

Focused Review
**Diagnosis, Treatment, and
Rehabilitation for Adult
Glioma**



Classification and Diagnosis of Adult Glioma: A Scoping Review

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Received: Oct 11, 2022

Accepted: Nov 15, 2022

Published online: Nov 22, 2022

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HIGHLIGHTS

- Isocitrate dehydrogenase (IDH) mutation status is key to classify the adult-type diffuse gliomas.
- Molecular and genetic profiles have been integrated into the diagnosis of gliomas.
- Next-generation sequencing became essential for the diagnosis of gliomas.

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Funding
None.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Gliomas are primary central nervous system tumors that arise from glial progenitor cells. Gliomas have been classically classified morphologically based on their histopathological characteristics. However, with recent advances in cancer genomics, molecular profiles have now been integrated into the classification and diagnosis of gliomas. In this review article, we discuss the clinical features, imaging findings, and molecular profiles of adult-type diffuse gliomas based on the new 2021 World Health Organization Classifications of Tumors of the central nervous system.

Keywords: Glioma; Brain Neoplasms; Diagnosis; Classification

INTRODUCTION

Gliomas are a heterogeneous group of primary central nervous system (CNS) tumors that originate from glial progenitor cells [1]. These tumors constitute the most common type of malignant primary CNS tumors in adults. The annual incidence of gliomas is reported to be about 6 cases per 100,000 worldwide, and their incidence is significantly lower in non-Caucasian populations, especially for glioblastoma [2,3]. Classically, these tumors have been classified morphologically based on their histopathological characteristics, as with other tumors. However, with the vast advances in cancer genomics, there has been a paradigm shift in which molecular profiles have begun to be integrated into the diagnosis of gliomas [4,5]. This fundamental change is largely attributed to the acknowledgement that different genomic signatures lead to different clinical outcomes, thus necessitating different expectations and treatment methods; this reflects the basic concept of “precision medicine” [6]. This trend is clearly manifested in the new 2021 World Health Organization (WHO) Classification of Tumors of the CNS [7] which fully embraced the integrated diagnosis. Under this new classification, gliomas, glioneuronal tumors, and neuronal tumors are subcategorized into six groups: adult-type diffuse gliomas, pediatric-type diffuse low-grade gliomas, pediatric-type diffuse high-grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumors, and ependymal tumors. This review article will focus on the diagnosis and classification of adult-type diffuse gliomas, which account for the majority of gliomas. This study was approved by the Institutional Review Board of Seoul National University Hospital (No. 2206-067-1332) regarding the use of patients’ data.

CLASSIFICATIONS OF ADULT-TYPE DIFFUSE GLIOMAS

The 2021 WHO CNS classification separated adult-type diffuse gliomas from the pediatric type, and integrated the histopathological features of the tumors with the molecular profiles to provide a more concise diagnosis [8]. Adult-type diffuse gliomas are classified into: 1) astrocytoma, isocitrate dehydrogenase (IDH)-mutant (grade 2/3/4), 2) oligodendroglioma, IDH-mutant (grade 2/3) and 1p/19q-codeleted, and 3) glioblastoma, IDH-wildtype (grade 4).

Diffuse gliomas are first broadly divided into IDH-mutant and IDH-wildtype gliomas (**Fig. 1**). IDH-mutant glioma with histopathological high-grade features (WHO grade 4), including necrosis and/or microvascular proliferation, is diagnosed as astrocytoma, IDH-mutant, WHO grade 4. IDH-mutant gliomas without these features are graded as either WHO grade 2 or 3 and are subdivided according to their molecular profiles. IDH-mutant glioma with concurrent 1p/19q-codeletion is diagnosed as oligodendroglioma, IDH-mutant, 1p/19q-codeleted. IDH-mutant glioma without 1p/19q-codeletion is diagnosed as astrocytoma, IDH-mutant, grade 2 or 3. As alpha-thalassemia/mental retardation, X-linked (*ATRX*) mutations are mutually exclusive with 1p/19q-codeletion, the diagnosis of astrocytoma, IDH-mutant could be made if *ATRX* and/or *TP53* mutations are present without further inspection for 1p/19q-codeletion. A point to note is that astrocytoma, IDH-mutant with cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) deletion is diagnosed as astrocytoma, IDH-mutant, WHO grade 4, even in the absence of histopathological high-grade features. This is based on studies that have shown *CDKN2A/B* deletion to be an independent negative prognostic factor in IDH-mutant astrocytoma [9].

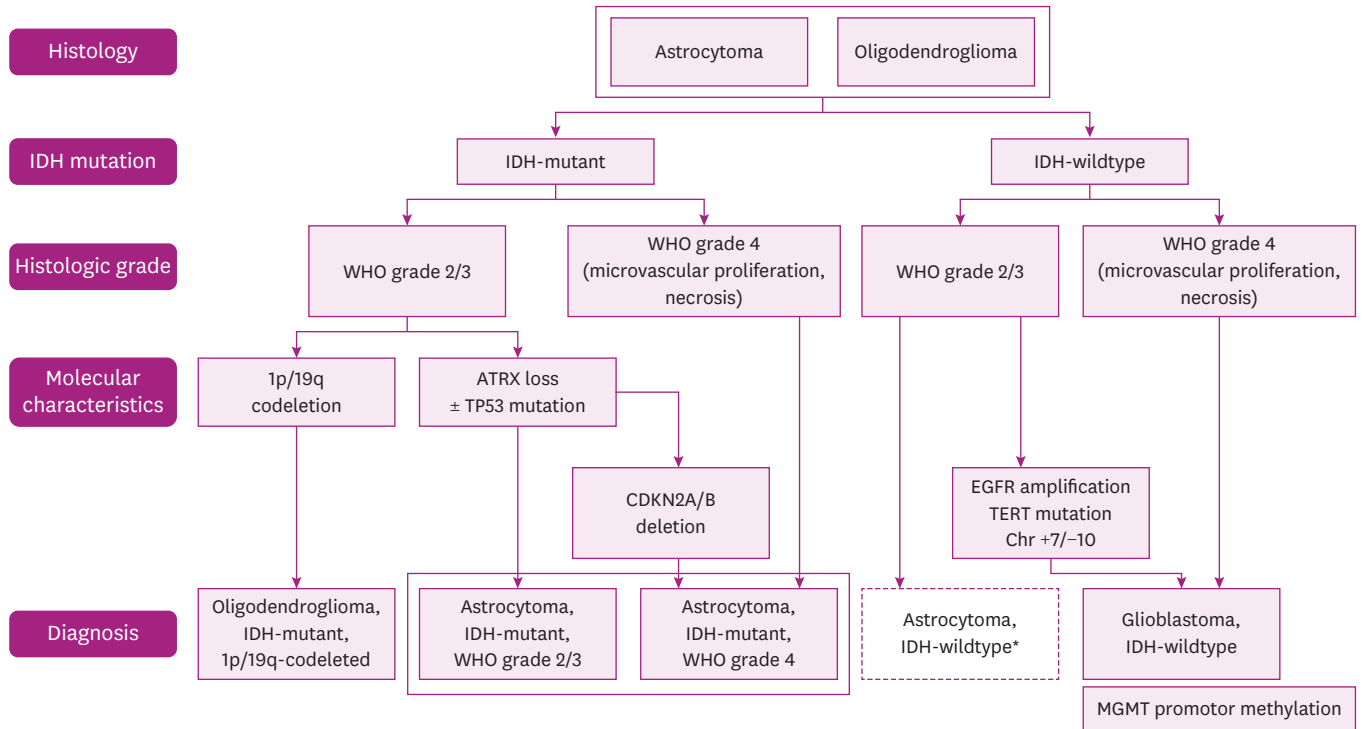


Fig. 1. The 2021 WHO classification of adult-type diffuse gliomas.

Adult-type diffuse gliomas are classified as: 1) astrocytoma, IDH-mutant, 2) oligodendroglioma, IDH-mutant and 1p/19q-codeleted, and 3) glioblastoma, IDH-wildtype. WHO, World Health Organization; IDH, isocitrate dehydrogenase; *ATRX*, alpha-thalassemia/mental retardation, X-linked; *CDKN2A/B*, cyclin-dependent kinase inhibitor 2A/B; *EGFR*, epidermal growth factor receptor; *TERT*, telomerase reverse transcriptase; *MGMT*, O-5-methylguanine-DNA methyltransferase.

*IDH-wildtype glioma without high-grade features (WHO grade 2/3) should be investigated further and classified into other categories.

IDH-wildtype glioma with high-grade features is diagnosed as glioblastoma, IDH-wildtype. IDH-wildtype glioma without high-grade features should be investigated further to determine its further classification into other categories. Of note, IDH-wildtype glioma with epidermal growth factor receptor (*EGFR*) amplification, telomerase reverse transcriptase (*TERT*) promoter mutation, or chromosome 7 gain/chromosome 10 loss is diagnosed as glioblastoma, IDH-wildtype even in the absence of histopathological high-grade features. This is due to studies showing that astrocytoma, IDH-wildtype, WHO grade 2/3 with these mutations carries the same prognosis as histologically diagnosed glioblastoma [10]. When glioblastoma, IDH-wildtype is diagnosed, the presence of O-5-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation should additionally be assessed, as it is associated with a better response to temozolomide and longer survival [11].

CLINICAL FEATURES

Gliomas present with various symptoms, which are often related to the location and grade of the tumor. Generally, low-grade, slow-growing tumors present with new-onset seizure or a more subtle progressive neurologic deficit [12]. In contrast, higher-grade, faster-growing tumors often present with more acute neurologic symptoms combined with other symptoms [13]. Common presenting symptoms include headache, seizure, cognitive dysfunction, and focal neurologic deficits [14]. Headache is one of the most common non-specific symptoms in patients with brain tumors; however, it has a very low positive predictive value [15]. Therefore, high clinical suspicion is required in patients with an acute onset of a new type of headache or with significant changes in the pattern of headaches. The incidence of cognitive dysfunction increase with the patient's age and tumor grade, and it seems to be worse when the dominant hemisphere is involved [16]. However, these symptoms may not be confined to the affected lobe, as the tumor could interrupt the integrity of the neural network [17].

IMAGING FINDINGS (RADIOGENOMICS)

In recent years, there has been significant growth in the field of radiogenomics, where vast numbers of quantitative imaging features have been correlated with the molecular/genetic profiles of tumors [18]. There have been ongoing efforts to utilize radiogenomics for diagnosing glioma based on the new genetic classification, ultimately aiming to stratify patients to optimize individual treatment. Magnetic resonance imaging (MRI) is the most common imaging modality used to diagnose gliomas, and many attempts have been made to uncover the specific MRI features of genetic mutations related to gliomas [19].

IDH-mutated gliomas tend to be more frequently confined to a single lobe with larger areas of non-enhancing lesions and sharper borders than IDH-wildtype gliomas [20,21]. The imaging features of oligodendroglioma, IDH-mutant, 1p/19q-codeleted are well established, with the tumor traditionally localized to the frontal lobe, commonly showing calcification, cortical involvement, heterogeneous signal intensity on T1- and T2-weighted images, and indistinct tumor margins [22]. Additionally, the T2-fluid-attenuated inversion recovery (FLAIR) mismatch sign has been fairly recently introduced to identify IDH-mutant, 1p/19q intact tumors [23]. The T2-FLAIR mismatch sign is considered positive when a tumor shows homogeneously hyperintense T2 signal with relatively low signal intensity on FLAIR, except for a hyperintense peripheral rim. The sign is highly specific and helps to rule in IDH-mutant, 1p/19q intact tumors when positive [24].

HISTOPATHOLOGIC CHARACTERISTICS AND RELEVANT MOLECULAR PROFILES

Astrocytoma, IDH-mutant

In the new 2021 WHO classification, WHO grade 2, 3, and 4 astrocytomas with *IDH* mutations are all included in the diagnosis of astrocytoma, IDH-mutant. Astrocytic tumors typically show diffusely infiltrating fibrillary glial cells with a microcytic background and regional heterogeneity. Astrocytomas are classified as grade 3 when nuclear atypia and increased mitotic activity are present (**Fig. 2**), and grade 4 when microvascular proliferation or necrosis is present. An *IDH* mutation (*IDH1* or *IDH2*) is one of the most important mutations in adult diffuse glioma, having both diagnostic and prognostic significance. *IDH* mutations lead to the overproduction and accumulation of the 2-hydroxyglutarate metabolite [25]. This leads to alteration in global DNA methylation and ultimately results in changes

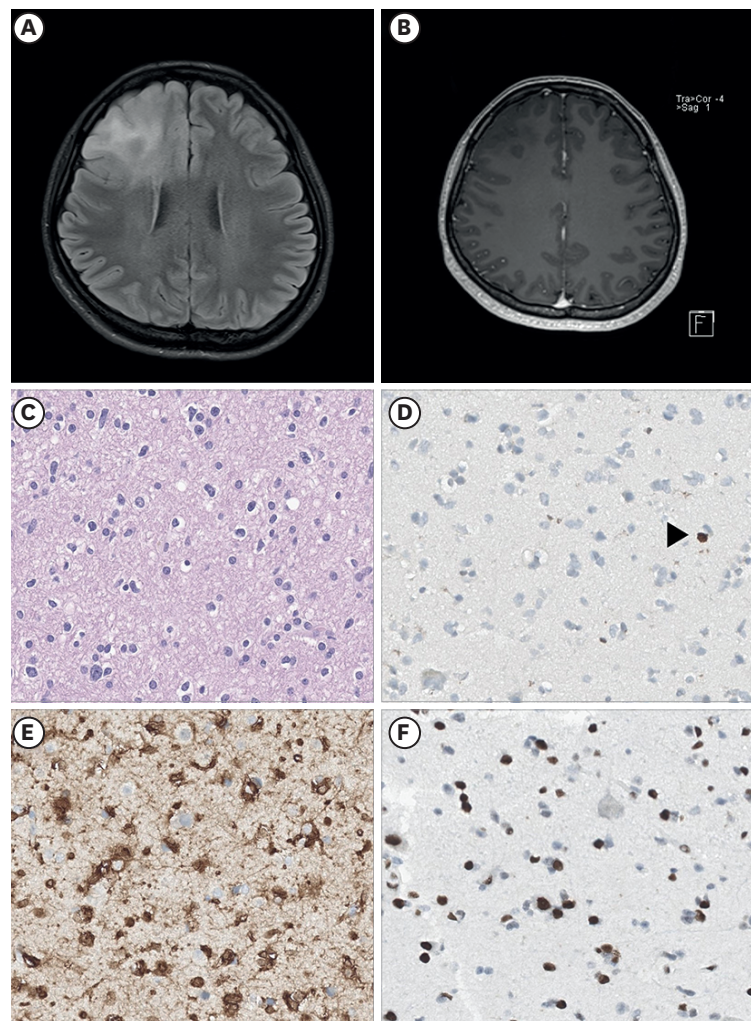


Fig. 2. Diffuse astrocytoma, IDH-mutant, grade 3.

(A) A T2-FLAIR image and (B) a T1 contrast-enhanced image show an ill-defined T2 high SI lesion without significant contrast enhancement in the right frontal cortex. The tumor shows (C) increased cellularity and nuclear polymorphism, (D) an intermediate mitotic count (3/10 HPF) on PHH3 immunohistochemistry (arrowhead), (E) *IDH1* mutation positivity, and (F) *ATRX* mutation positivity (*ATRX* loss).

FLAIR, fluid-attenuated inversion recovery; SI, signal intensity; PHH3, phosphohistone H3; HPF, high-power field; IDH, isocitrate dehydrogenase, *ATRX*, alpha-thalassemia/mental retardation, X-linked.

in the epigenetic status and blocking of cellular differentiation [26,27]. Ironically, *IDH* mutations, which seem to instigate tumorigenesis, are associated with positive prognostic factors. Gliomas with *IDH* mutations have much better prognosis than their IDH-wildtype counterparts [28].

The majority of IDH-mutant gliomas are also associated with loss-of-function mutations in *ATRX* and *TP53* [29]. *ATRX* is an X-linked gene associated with alpha thalassemia and intellectual disability located in Xq21.1. Its loss of function is most importantly associated with lengthening of telomeres, which essentially leads to a more robust oncogenic cellular proliferation [30]. *ATRX* mutation is mutually exclusive with 1p/19q-codeletion. Therefore, oligodendroglioma (1p/19q-codeleted) can be ruled out in tumors with *ATRX* mutation without additional 1p/19q testing. *ATRX* mutant gliomas also commonly harbor a mutation of *TP53*, which is a well-known tumor suppressor gene located in 17p13.1. *TP53* mutation leads to unregulated oncogenic cellular proliferation. *CDKN2A/B* is located in 9p21.3 and is associated with regulating Rb and p53-dependent signaling pathways [31]. *CDKN2A/B* mutations in astrocytic gliomas have shown strong associations with poorer survival [32]. Therefore, when a *CDKN2A/B* mutation is present, astrocytoma, IDH-mutant, WHO grade 4 can be diagnosed even in the absence of high-grade histopathologic features.

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Classically, oligodendroglioma (WHO grade 2) is a relatively slow-growing tumor with a predilection for the frontal lobe and is often associated with seizures [33]. Common histopathologic findings include a “fried egg” appearance with uniformly rounded nuclei and clear halos, “chicken-wire” patterned branching capillaries, and extensive calcifications [34]. Oligodendroglioma with features of microvascular proliferation, necrosis, and/or significantly increased mitotic activity is classified as WHO grade 3 and shows more aggressive features than WHO grade 2 tumors (**Fig. 3**). 1p/19q-codeletion is a disease-defining chromosomal alteration resulting from failed translocation of the corresponding chromosomes. The molecular manifestations that result from this alteration are currently unknown. However, it is generally associated with a favorable prognosis and a good response to chemotherapy [35].

Glioblastoma, IDH-wildtype

Glioblastoma is a highly malignant tumor that occurs most commonly in elderly patients, accounting for around 49% of primary malignant brain tumors [36]. It is characterized by rapid progression and has a median survival of 14–16 months after diagnosis [37]. The histologic hallmark of glioblastoma is necrosis and vascular proliferation, commonly seen together with marked pleomorphism and increased mitotic activity (**Fig. 4**) [38]. Molecular alterations including *EGFR* amplification, *TERT* promoter mutation, and gain of chromosome 7/loss of chromosome 10 have shown to be strongly associated with glioblastoma. If one of these three molecular alterations is present, glioblastoma can be diagnosed even in the absence of high-grade histopathologic features.

EGFR (also known as *HER1* or *ERBB1*) is located on chromosome 7q and its protein product serves as a type of transmembrane receptor tyrosine kinase. The *EGFRvIII* mutation is defined as deletion of exons 2–7 of the *EGFR* gene and is the most commonly seen *EGFR* mutation in glioblastoma. The *EGFRvIII* mutation is closely associated with *EGFR* amplification and is known to promote cell proliferation, angiogenesis, and invasion in various models [39]. *TERT* promoter mutations are associated with abnormal maintenance of telomeres, which ultimately leads to cellular longevity and cellular proliferation [40]. *TERT* mutations are

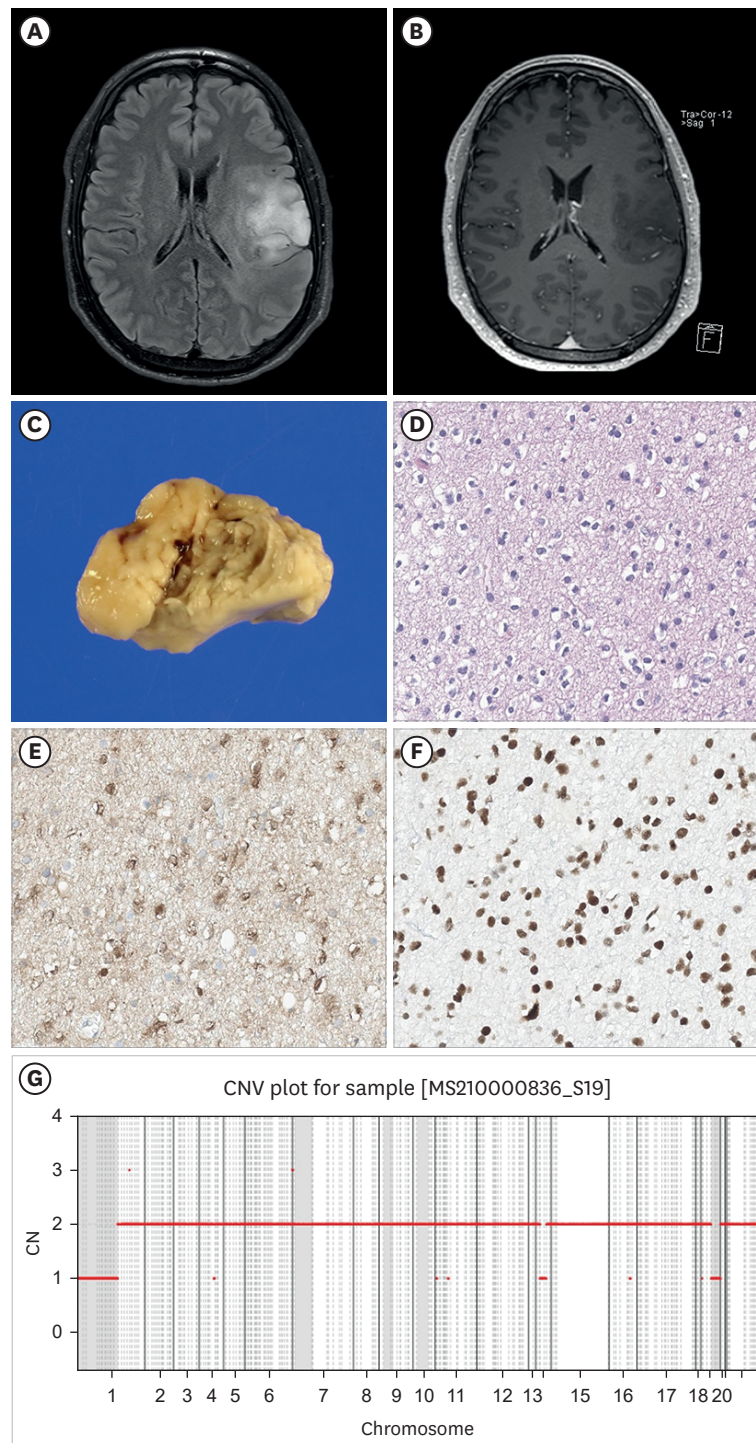


Fig. 3. Oligodendroglioma, IDH-mutant, 1p/19q-codeleted.

(A) A T2-FLAIR image and (B) a T1 contrast-enhanced image show an ill-defined T2 high-SI lesion without significant contrast enhancement in the left frontoparietal lobe. (C) Gross photograph of the resected tumor. The tumor shows (D) a “fried egg” appearance with uniformly rounded nuclei and clear halos, (E) *IDH1* mutation positivity, (F) *ATRX* mutation negativity, and (G) 1p/19q co-deletion.

IDH, isocitrate dehydrogenase; FLAIR, fluid-attenuated inversion recovery; SI, signal intensity; *ATRX*, alpha-thalassemia/mental retardation, X-linked; CNV, copy number variation.

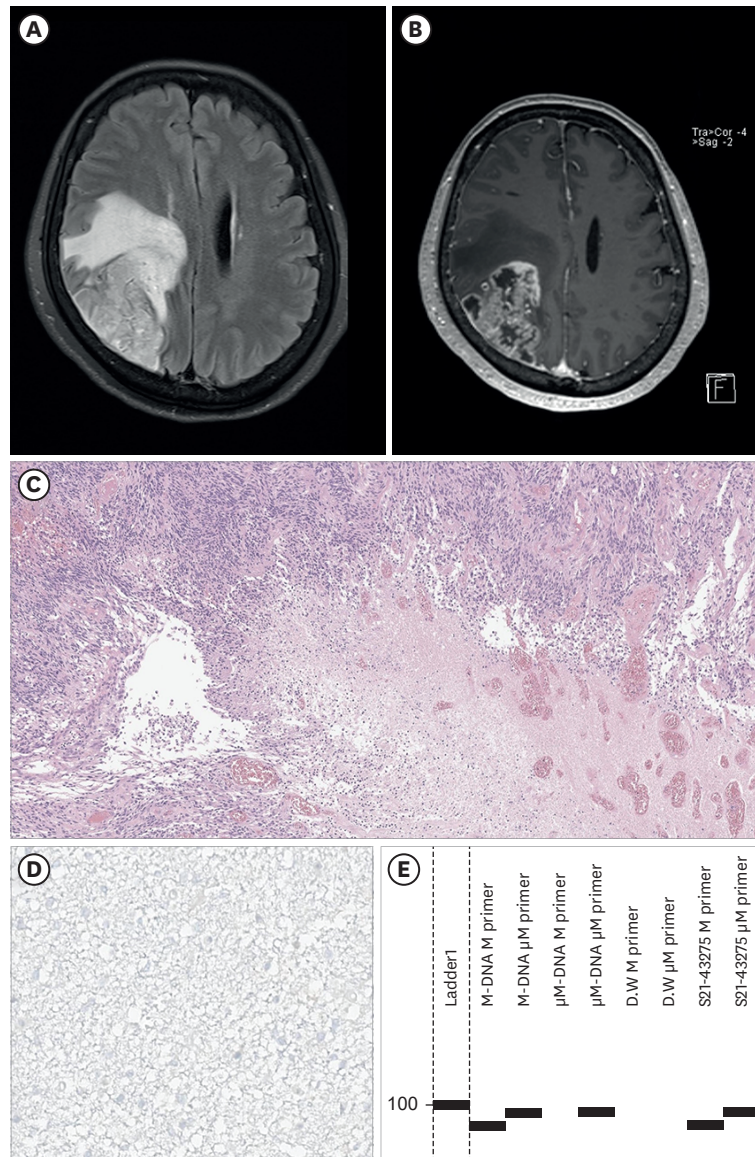


Fig. 4. Glioblastoma, IDH-wild type.

(A) A T2-FLAIR image and (B) a T1 contrast-enhanced image show an enhancing mass in the left parietal lobe with multiple necrosis and perilesional T2 high-SI infiltrations. The tumor shows (C) necrosis and microvascular proliferation, (D) *IDH1* mutation negativity, and (E) positive results for *MGMT* methylation.

IDH, isocitrate dehydrogenase; FLAIR, fluid-attenuated inversion recovery; SI, signal intensity; *MGMT*, O-5-methylguanine-DNA methyltransferase.

mutually exclusive with *ATRX* mutations and are commonly seen in glioblastoma. The most significant aneuploidy harbored by glioblastoma involves chromosomes 7 and 10, typically showing trisomy of chromosome 7 and monosomy of chromosome 10 [41]. *MGMT* encodes a DNA repair enzyme that functions to remove alkyl adducts from DNA, preventing double-strand breaks and base mispairing [42]. Methylation of the *MGMT* promoter silences this gene and leads to inefficient repair of DNA alkylation, thereby enhancing the response to alkylating chemotherapeutic agents such as temozolomide [43]. Therefore, an evaluation for *MGMT* promoter methylation is advised when glioblastoma is diagnosed as a supportive measure to predict the response to temozolomide treatment and overall survival.

MOLECULAR TESTING METHODS

Various molecular testing methods are used to detect genetic mutations in gliomas, which have now become a prerequisite information for the diagnosis of these tumors. Classically, immunohistochemistry studies have been universally used to supplement the conventional hematoxylin and eosin histology [44]. The *IDH1* mutation, which is a gain-of-function mutation, can be detected using mutation-specific monoclonal antibodies [45]. The *ATRX* mutation is detected by identifying the loss of nuclear *ATRX*, since it is a loss-of-function mutation. Fluorescence in situ hybridization has been most frequently used to identify *EGFR* amplification, 1p/19q-codeletion, and chromosome 7 and 10 alterations. The test requires a minimal tissue sample and can even detect deletions smaller than whole-arm deletions [46]. *TERT* promoter mutations could be detected by direct sequencing, whereas *MGMT* promoter methylation status is verified using methylation-specific polymerase chain reaction.

In recent years, next-generation sequencing (NGS) has been actively embraced by a growing number of institutions as the standard diagnostic tool for detecting gene mutations when diagnosing gliomas [47,48]. NGS enables an efficient analysis of a large number of genetic variations in a single session by sequencing millions of small fragments of DNA in parallel [49]. NGS technology continues to be developed with the goal of reducing its costs and improving the accuracy of DNA sequencing. Although NGS is not yet used in all medical institutions, many efforts are being made to utilize NGS in clinical practice.

SUMMARY

Advances in cancer genomics and molecular testing methods have led to a new era of glioma diagnosis. The integration of molecular profiles into the diagnosis of gliomas has resulted in a clearer classification of these tumors. The new classification based on an integrated diagnosis is expected to help better understand and treat gliomas, as different genomic signatures lead to different clinical outcomes.

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