

PTEN (tumour suppressor phosphatase and tensin homologue) regulates AKT activation/phosphorylation; PTEN inactivation by mutations contributes to increased activity of PI3K/AKT, as often observed on primary glioblastomas. New PTEN mutations frequently occur on recurrent glioblastomas.

Angiogenesis and its role in brain tumour formation is a complex process that in gliomas is closely correlated with the degree of malignancy and the prognosis of patients. The VEGF is a key mediator of angiogenesis in malignant gliomas, regulating biological functions of vascular endothelial cells, pericytes and tumour cells. VEGF is the more important target for anti-angiogenic therapy and bevacizumab is its inhibitor.

Platelet-derived growth factor (PDGF) and its receptors (PDGFR) are also involved in glial tumourigenesis, angiogenesis and in malignant progression of gliomas. PDGFR may be over expressed in about 33% of glioblastomas, associated to the IDH1–R132H mutation, on tumour cells and on neoplastic endothelial cells and may represent a therapeutic target. PDGFR expression could be a prognostic and predictive marker in glioblastomas.

Conflict of interest The author declares that there is no conflict of interest related to the publication of this article.

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