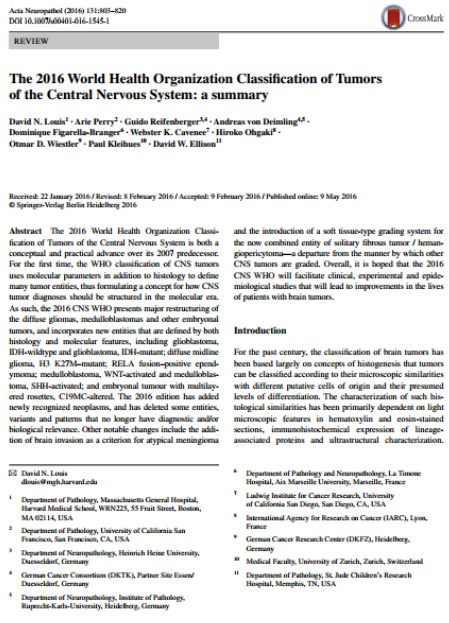

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REVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis[1] · Arie Perry[2] · Guido Reifenberger[3,4] · Andreas von Deimling[4,5] · Dominique Figarella-Branger[6] · Webster K. Cavenee[7] · Hiroko Ohgaki[8] · Otmar D. Wiestler[9] · Paul Kleihues[10] · David W. Ellison[11]

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Abstract The 2016 World Health Organization Classification of Tumors of the Central Nervous System is both a conceptual and practical advance over its 2007 predecessor. For the first time, the WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era. As such, the 2016 CNS WHO presents major restructuring of the diffuse gliomas, medulloblastomas and other embryonal tumors, and incorporates new entities that are defined by both histology and molecular features, including glioblastoma, IDH-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M-mutant; RELA fusion-positive ependymoma; medulloblastoma, WNT-activated and medulloblastoma, SHH-activated; and embryonal tumour with multilayered rosettes, C19MC-altered. The 2016 edition has added newly recognized neoplasms, and has deleted some entities, variants and patterns that no longer have diagnostic and/or biological relevance. Other notable changes include the addition of brain invasion as a criterion for atypical meningioma and the introduction of a soft tissue-type grading system for the now combined entity of solitary fibrous tumor / hemangiopericytoma—a departure from the manner by which other CNS tumors are graded. Overall, it is hoped that the 2016 CNS WHO will facilitate clinical, experimental and epidemiological studies that will lead to improvements in the lives of patients with brain tumors.

Introduction

For the past century, the classification of brain tumors has been based largely on concepts of histogenesis that tumors can be classified according to their microscopic similarities with different putative cells of origin and their presumed levels of differentiation. The characterization of such histological similarities has been primarily dependent on light microscopic features in hematoxylin and eosin-stained sections, immunohistochemical expression of lineage-associated proteins and ultrastructural characterization.

✉ David N. Louis
dlouis@mgh.harvard.edu

[1] Department of Pathology, Massachusetts General Hospital, Harvard Medical School, WRN225, 55 Fruit Street, Boston, MA 02114, USA
[2] Department of Pathology, University of California San Francisco, San Francisco, CA, USA
[3] Department of Neuropathology, Heinrich Heine University, Duesseldorf, Germany
[4] German Cancer Consortium (DKTK), Partner Site Essen/Duesseldorf, Germany
[5] Department of Neuropathology, Institute of Pathology, Ruprecht-Karls-University, Heidelberg, Germany
[6] Department of Pathology and Neuropathology, La Timone Hospital, Aix Marseille University, Marseille, France
[7] Ludwig Institute for Cancer Research, University of California San Diego, San Diego, CA, USA
[8] International Agency for Research on Cancer (IARC), Lyon, France
[9] German Cancer Research Center (DKFZ), Heidelberg, Germany
[10] Medical Faculty, University of Zurich, Zurich, Switzerland
[11] Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN, USA

Table 2 Summary of the major changes in the 2016 CNS WHO

Formulating concept of how CNS tumor diagnoses are structured in the molecular era
Major restructuring of diffuse gliomas, with incorporation of genetically defined entities
Major restructuring of medulloblastomas, with incorporation of genetically defined entities
Major restructuring of other embryonal tumors, with incorporation of genetically defined entities and removal of the term "primitive neuroectodermal tumor"
Incorporation of a genetically defined ependymoma variant
Novel approach distinguishing pediatric look-alikes, including designation of novel, genetically defined entity
Addition of newly recognized entities, variants and patterns
IDH-wildtype and IDH-mutant glioblastoma (entities)
Diffuse midline glioma, H3 K27M–mutant (entity)
Embryonal tumour with multilayered rosettes, C19MC-altered (entity)
Ependymoma, RELA fusion–positive (entity)
Diffuse leptomeningeal glioneuronal tumor (entity)
Anaplastic PXA (entity)
Epithelioid glioblastoma (variant)
Glioblastoma with primitive neuronal component (pattern)
Multinodular and vacuolated pattern of ganglion cell tumor (pattern)
Deletion of former entities, variants and terms
Gliomatosis cerebri
Protoplasmic and fibrillary astrocytoma variants
Cellular ependymoma variant
"Primitive neuroectodermal tumour" terminology
Addition of brain invasion as a criterion for atypical meningioma
Restructuring of solitary fibrous tumor and hemangiopericytoma (SFT/HPC) as one entity and adapting a grading system to accommodate this change
Expansion and clarification of entities included in nerve sheath tumors, with addition of hybrid nerve sheath tumors and separation of melanotic schwannoma from other schwannomas
Expansion of entities included in hematopoietic/lymphoid tumors of the CNS (lymphomas and histiocytic tumors)

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【一般原則】

・組織形態学な所見に遺伝・分子学的な情報を加えた統合的な診断・分類

・病名は histopathological name の後に genetic feature を併記する。（例：Oligodendroglioma, IDH-mutant and 1p/19q-codel）。遺伝・分子学的評価が不十分である場合は not otherwise specified(NOS)と併記する。

組織形態と genetic feature に乖離が生じる場合（ex.組織は DA なのに IDH mut, 1p/19q codel などなど）

→ "The genotype trumps the histological phenotype."

では、Genotype だけで診断可能か？→不可（例：histological に DA と考えたが IDH-wild だった。→実は ganglioglioma だった。AA と考えたが IDH wild type → 実は GBM を underestimate していた。などなど。）

【diffuse glioma】

・DA,AA,DO,AO に IDH(IDH2mut や R132H 以外の minor な mutation が存在するため IDH R132H の IHC で偽陰性の場合がある。IHC で不十分な場合は sequencing まで)と 1p/19q codel で。

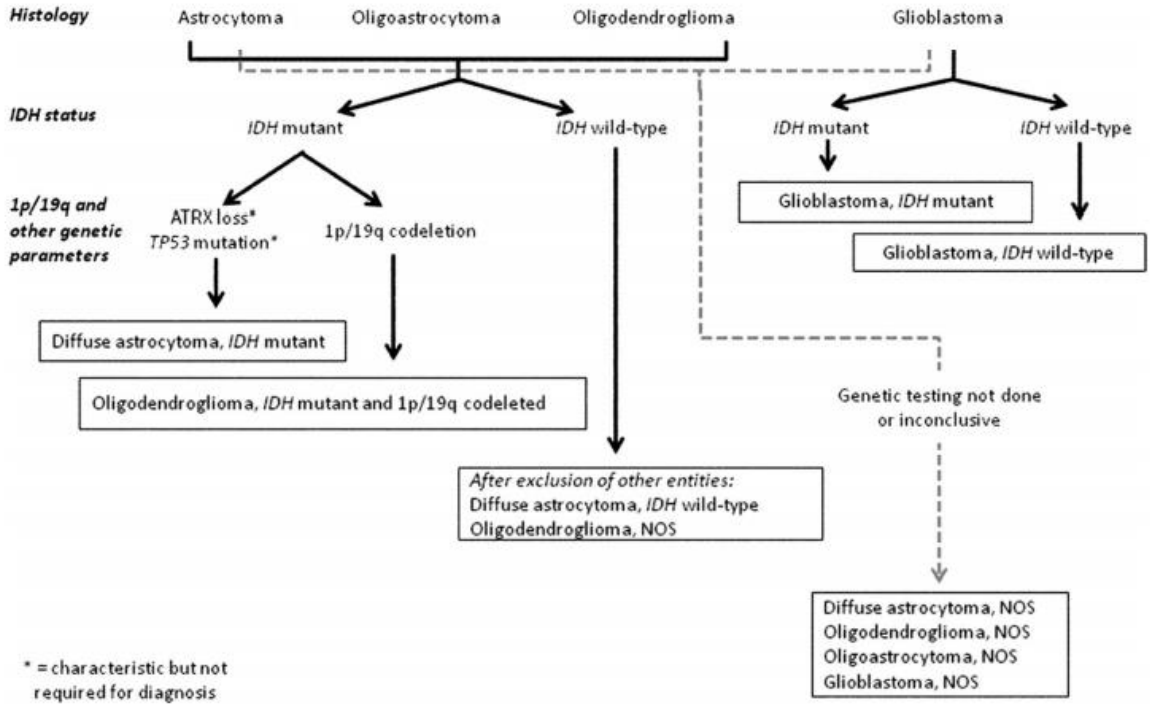
・OA,AOA に関しては基本的には遺伝子評価が不十分な場合に限られるので NOS designation でのみの病名となる。基本的にはこの診断は好ましくない。（極稀に同一腫瘍内に astro/oligo が混在するものも報告あるので完全に無い訳ではない。）

・Protoplasmic Astro, Fibrillary Astro は無くなり Gemistocytic Astro は variant として残る。

・gliomatosis cerebri の概念もなくなる。（浸潤の仕方の問題。DA,AA,DO,AO、GBM でも同様の進展の仕方を取り得る。一つの疾患単位とする根拠が現段階ではない。）

【GBM】

・IDH で分類。IDHwt が全体の 90%、primaryGBM に相当。つまり 90%は IHC で染まらない。IHC だけでは（偽陰性があるので）大部分が NOS になってしまう。IDH 評価を sequencing 含め full で行うことが望まれているが、病歴や年齢、他の遺伝子情報（P53,ATRX の IHC など）から secondaryGBM を疑う場合だけでいいのでは?　（下表参照）



Key characteristics of IDH-wildtype and IDH-mutant glioblastomas

	IDH-wildtype glioblastoma	IDH-mutant glioblastoma	References
Synonym	Primary glioblastoma, IDH-wildtype	Secondary glioblastoma, IDH-mutant	{1830}
Precursor lesion	Not identifiable; develops de novo	Diffuse astrocytoma Anaplastic astrocytoma	{1827}
Proportion of glioblastomas	~90%	~10%	{1797}
Median age at diagnosis	~62 years	~44 years	{214,1078,1797, 2103}
Male-to-female ratio	1.42:1	1.05:1	{214,1417,1797}
Mean length of clinical history	4 months	15 months	{1797}
Median overall survival			
Surgery + radiotherapy	9.9 months	24 months	{1797}
Surgery + radiotherapy + chemotherapy	15 months	31 months	{2810}
Location	Supratentorial	Preferentially frontal	{1417}
Necrosis	Extensive	Limited	{1417}
TERT promoter mutations	72%	26%	{1801,1830}
TP53 mutations	27%	81%	{1797}
ATRX mutations	Exceptional	71%	{1519}
EGFR amplification	35%	Exceptional	{1797}
PTEN mutations	24%	Exceptional	{1797}

新たな variant

・Epithelioid glioblastoma　(younger adult , children,IDH-wt, rhabdoid cell ,BRAF V600E .etc　PXA との関連？？),

・GBM with primitive neuronal component (かつての GBM with PNET-like component　※PNET はなくなる。神経細胞への分化傾向：Homer Wright rosette,synptophysin+,GFAP-, MYC or MYCN amp .etc)

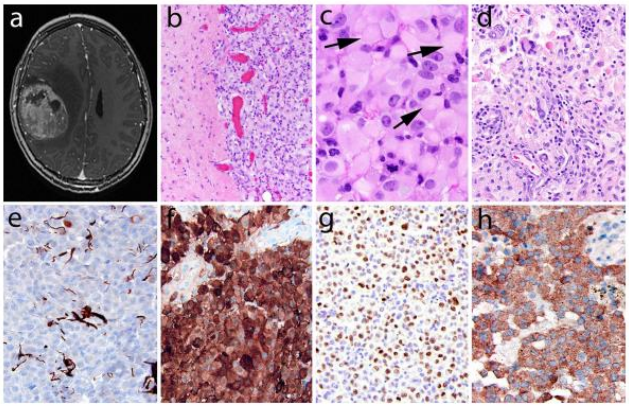


Fig. 2 Epithelioid glioblastomas (Ep-GBM). Although the neuroimaging features are not specific, many cases show a superficial localization and sharp demarcation, as seen on this post-contrast T1-weighted MR image (**a**). Histologically, the Ep-GBM may also show a discrete border with adjacent brain, often suggestive of a metastasis (**b**). This mimicry is further complicated by the tumor cytology featuring large epithelioid cells with abundant eosinophilic cytoplasm, vesicular nuclei, and large melanoma-like nucleoli (**c**). Not uncommonly, a subset of tumor cells display eccentric nuclei and paranuclear inclusions that overlap with rhabdoid neoplasms (*arrows*). Some Ep-GBMs show features of a lower grade precursor in adjacent tissue; in this particular example, there was focal evidence of pleomorphic xanthoastrocytoma, including bizarre giant cells despite lack of mitotic activity, numerous eosinophilic granular bodies, and xanthomatous appearing vacuolated astrocytes (**d**). GFAP expression is often limited (**e**) and may even be lacking entirely. In contrast, S100 protein is strongly expressed (**f**), whereas other melanoma markers are typically negative (not shown). Other glial markers, such as OLIG2 may also be positive (**g**), but many lack this protein as well. Roughly half of Ep-GBMs express BRAF V600E mutant protein as seen in this example (**h**)

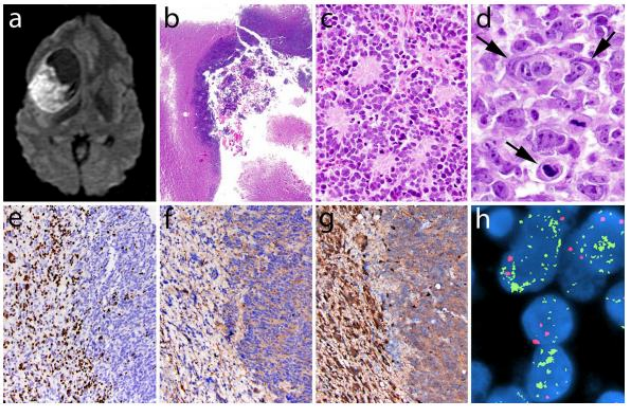


Fig. 3 Glioblastomas with primitive neuronal components (GBM-PNC; **b** and **e–g** show the astrocytic component on the *left* and the primitive neuronal component on the *right*). In this GBM-PNC, the imaging was essentially identical to that of conventional GBM, including a rim-enhancing mass; however, the markedly restricted diffusion on this DWI MR image highlights the more cellular primitive component (**a**). The primitive clone in this GBM-PNC is evident as a highly cellular nodule within an otherwise classic diffuse astrocytoma (**b**). Well-formed Homer Wright rosettes were seen in the primitive portion of this GBM-PNC (**c**). Large cell/anaplastic features (similar to those of medulloblastoma) are seen in a subset of GBM-PNC; note the increased cell size, vesicular chromatin, macronucleoli, and cell–cell wrapping (*arrows*) in this case (**d**). The primitive component typically displays loss of glial marker expression, including GFAP (not shown) and OLIG2 (**e**), along with gain of neuronal features, such as synaptophysin positivity (**f**, note also staining of Homer Wright rosettes). A subset of cases demonstrates features of secondary glioblastoma, including IDH1 R132H mutant protein expression (**g**). FISH revealed MYCN gene amplification limited to the primitive foci of this GBM-PNC (**h**; centromere 2 signals in *red* and MYCN signals in *green*)

【Pediatric diffuse glioma】

・DIPG の中に histone H3 K27M mutation を呈する予後不良な群：diffuse midline glioma,H3K27M-mutant として新たな entity として分類。

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DOI 10.1007/s00401-012-0998-0

ORIGINAL PAPER

K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas

Dong-Anh Khuong-Quang · Pawel Buczkowicz · Patricia Rakopoulos · Xiao-Yang Liu · Adam M. Fontebasso · Eric Bouffet · Ute Bartels · Steffen Albrecht · Jeremy Schwartzentruber · Louis Letourneau · Mathieu Bourgey · Guillaume Bourque · Alexandre Montpetit · Genevieve Bourret · Pierre Lepage · Adam Fleming · Peter Lichter · Marcel Kool · Andreas von Deimling · Dominik Sturm · Andrey Korshunov · Damien Faury · David T. Jones · Jacek Majewski · Stefan M. Pfister · Nada Jabado · Cynthia Hawkins

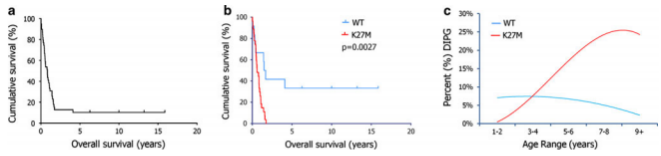

Fig. 1 K27M-H3.3 is associated with worse overall survival and higher age of diagnosis in DIPG. **a** Kaplan–Meier curve of overall survival for all DIPG patients ($n = 39$). **b** DIPG patients carrying K27M-H3.3 mutation have worse overall survival compared to patients wild-type for this histone as determined by Kaplan–Meier analysis (Log-rank, $p = 0.0027$). Notably, all long term survivors were wild-type for *H3F3A*. **c** Age distribution of DIPG patients based on K27M-H3.3 mutational status. DIPG patients mutated for K27M-H3.3 have a higher age of diagnosis 8.13 years (±3.75) as compared to wild-type patients [4.57 years (±4.07), $p = 0.010$]

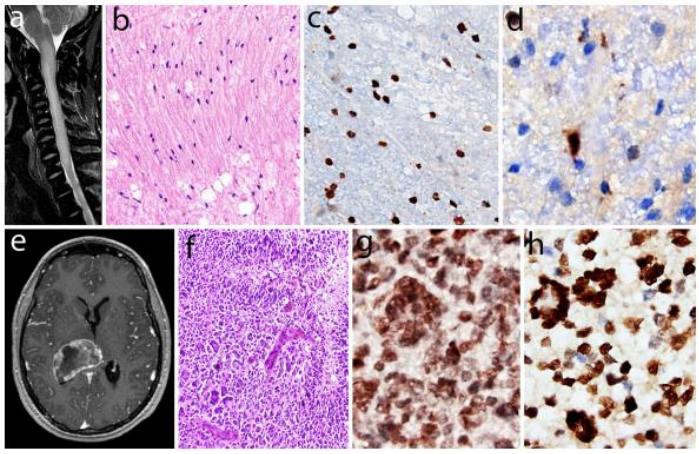

Fig. 4 Diffuse midline gliomas, H3 K27M–mutant. These tumors most often involve the brain stem (especially pons), spinal cord (**a–d**), and thalamus (**e–f**) in children and young adults. The morphologic spectrum varies widely, as in these two examples. This spinal lesion presented as a non-enhancing intramedullary mass with expansion and signal abnormalities on T2-weighted MRI (**a**). There was only minimal hypercellularity and cytologic atypia (**b**), but tumor cells strongly expressed the H3 K27–mutant protein (**c**) and also showed loss of ATRX expression (**d**). In contrast, the thalamic example showed a rim-enhancing mass on post-contrast T1 MRI (**e**) and histology demonstrated classic features of glioblastoma with prominent multinucleated giant cells (**f**). In addition to H3 K27M–mutant protein expression (**g**), there was strong p53 staining (**h**)

【Other astrocytoma】

・Anaplastic PXA WHO gradeⅢ(かつて PXA with anaplastic feature。10HPF に mitosis≧5　)が追加。

・Pilomyxoid A の grading が保留（Pilocytic A WHO grade Ⅰ と genetic な overlap が多い。）

【Ependymoma】

・RELA-fusion-positive(grade　ⅡorⅢ)が新たな entity として分類。（主に小児のﾃﾝﾄ上、LICAM 発現）

・clear cell ependymoma は delete

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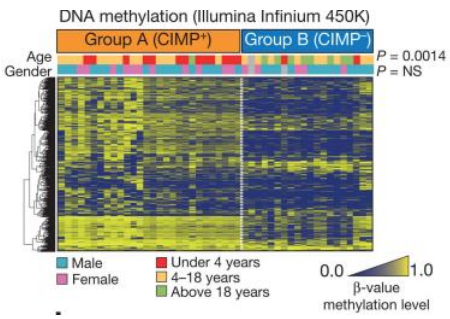
Posterior fossa group A/B（PFA→CIMP+ 5 生率 65%　PFB→CIMP- 5 生率 95%）は？？



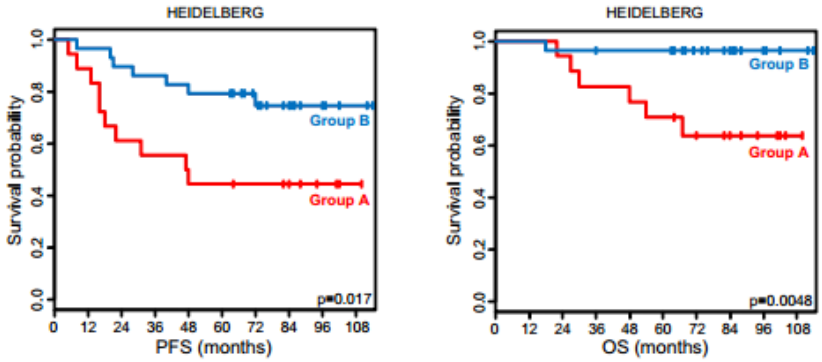
Nature. 2014 February 27; 506(7489): 445–450. doi:10.1038/nature13108.

Epigenomic alterations define lethal CIMP-positive ependymomas of infancy

Cancer Cell
Article

Delineation of Two Clinically and Molecularly Distinct Subgroups of Posterior Fossa Ependymoma

Hendrik Witt,[1,2,19] Stephen C. Mack,[3,4,19] Marina Ryzhova,[5] Sebastian Bender,[1,2] Martin Sill,[6] Ruth Isserlin,[7] Axel Benner,[6] Thomas Hielscher,[6] Till Milde,[2,8] Marc Remke,[1,2] David T.W. Jones,[1] Paul A. Northcott,[3,4] Livia Garzia,[3] Kelsey C. Bertrand,[3,4] Andrea Wittmann,[1] Yuan Yao,[3,4] Stephen S. Roberts,[9] Luca Massimi,[10] Tim Van Meter,[11] William A. Weiss,[12] Nalin Gupta,[13] Wiesia Grajkowska,[14] Boleslaw Lach,[15] Yoon-Jae Cho,[16] Andreas von Deimling,[17,18] Andreas E. Kulozik,[2] Olaf Witt,[2,8] Gary D. Bader,[7] Cynthia E. Hawkins,[3,4] Uri Tabori,[3,4] Abhijit Guha,[3] James T. Rutka,[3,4] Peter Lichter,[1] Andrey Korshunov,[17,18] Michael D. Taylor,[3,4,*] and Stefan M. Pfister[1,2,*]



→ 現段階で grading に関してはまだまだ検討の余地がある。

【Neuronal and mixed neuronal-glial tumors】

・new entity　：　Diffuse leptomeningeal glioneuronal tumor (DLGNT)が追加。

→disseminated oligodendroglial-like leptomeningeal tumor with or without parenchymal component, most often in children and adolescents.

→BLAF KIAA fusion gene (+) ・・・・genetic には pilocytic astrocytoma と overlap するところが多い??

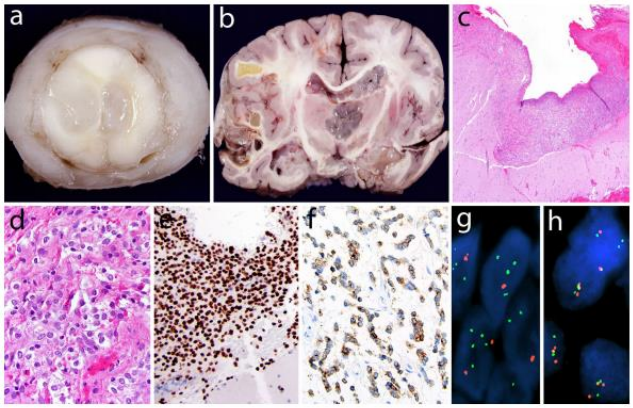
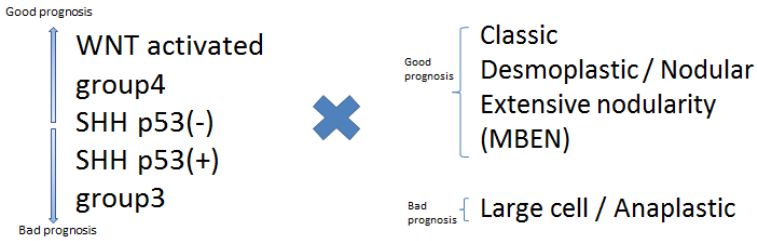


Fig. 5 Diffuse leptomeningeal glioneuronal tumors (DLGNT). At autopsy, this DLGNT patient had widespread expansion and fibrosis of spinal (**a**) and cerebral (**b**) subarachnoid spaces, along with intraventricular masses and variably cystic, mucoid intraparenchymal extensions along perivascular Virchow-Robin spaces (gross photos courtesy of Dr. William McDonald, Minneapolis, MN, USA). The DLGNT biopsy specimen showed a leptomeningeal infiltrate (**d**) with oligodendroglioma-like cytologic features (**d**). DLGNT cells are OLIG2-positive (**e**), along with variable synaptophysin immunoreactivity (**f**). Common genetic alterations detected by fluorescence in situ hybridization (FISH) include chromosome 1p deletion (**g**; tumor cells showing roughly half as many red 1p as green 1q signals) and *BRAF* fusion/duplication (**h**; increased *red BRAF* and *green* KIAA1549 copy numbers, in addition to *yellow* fusion signals)

【Medulloblastoma】

・WNT, group4, group3,SHH(TP53-mut+/-)　+　histology (Classic, D/N, MBEN, Large cell etc.)



Summary of the most common integrated medulloblastoma diagnoses, with clinical correlates

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance

【Medulloblastma 以外の胎児性腫瘍】

・PNET という terminology は無くなる。その variant である medulloepithelioma, ependymoblastoma, ETANTR(embryonal tumor with abundant neuropil and true rosettes) →組織学的な共通性と遺伝的な共通性（C19MC-amp）→まとめて、ETMR(embryonal tumor with multi layered rosettes),C19MC-altered

・AT/RT→INI-1（または極稀に BRG1）陰性が証明されなければならない。いずれも証明されない場合は CNS embryonal tumor with rhabdoid feature と記述。

・胎児性腫瘍の分類は変遷のさなかにある。これまで wastebasket category として用いられてきた CNS PNET に対して CNS embryonal tumor, NOS の designation が設けられた。

【Nerve sheath tumors】

・melanotic schwanoma→malignant behavior と genetic profiles(Carney complex and PRKAR1A gene)から単なる variant からひとつの entity に。

・Hybrid nerve sheath tumors

・malignant peripheral nerve sheath tumor (MPNST)に２つの subtype を追加。

→epithelioid MPNST, MPNST with perineurial differentiation

【Meningioma】

・classification / grading → no revision

・brain invasion があればそれ単独で Atypical meningioma WHO grade Ⅱ と診断可。

（これまでは major criterion：mitosis>4/10HPF　または minor criteria 5 つのうち３つ以上だった。）

【Solitary fibrous tumor / Hemangiopericytoma】

・NAB2-STAT6 fusion gene→同一スペクトラム

・SFT / HPC　grade Ⅰ / Ⅱ / Ⅲと表記。(軟組織腫瘍に準じた grading が採用)

【Lymphomas and histiocytic tumors】

Hematopoietic/Lymphoid WHO classifications に準ずる。

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O. *Italics*: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*

Grading of selected CNS tumors according to the 2016 CNS WHO

WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

病理診断を依頼する際に ～予後や治療法に関する情報を引き出すために IHC で出来る事～

●Medulloblastoma

→

「β-catenin」； 5%以上の細胞にβ-catenin 陽性の場合 CTNNB1 変異陽性の可能性が高い。つまり WNT-activated type（Low risk）の可能性が高い。

「TP53」； SHH-activated type,TP53-wild type → Standard risk～Low-risk
SHH-activated type,TP53-mutant type → High risk （Li fraumani 症候群との関連）

●浸潤性 glioma

→

「IDH1」； 必須。

「TP53」: 1p/19q codel とは基本的に相互排他的。FISH が無理ならせめて。
Secondary GBM は多くは p53 陽性、primary GBM では陰性。

「ATRX」； 「TERT」と相互排他的。Astro～ と Oligo～,GBM の鑑別。

「BRAF V600E」； 限局性 glioma などによくみられるが Ep-GBM を疑った場合にも有用。今のところ、治療方針に影響を与えるものではないが、メラノーマでは変異 BRAF に対する分子標的薬（Vemurafinive）が臨床試験で promising な結果を出しており、もしかすると今後 Ep-GBM にも・・・？

●下垂体腺腫

→

「TP53」「MIB-1」； 異形成下垂体腺腫の診断基準： p53 陽性と Ki67 index>3%（下垂体癌はこれらに加え遠隔転移)。組織形態学的悪性度は関係なし。

「CAM5.2」； densely granulated GHoma と sparsely granulated GHoma では染色パターンがことなります。(densely type と sparsely type では再発率や予後が異なります。)

「SSTR2A」； GHoma に対するソマトスタチンアナログの効果予測が可能。

●SFT/HPC

→

「CD34」； 悪性になると染まりにくい。

「STAT6」； NAB2-STAT6 融合遺伝子は SFT/HPC に特異的。ただし核内に染まる事。meningioma と迷った場合に。