

2016WHO脳腫瘍分類と細胞診

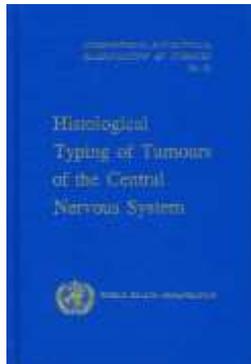
神戸大学大学院医学研究科・地域連携病理学
兵庫県立がんセンター・地域連携病理学研究所
廣瀬 隆則

第25回愛媛県臨床細胞学会学術集会(2017年1月29日)

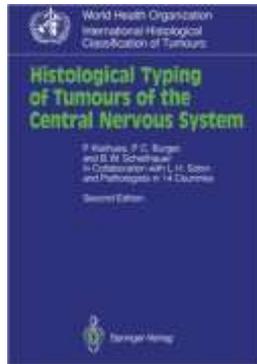
WHO腦腫瘍分類

Histological
(phenotype)

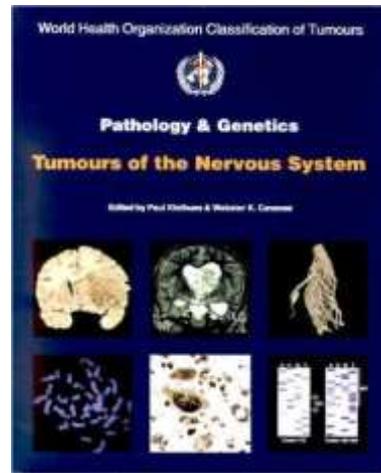
Histological/molecular
(genotype)



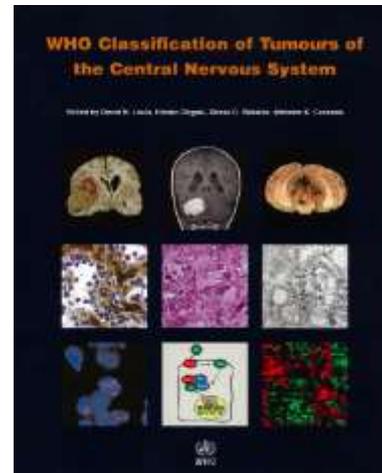
1979
1st edition



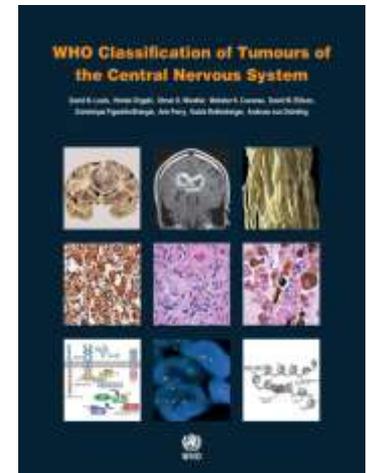
1993
2nd edition



2000
3rd edition



2007
4th edition

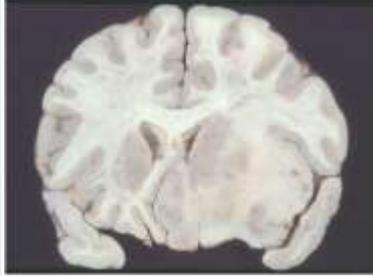
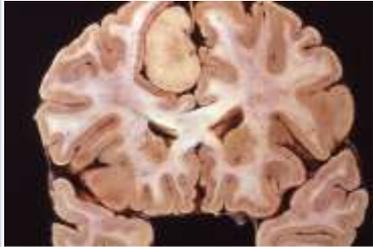


2016
Update of
4th edition

2016 WHO CNS: 主要な変更点

- 遺伝子異常に基づいた**びまん性神経膠腫diffuse glioma**分類の再構成
 - Diffuse astrocytoma, IDH-mutant
- 遺伝子異常に基づいた**髄芽腫medulloblastoma**分類の再構成
 - Medulloblastoma, WNT-activated
- 遺伝子異常に基づいた**胎児性腫瘍embryonal tumors (髄芽腫以外)**の再構成
- 遺伝子異常で定義された**上衣腫亜型**の導入
- 遺伝子異常の異なる**小児脳腫瘍**を成人腫瘍から分離

脳腫瘍の分類

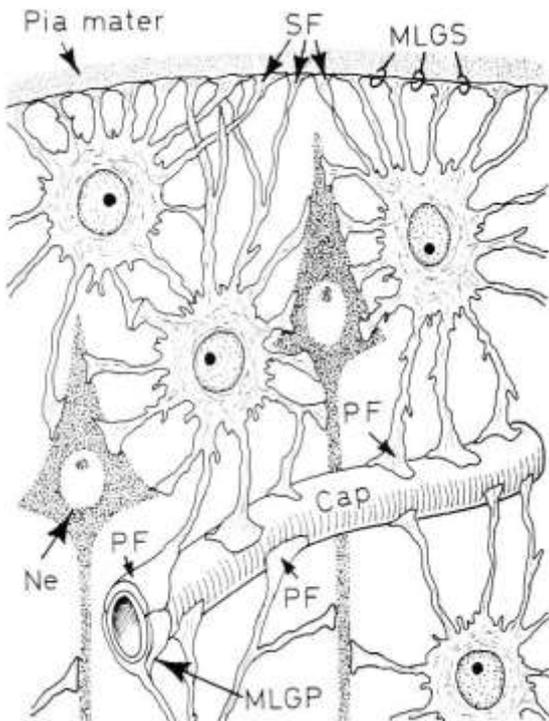
原発性	脳の中 (実質内)	神経膠腫、胎児性など		>1/3
	脳の外 (髄膜など)	髄膜腫、聴神経腫など		>1/3
転移性	脳以外から	肺がん、乳がんなど		<1/3

腦腫瘍分類

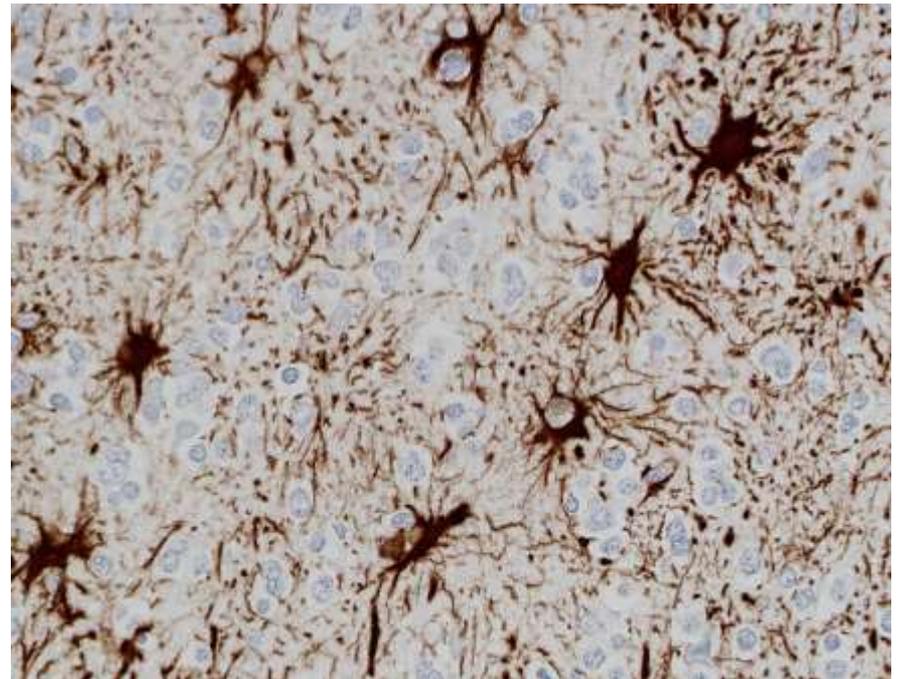
原發性腦腫瘍	實質內腫瘍	星細胞系腫瘍	
		星細胞腫	
		膠芽腫	
		毛樣細胞性星細胞腫	
		乏突起膠細胞系腫瘍	
		上皮細胞系腫瘍	
		神經細胞系腫瘍	
	胎兒性腫瘍	髓芽腫	
	實質外腫瘍	髓膜性腫瘍	髓膜腫
		末梢神經系腫瘍	聽神經腫
轉移性腦腫瘍			

星細胞系腫瘍 astrocytic tumors

星細胞 astrocyte



GFAP

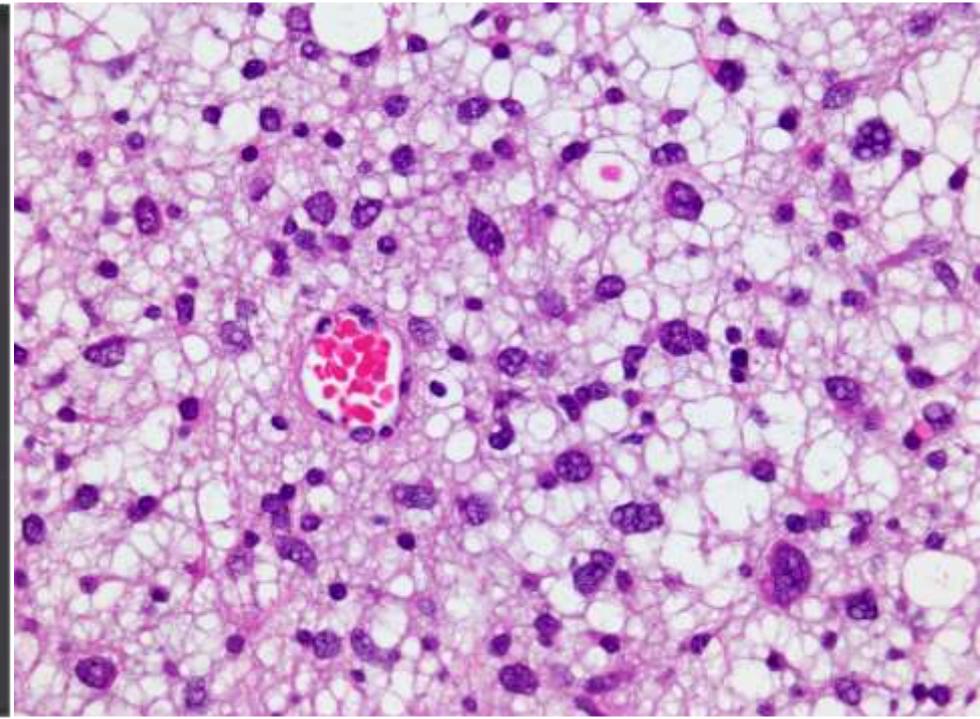
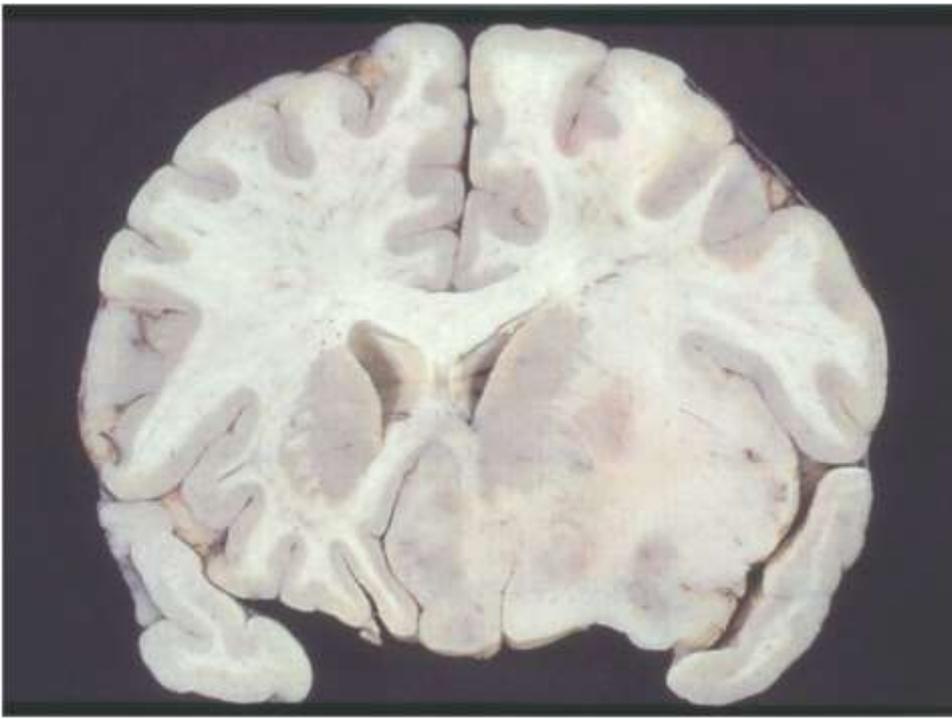


星細胞系腫瘍 astrocytic tumors

- 星細胞の腫瘍
- 浸潤性に増殖し、境界が不明瞭
- 細胞質突起が豊富
- 多くに *isocitrate dehydrogenase (IDH)* 変異

浸潤性増殖

異型核、細胞質突起



星細胞系腫瘍 astrocytic tumors

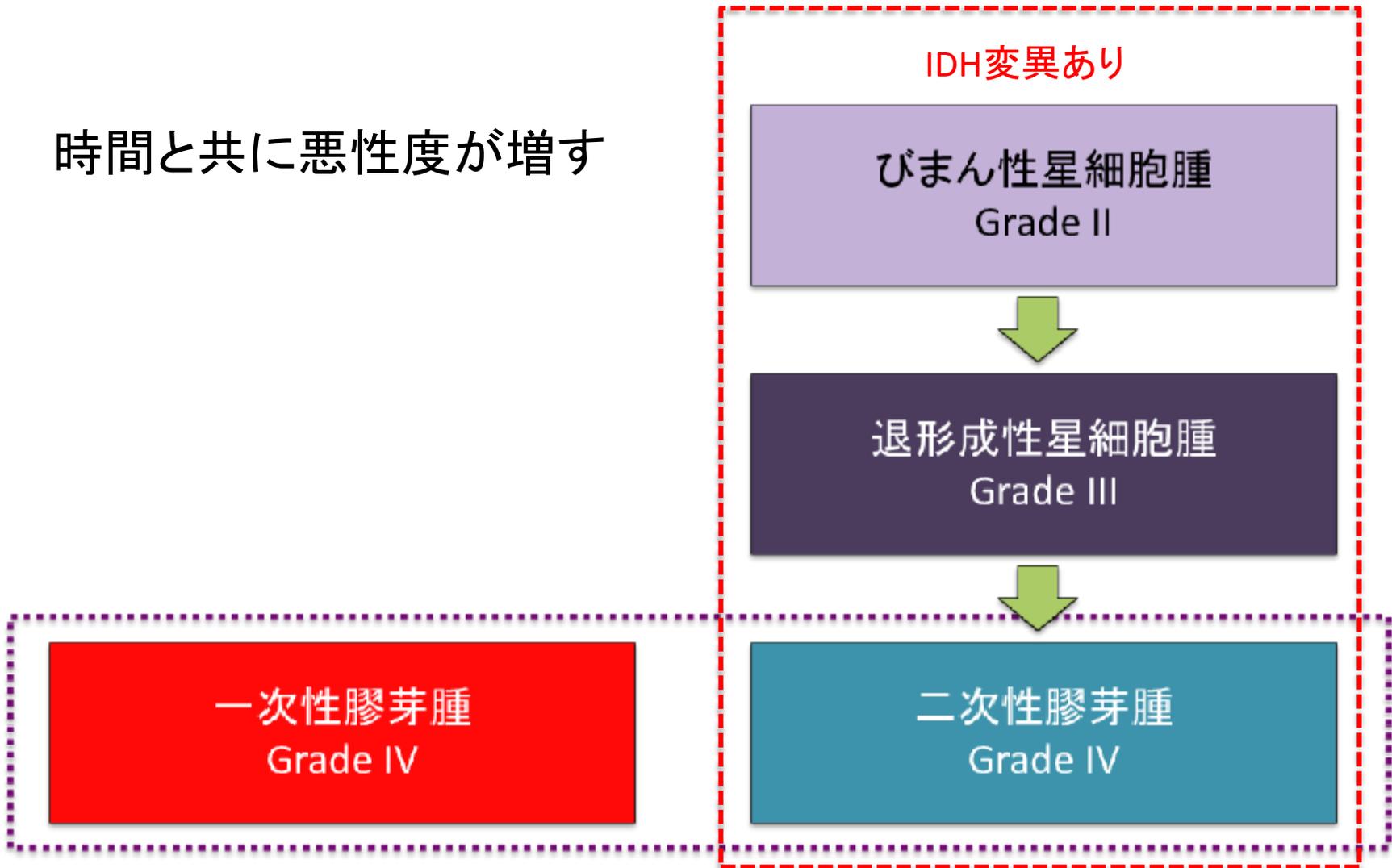
悪性度の違う3つの腫瘍がある

腫瘍型	Grade
びまん性星細胞腫 diffuse astrocytoma	II
退形成性星細胞腫 anaplastic astrocytoma	III
膠芽腫 glioblastoma	IV

星細胞系腫瘍 astrocytic tumors

時間と共に悪性度が増す

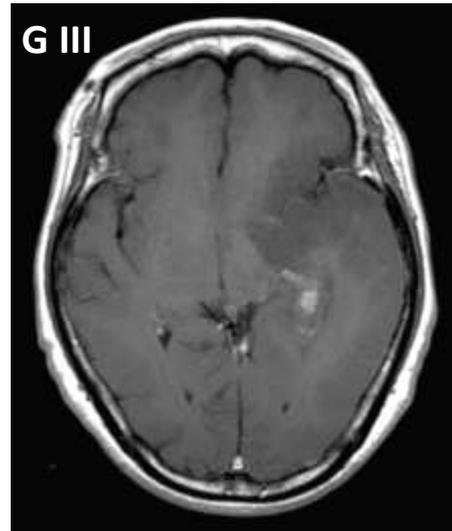
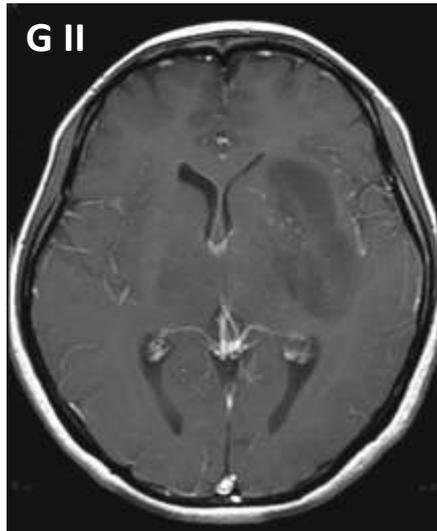
GBM



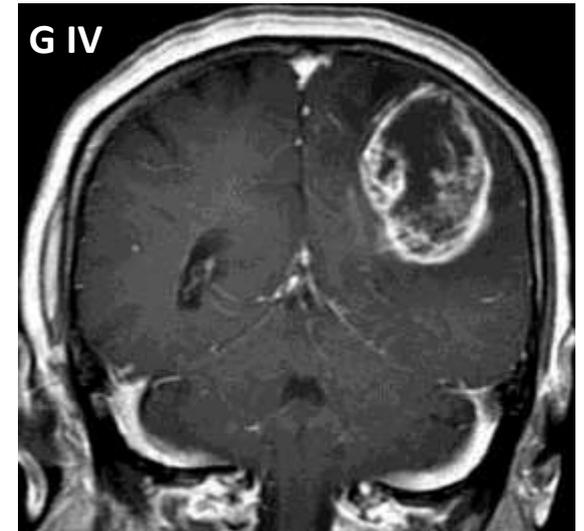
星細胞系腫瘍

- びまん性 30歳代、退形成性 40歳代、膠芽腫 50-60歳代
- 男>女
- 大脳半球（前頭葉、側頭葉、頭頂葉など）

部分的な増強

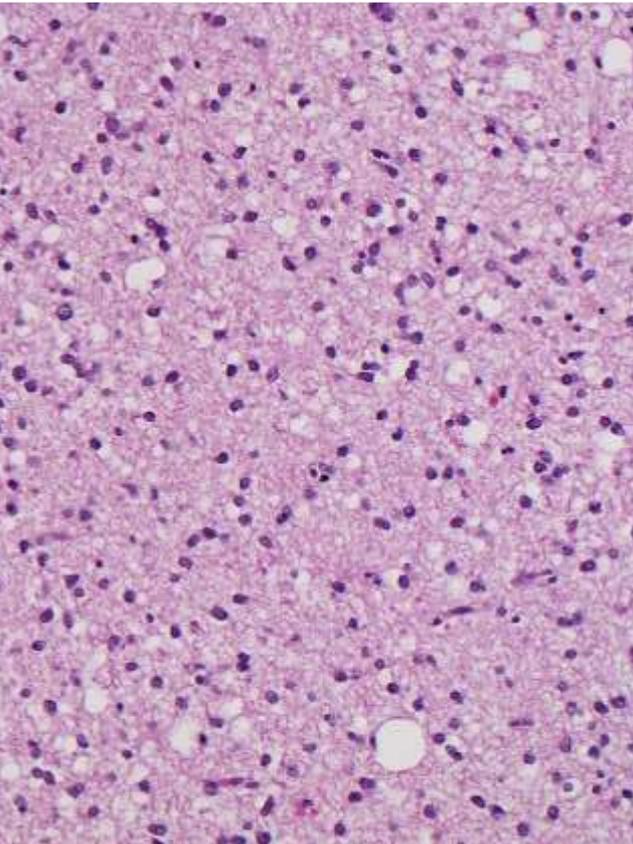


リング状増強効果

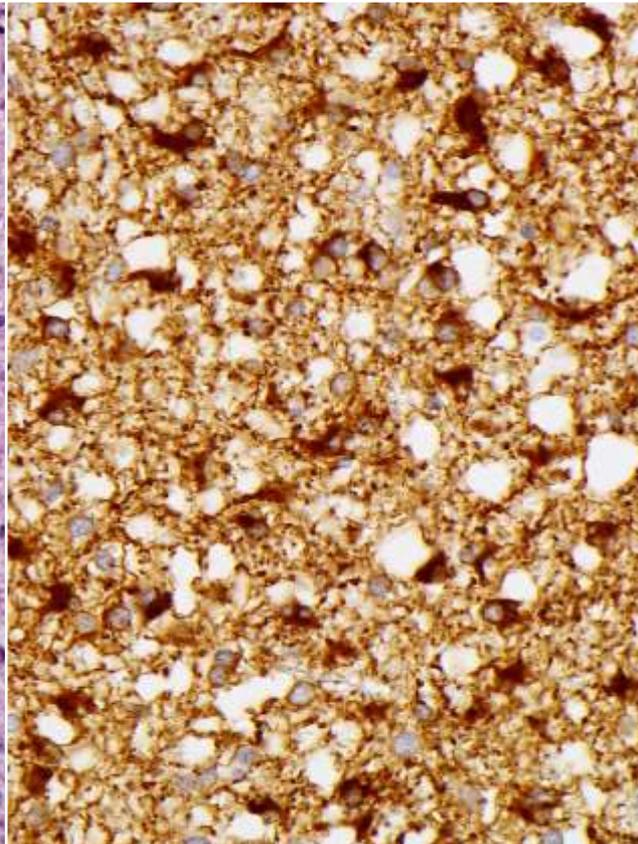


Diffuse astrocytoma, IDH-mutant

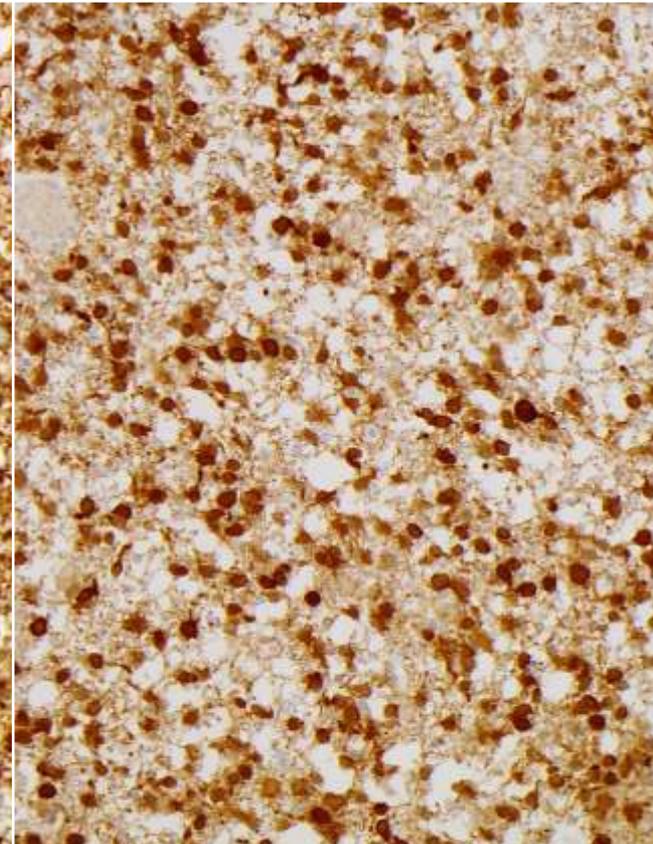
軽度の異型性



GFAP

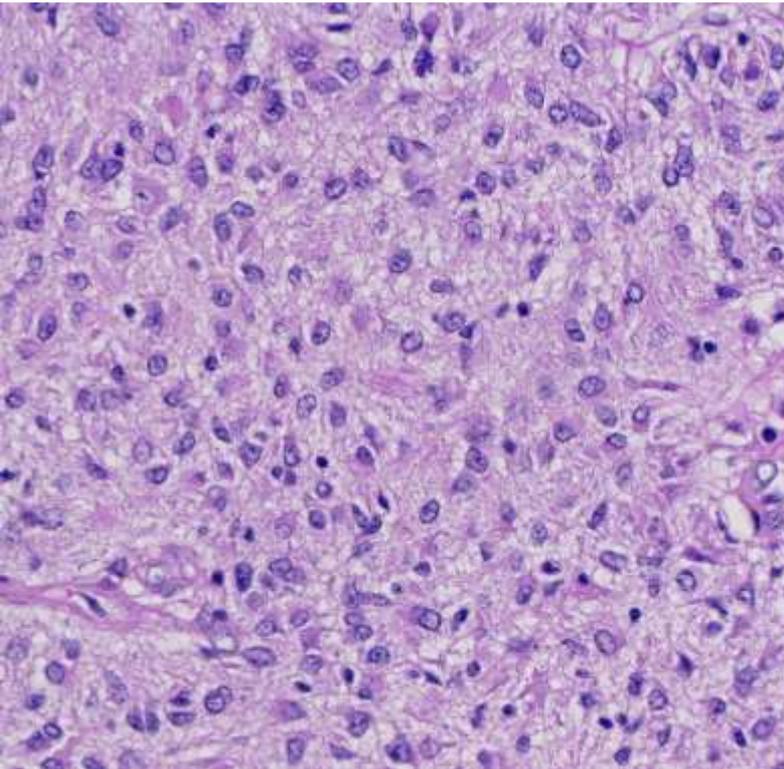


変異IDH1

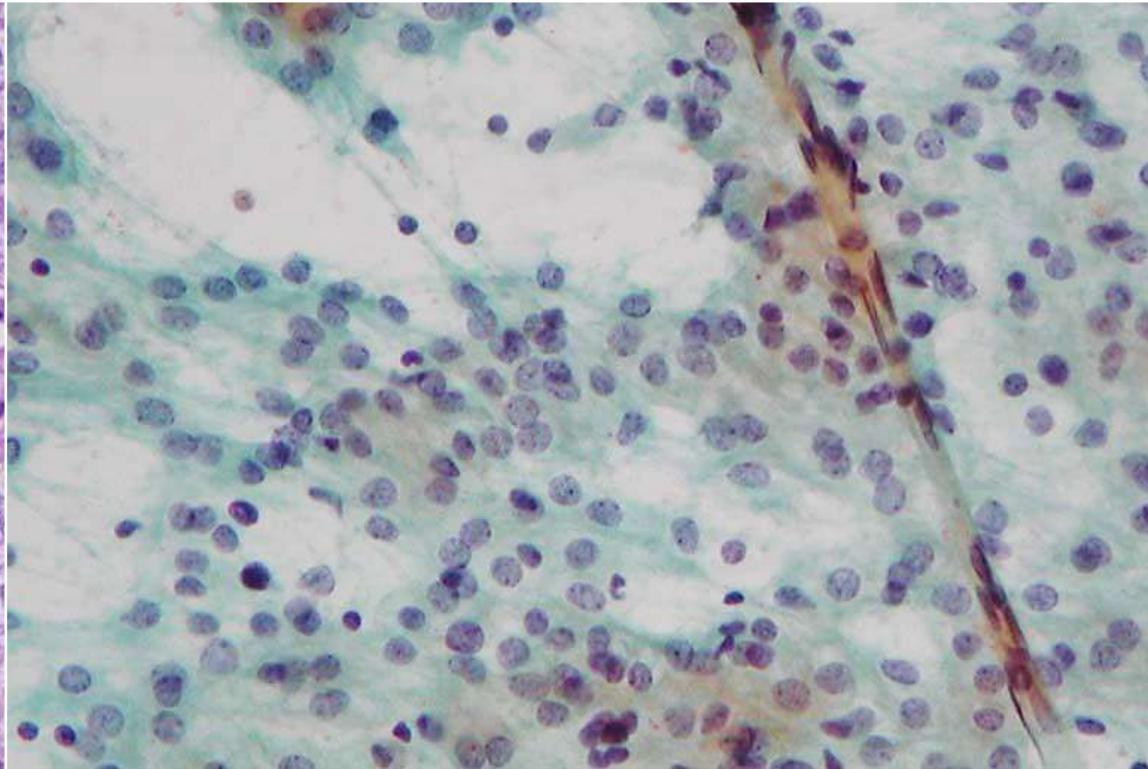


びまん性星細胞腫 diffuse astrocytoma

Fibrillary type

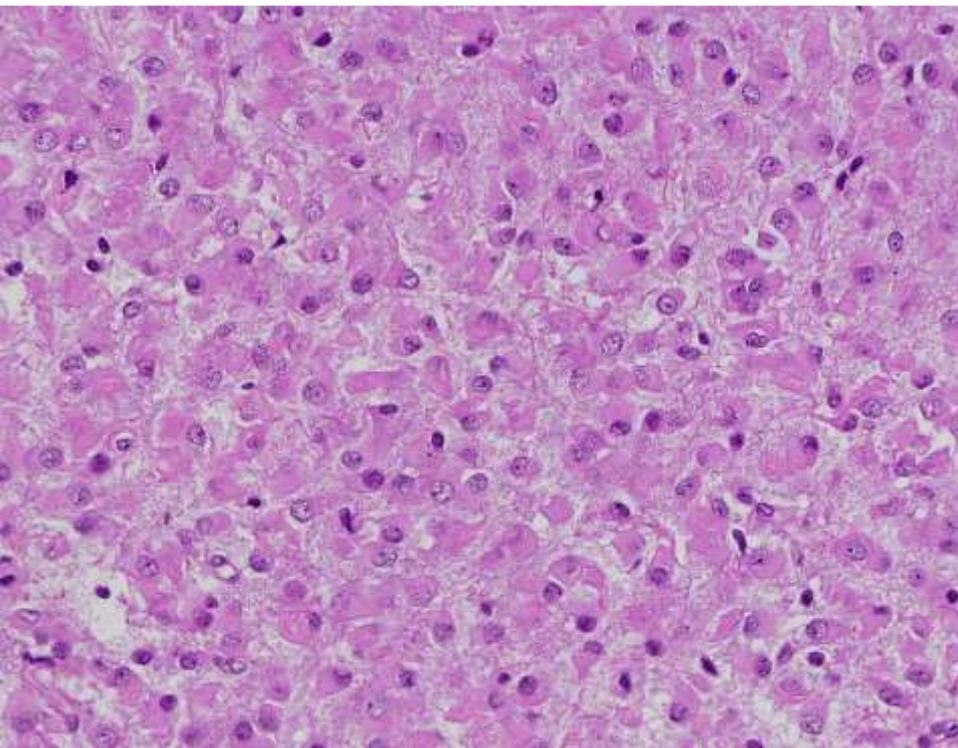


豊富な細胞質突起

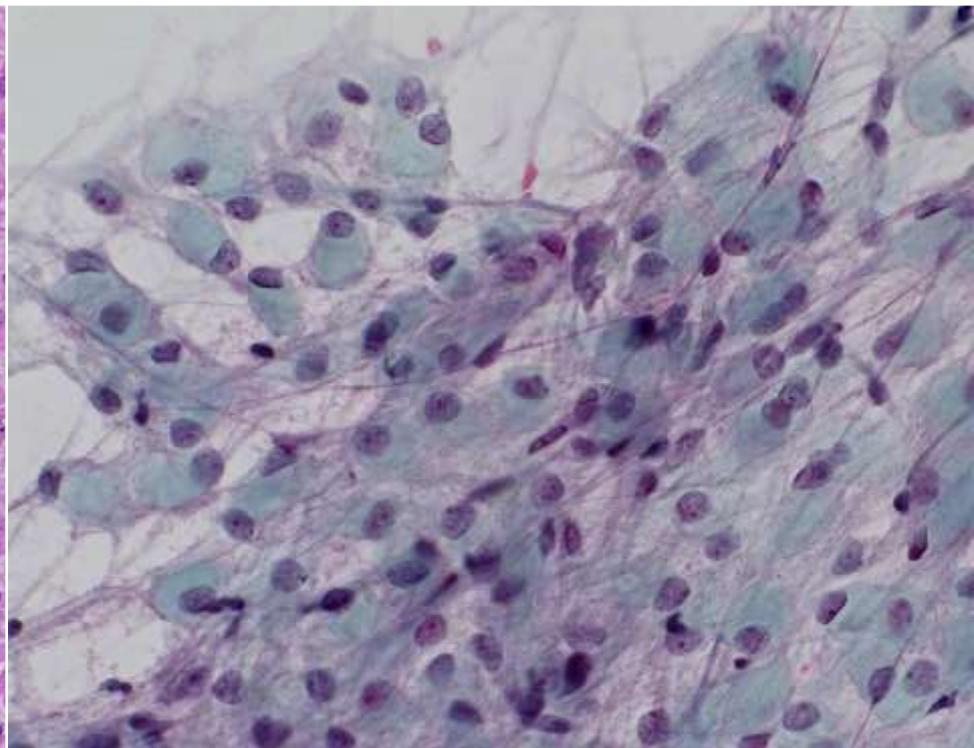


びまん性星細胞腫 diffuse astrocytoma

Gemistocytic type

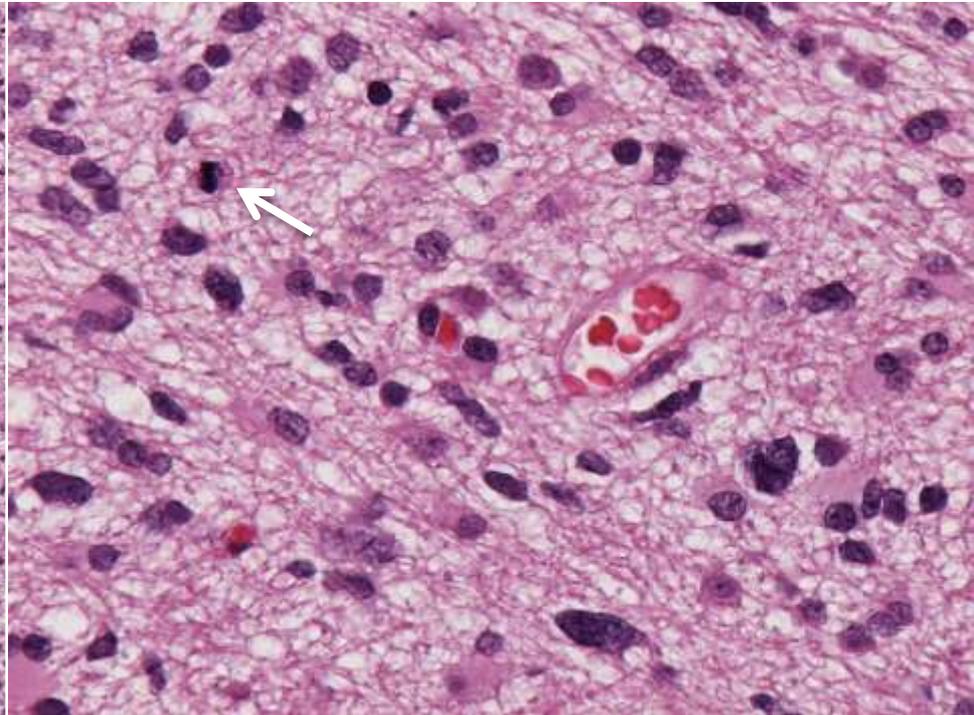
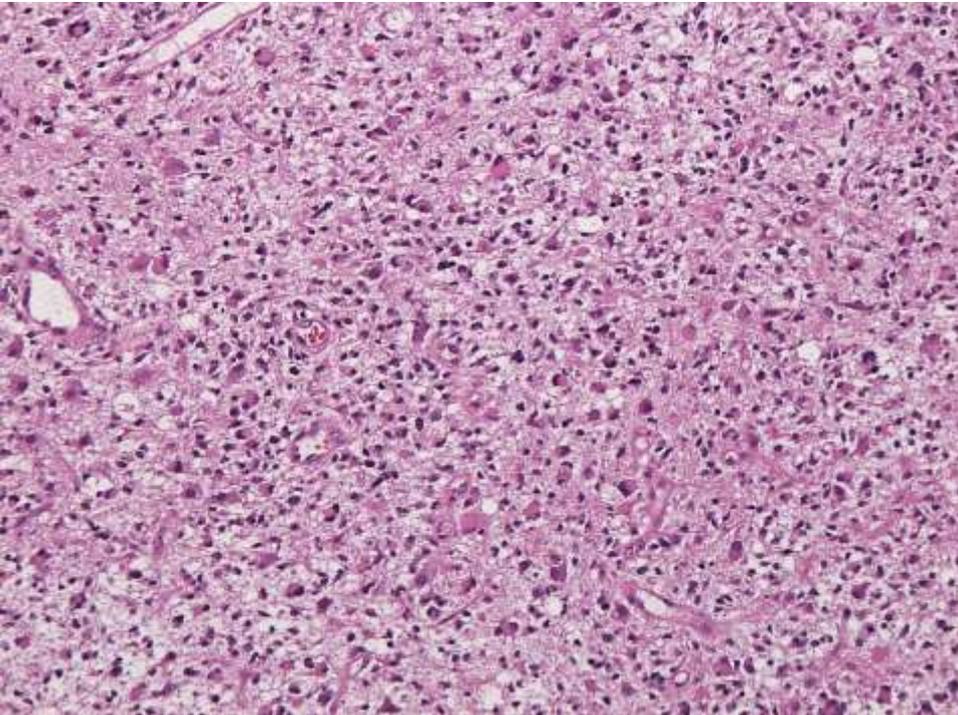


豊かな細胞質



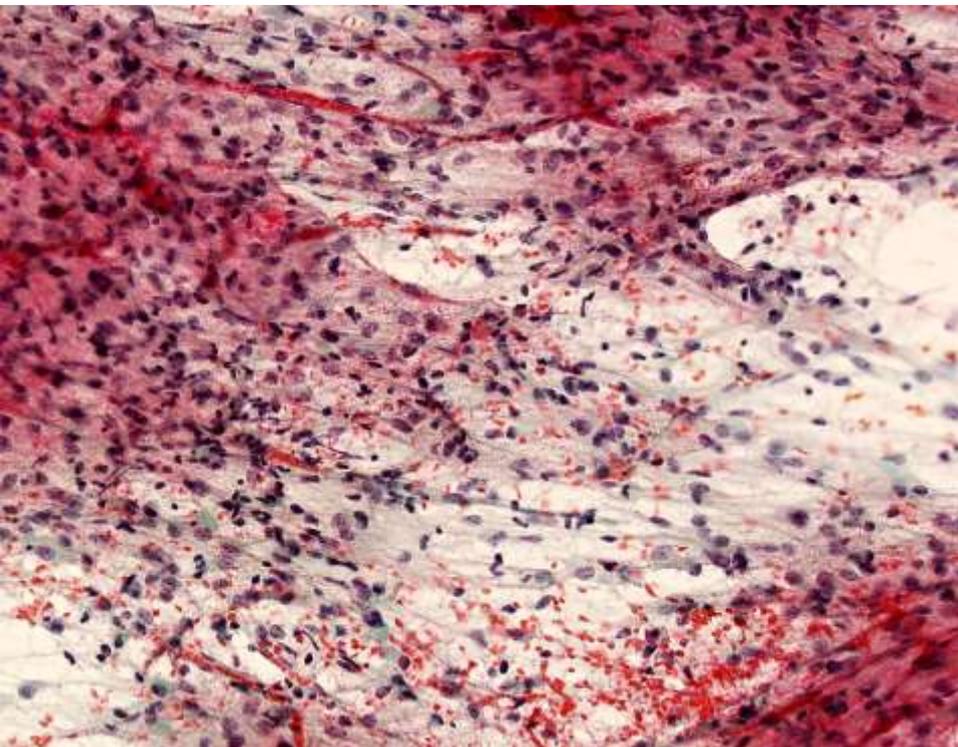
退形成性星細胞腫 anaplastic astrocytoma Grade III

細胞密度が高く、核分裂像が見られる

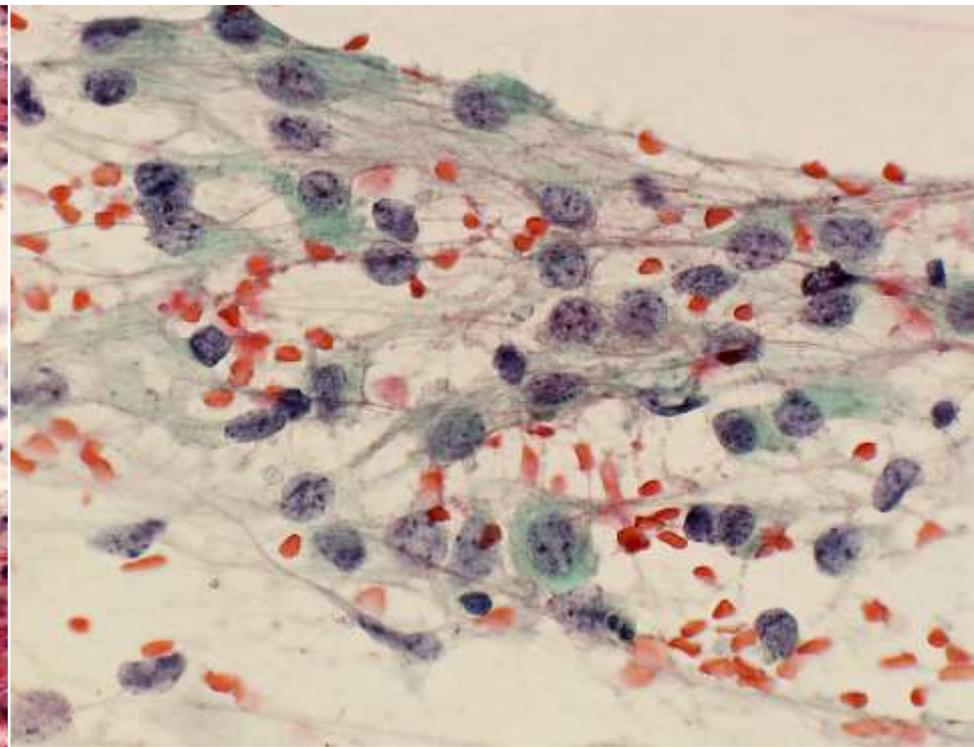


退形成性星細胞腫 Anaplastic astrocytoma

異型性の増加



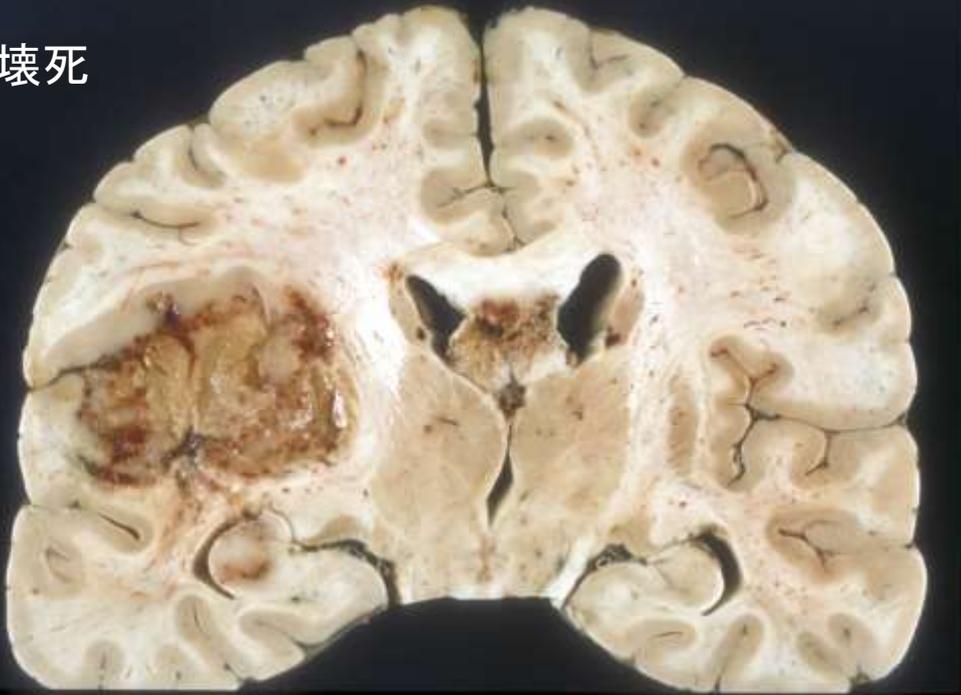
細胞質突起



膠芽腫 glioblastoma

- 最も高悪性度の腫瘍: 大半が1年以内に死亡
- Glioblastoma, IDH-wildtype (primary GBM)
- Glioblastoma, IDH-mutant (secondary GBM)

壊死

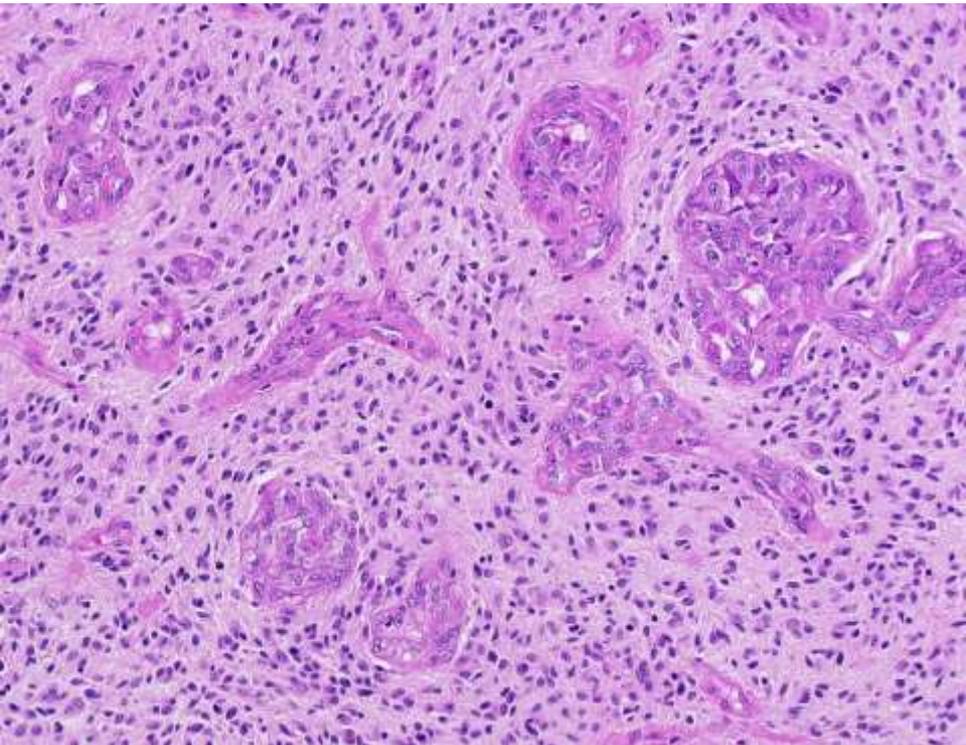


出血

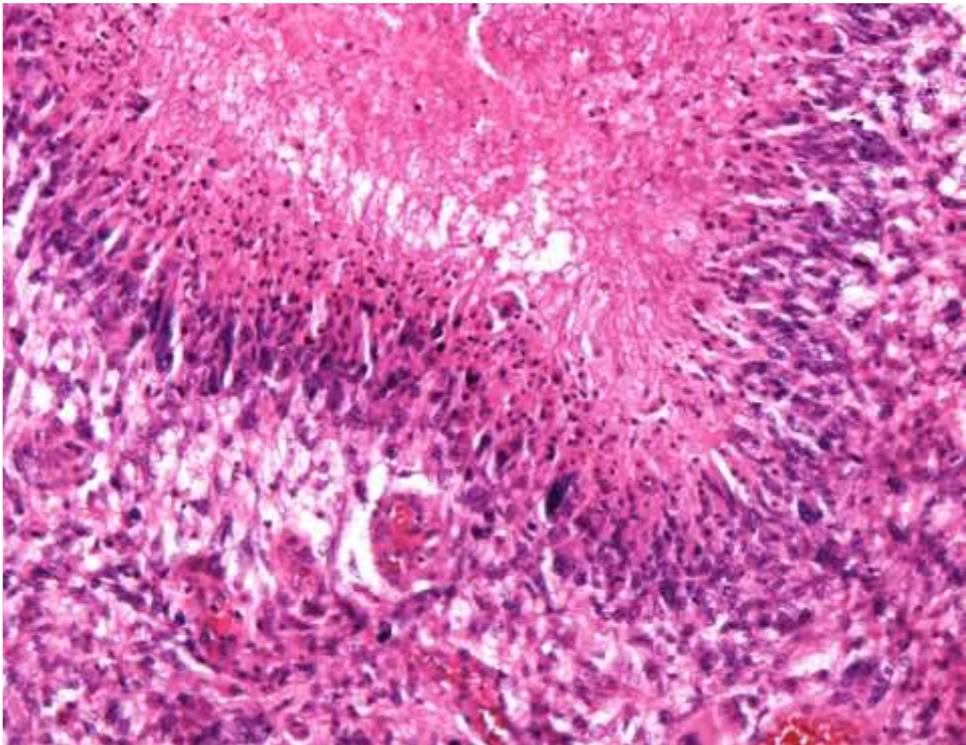


膠芽腫 glioblastoma, grade IV

微小血管增殖

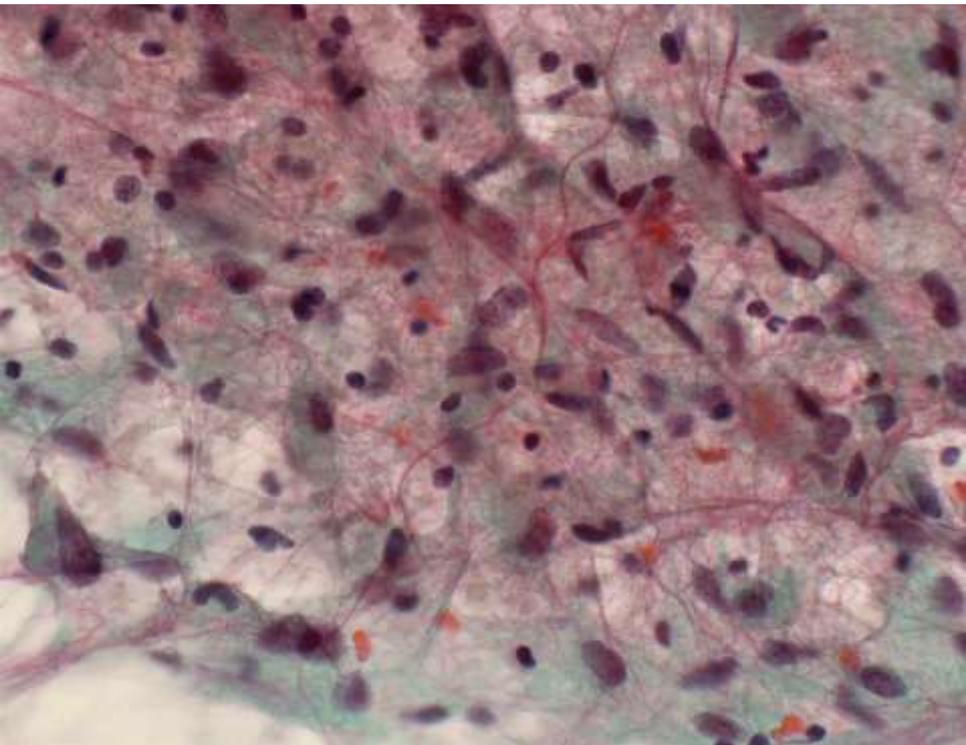


偽柵狀壞死

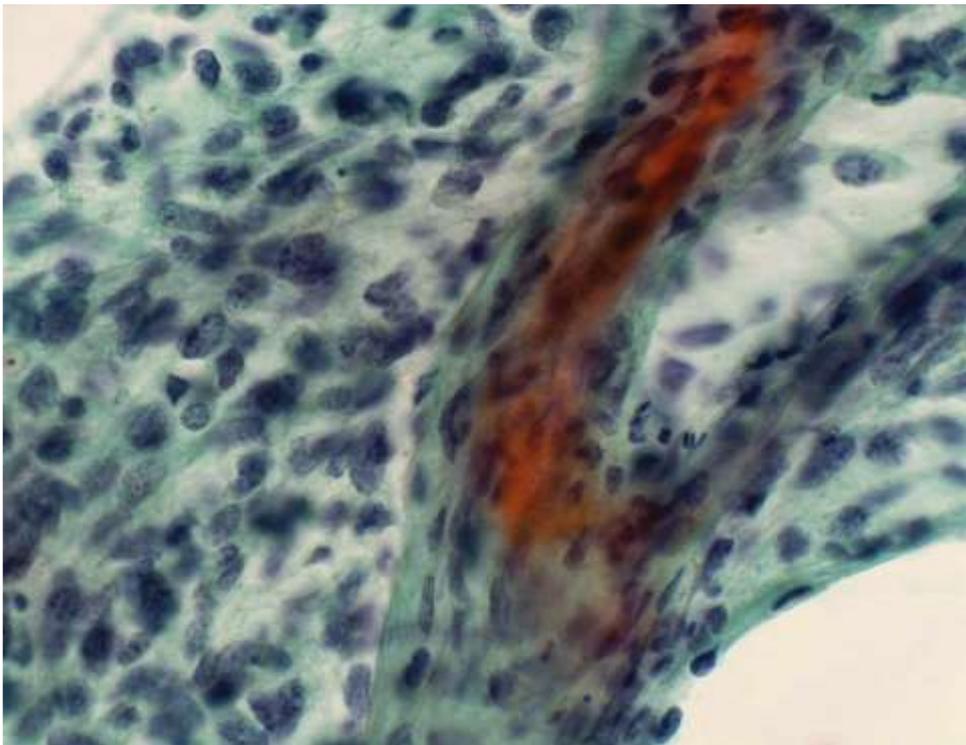


膠芽腫 glioblastoma

異型核、細胞質突起、LG好性細胞質



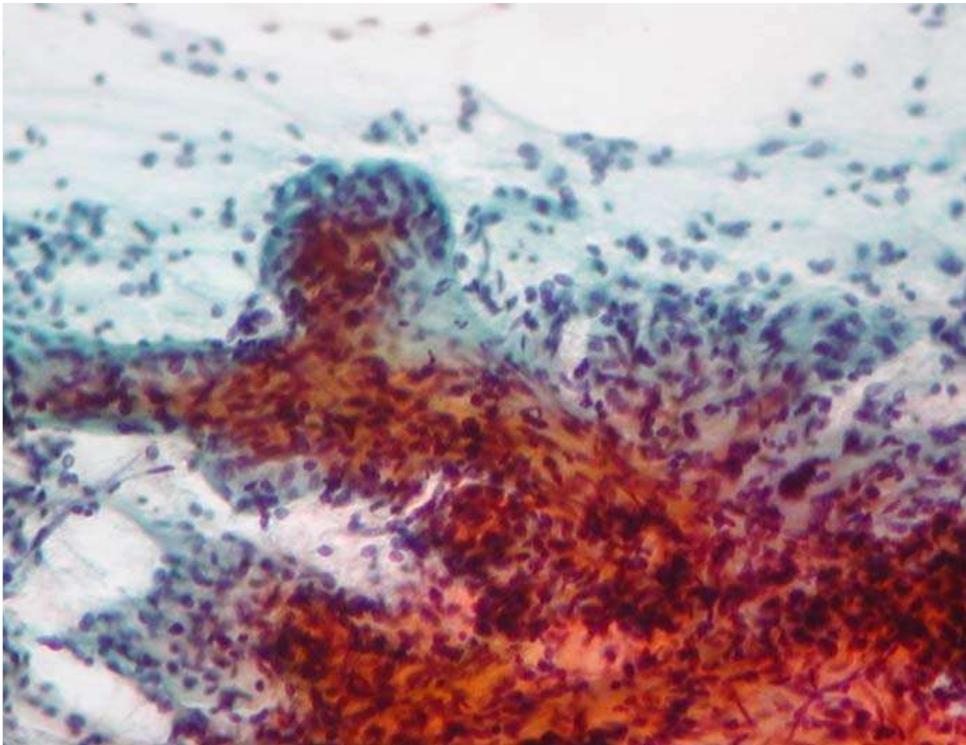
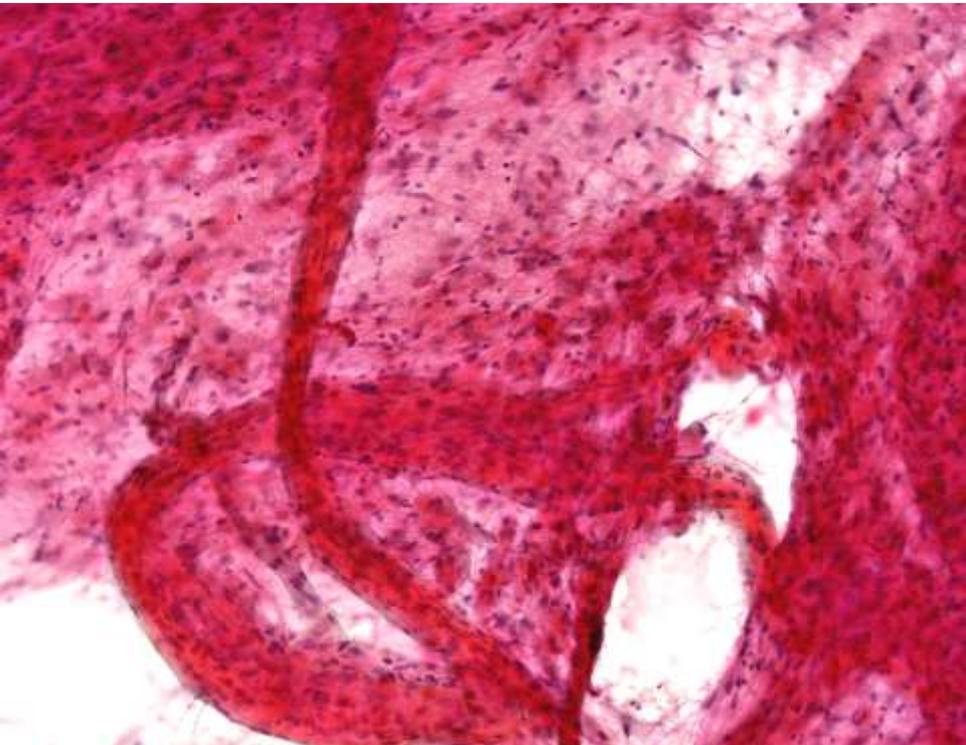
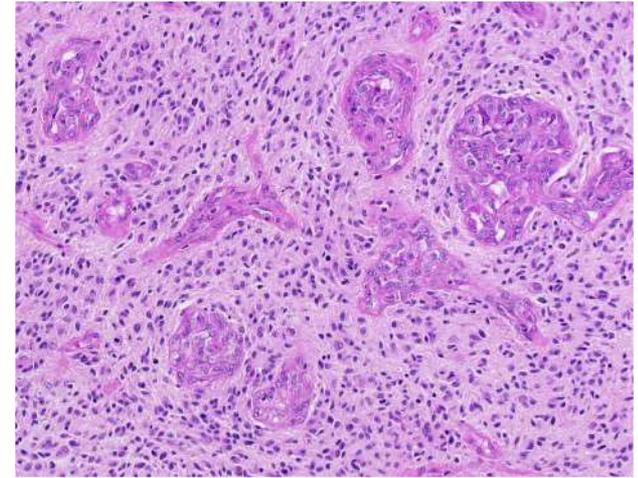
高度の細胞異型、微小血管増殖



Glioblastoma

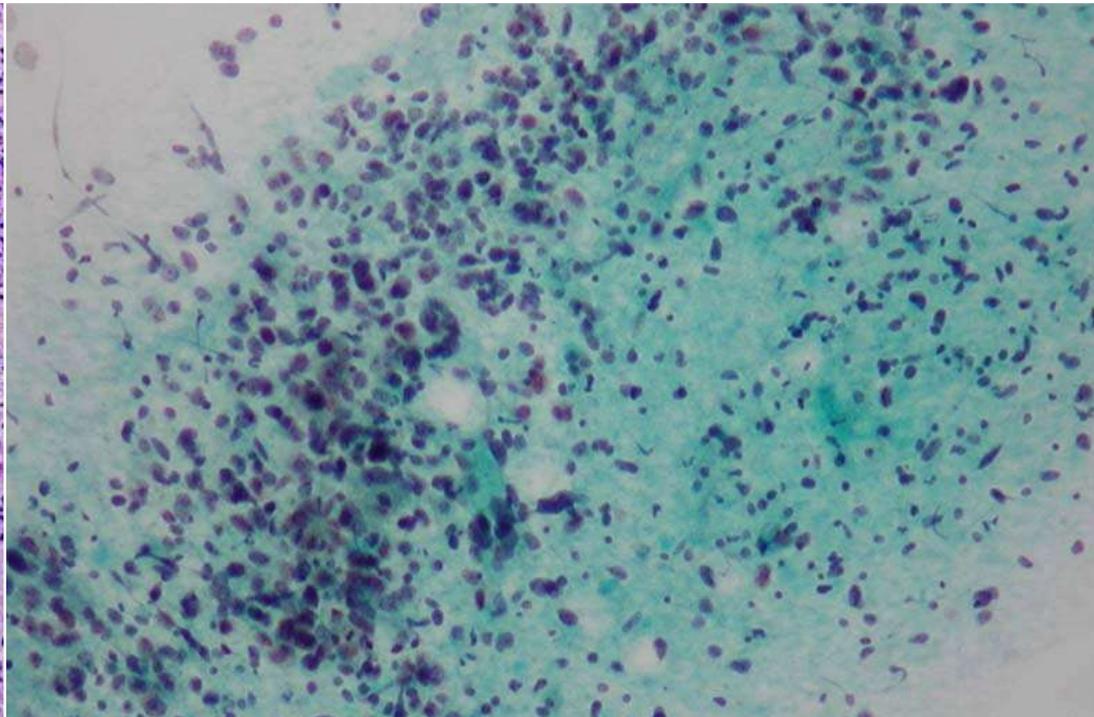
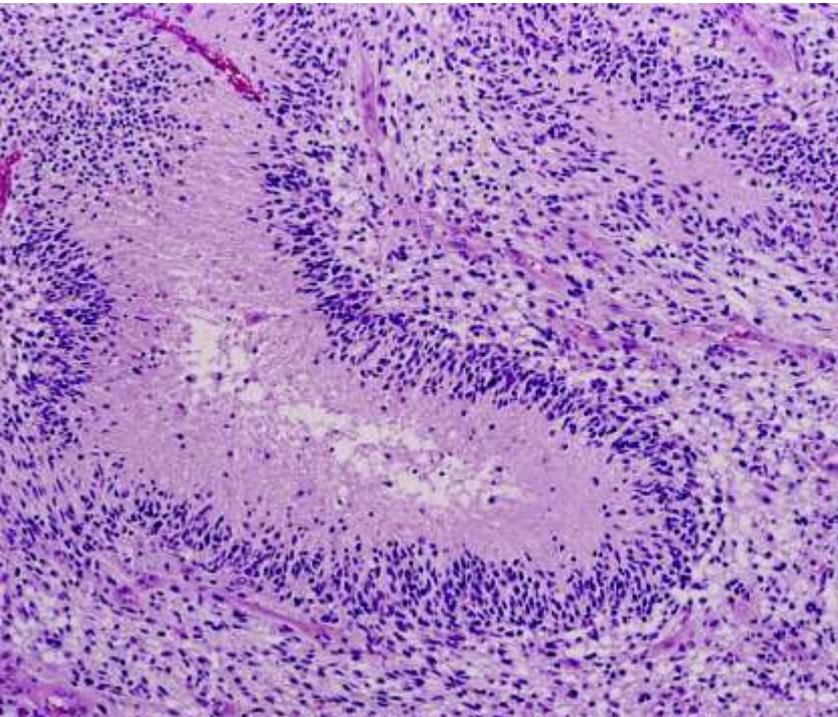
Microvascular proliferation

微小血管增殖



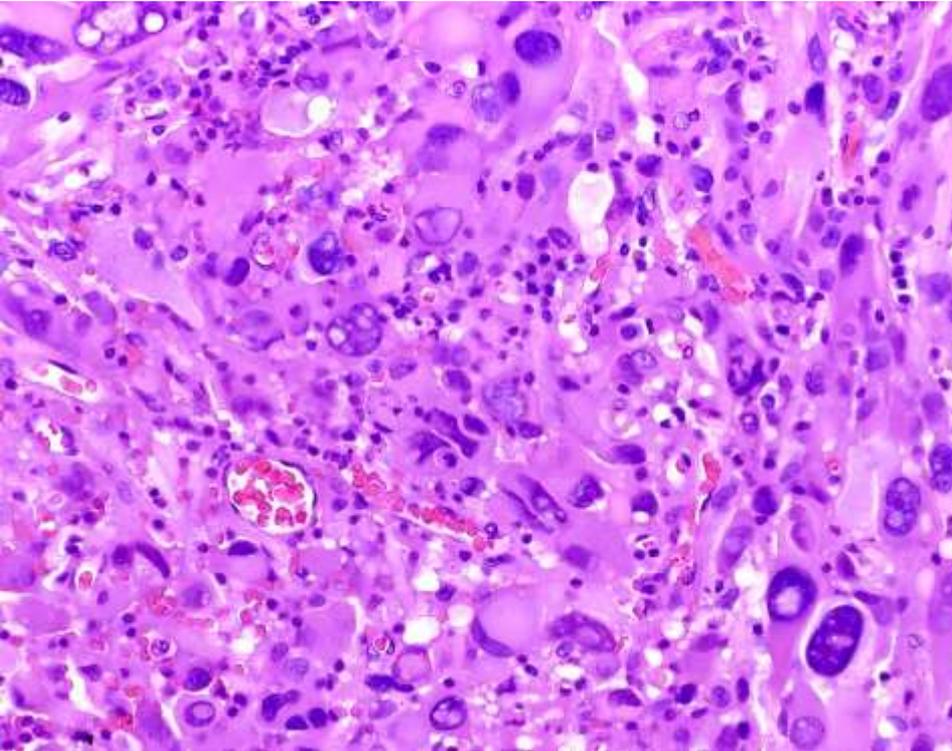
Glioblastoma: palisading necrosis

偽柵状壊死

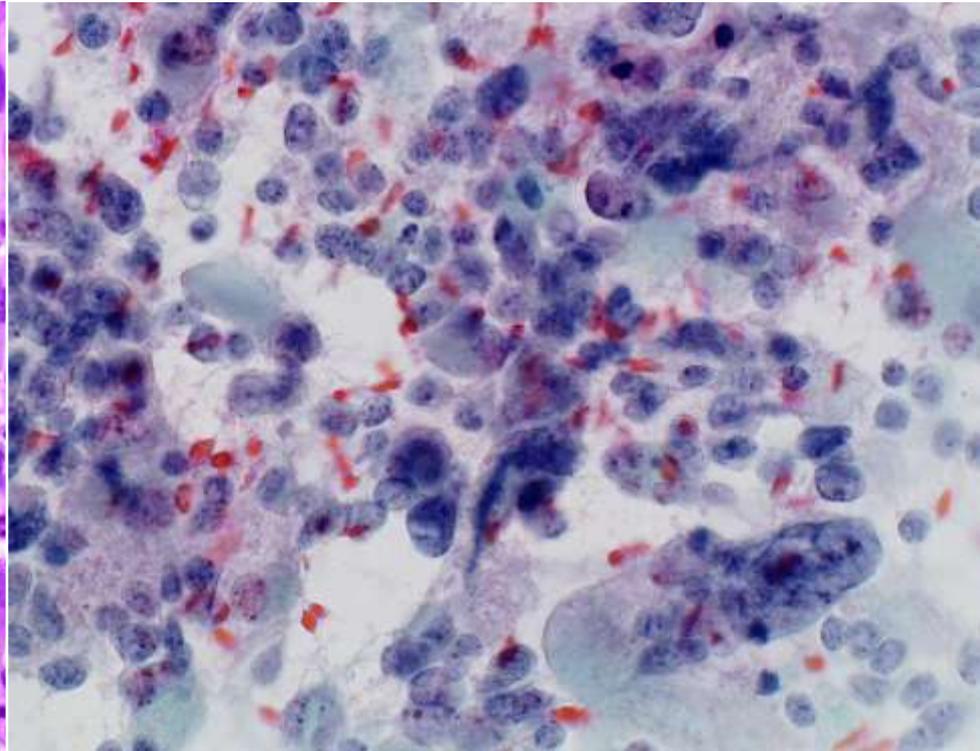


Glioblastoma: pleomorphism

巨細胞性膠芽腫

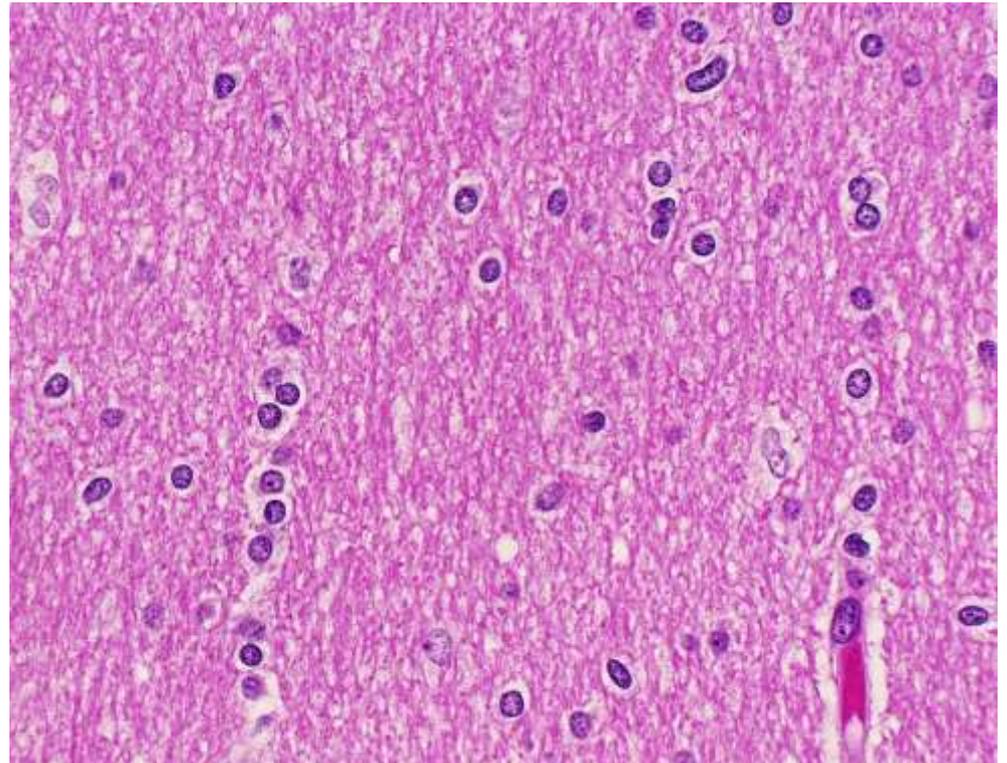
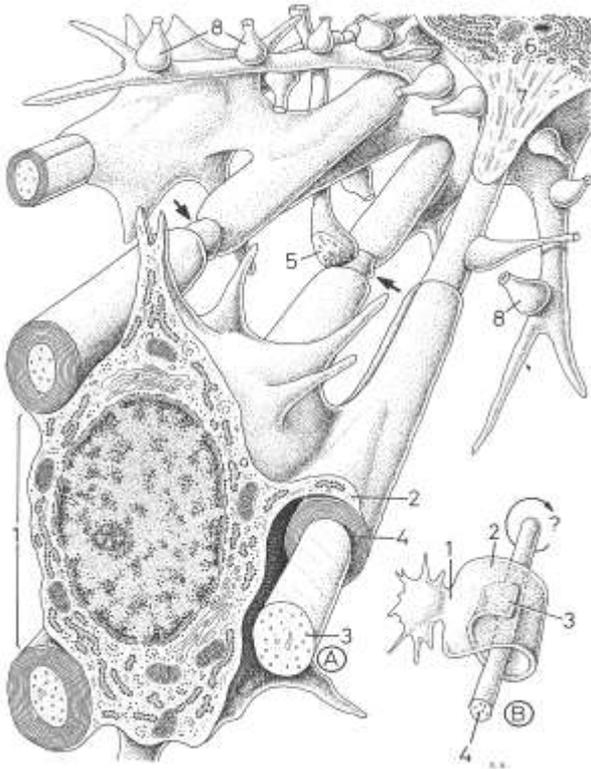


高度の多形性



乏突起膠腫 oligodendroglioma

乏突起膠細胞 oligodendroglia

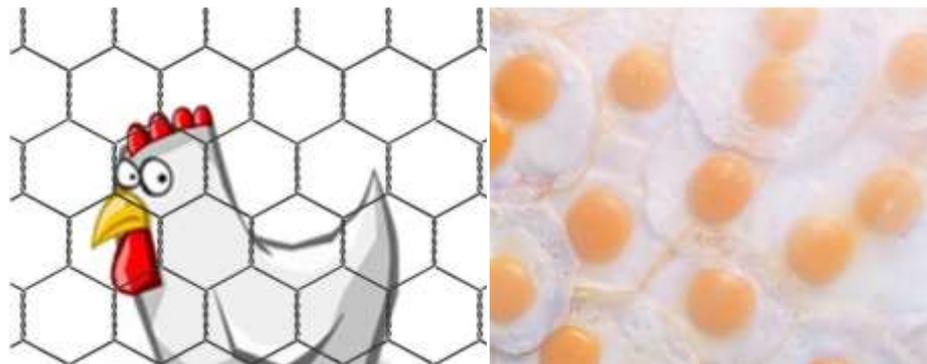


乏突起膠腫 oligodendroglioma

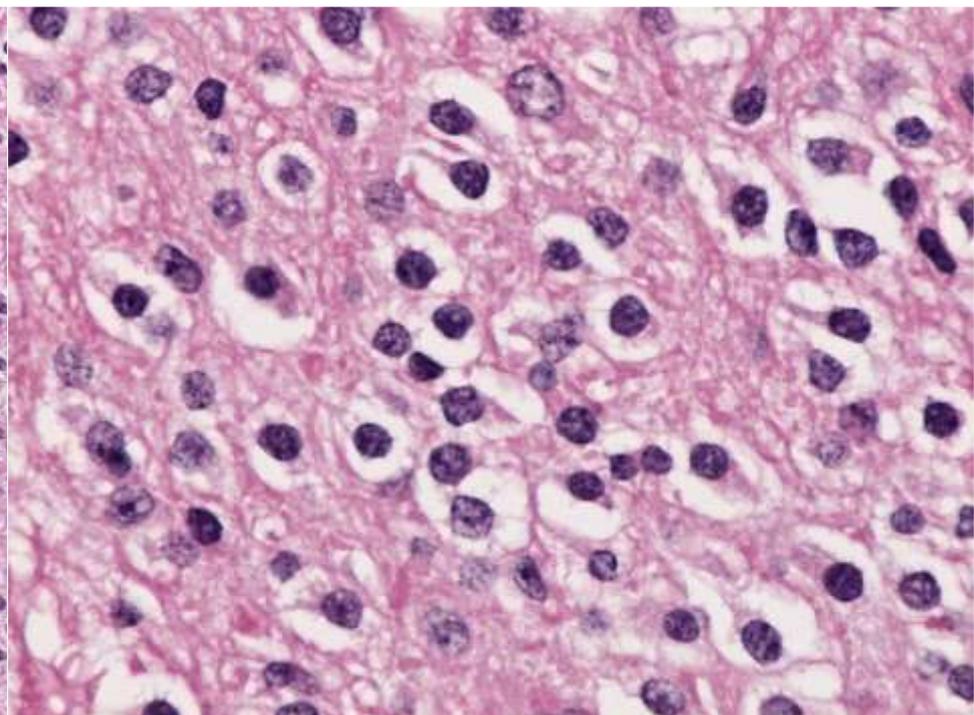
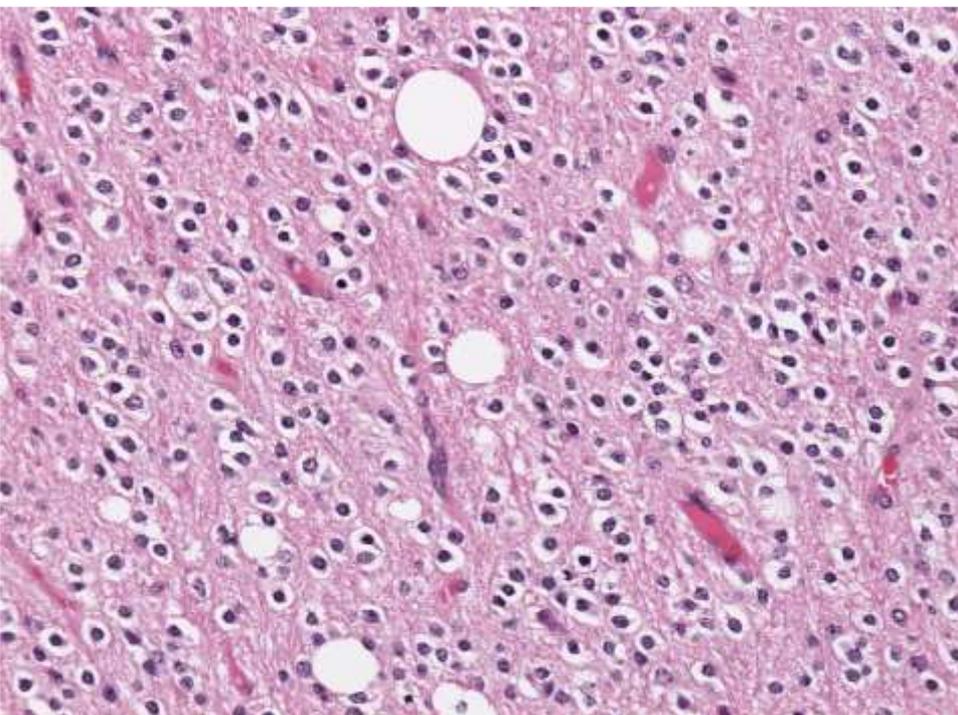
- 30-50歳代
- 大脳半球(前頭葉、側頭葉など)
- けいれん発作、頭痛など
- 比較的境界明瞭、石灰化
- 1p/19q loss
- IDH変異



乏突起膠腫

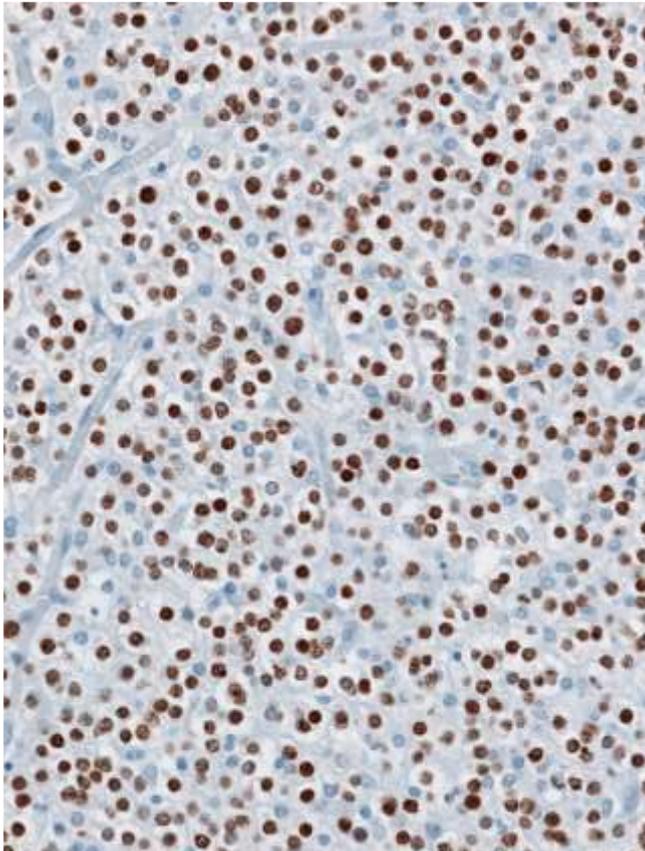


- 金網状血管 chicken wire vessels
- 目玉焼き様 fried egg appearance

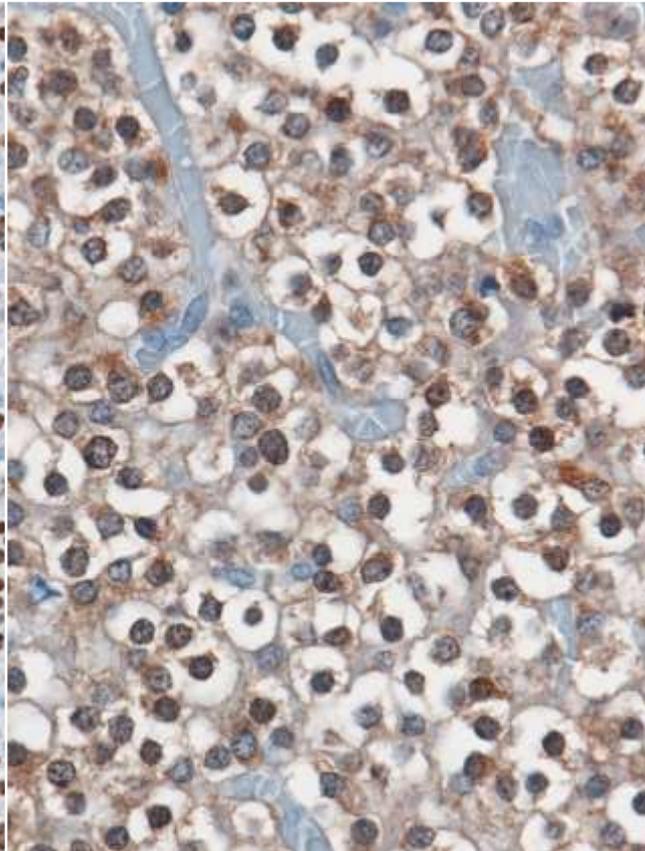


乏突起膠腫 oligodendroglioma

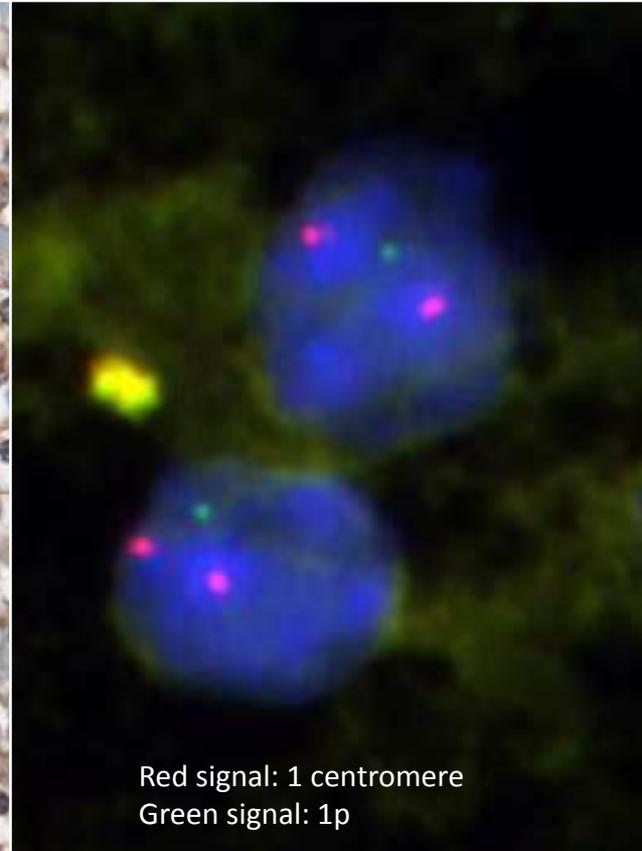
Olig2



變異IDH1

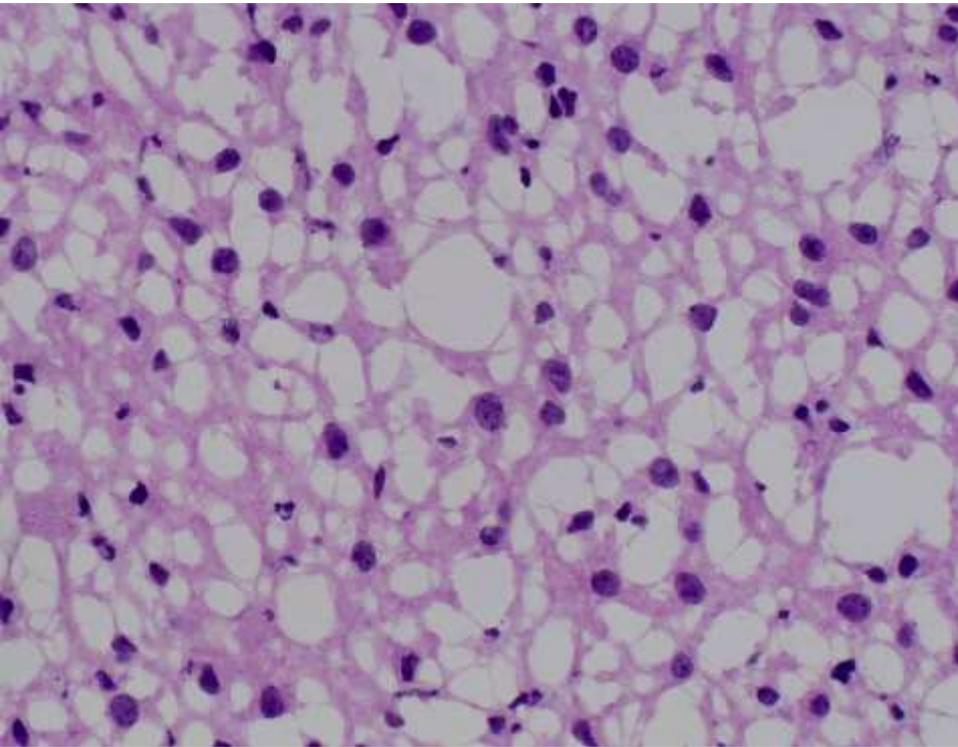


1p loss



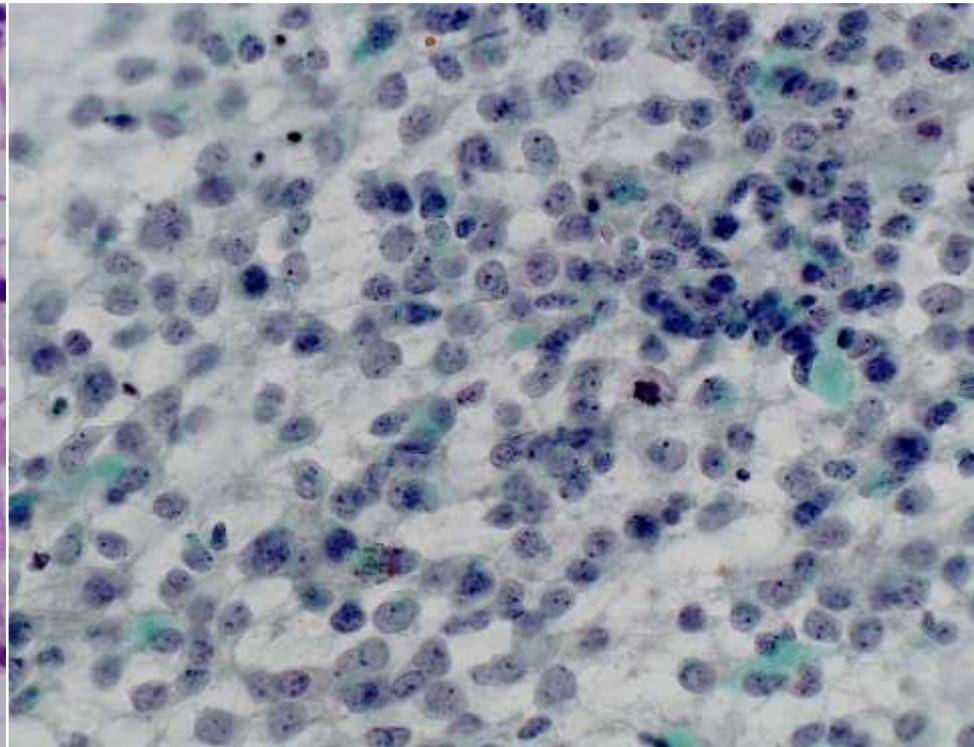
乏突起膠腫 oligodendroglioma

凍結切片



核周囲のハローはない

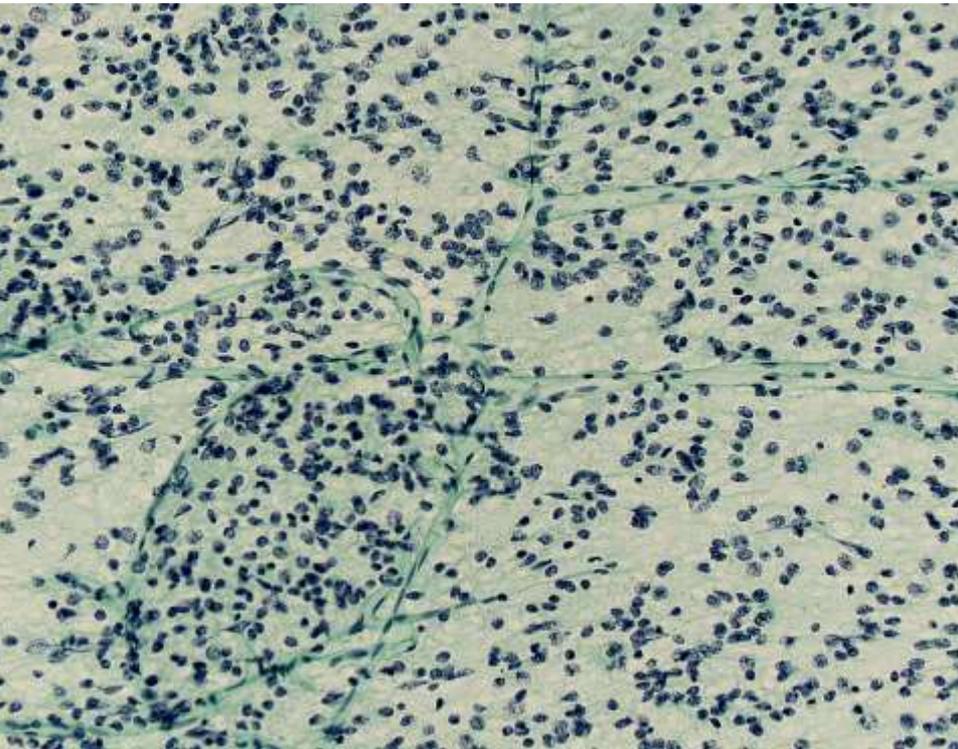
圧挫細胞診



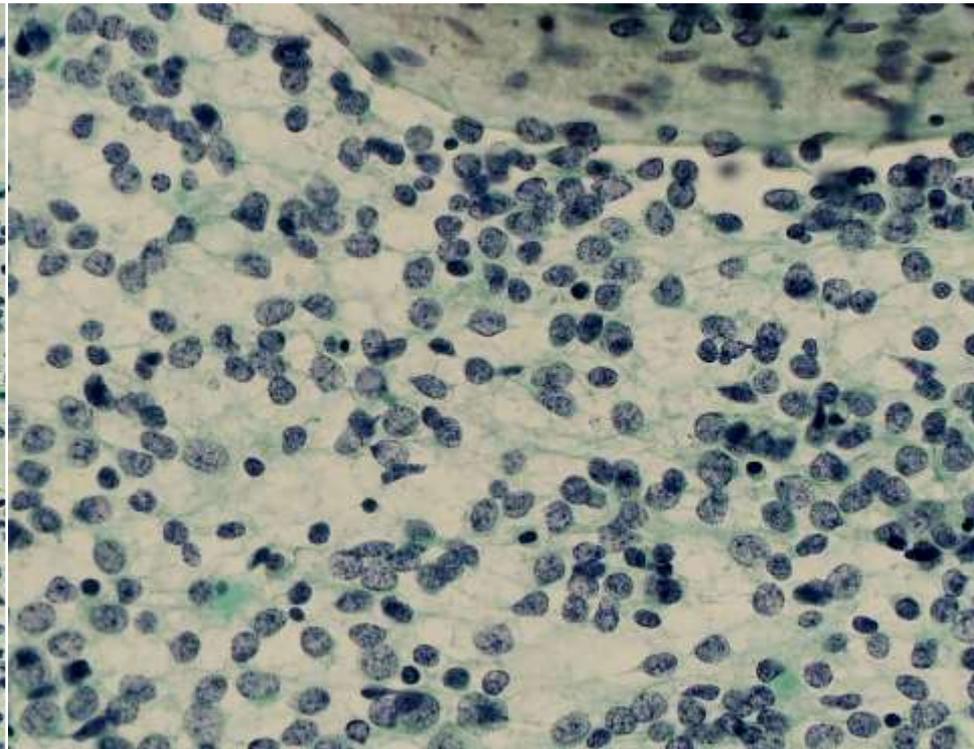
単調な円形核、線維状突起はない

乏突起膠腫 oligodendroglioma

金網状血管



単調な円形核、突起は乏しい



びまん性膠腫の新分類

2007 4th edition

- Astrocytic tumors
 - Pilocytic astrocytoma
 - PXA
 - Diffuse astrocytoma
 - Anaplastic astrocytoma
 - Glioblastoma
- Oligodendroglial tumors
- Oligoastrocytic tumors

2016 update of 4th +

- Diffuse astrocytic and oligodendroglial tumors
 - Diffuse astrocytoma
 - Anaplastic astrocytoma
 - Glioblastoma
 - Oligodendroglial tumors
- Other astrocytic tumors
 - Pilocytic astrocytoma
 - PXA
 - SEGA

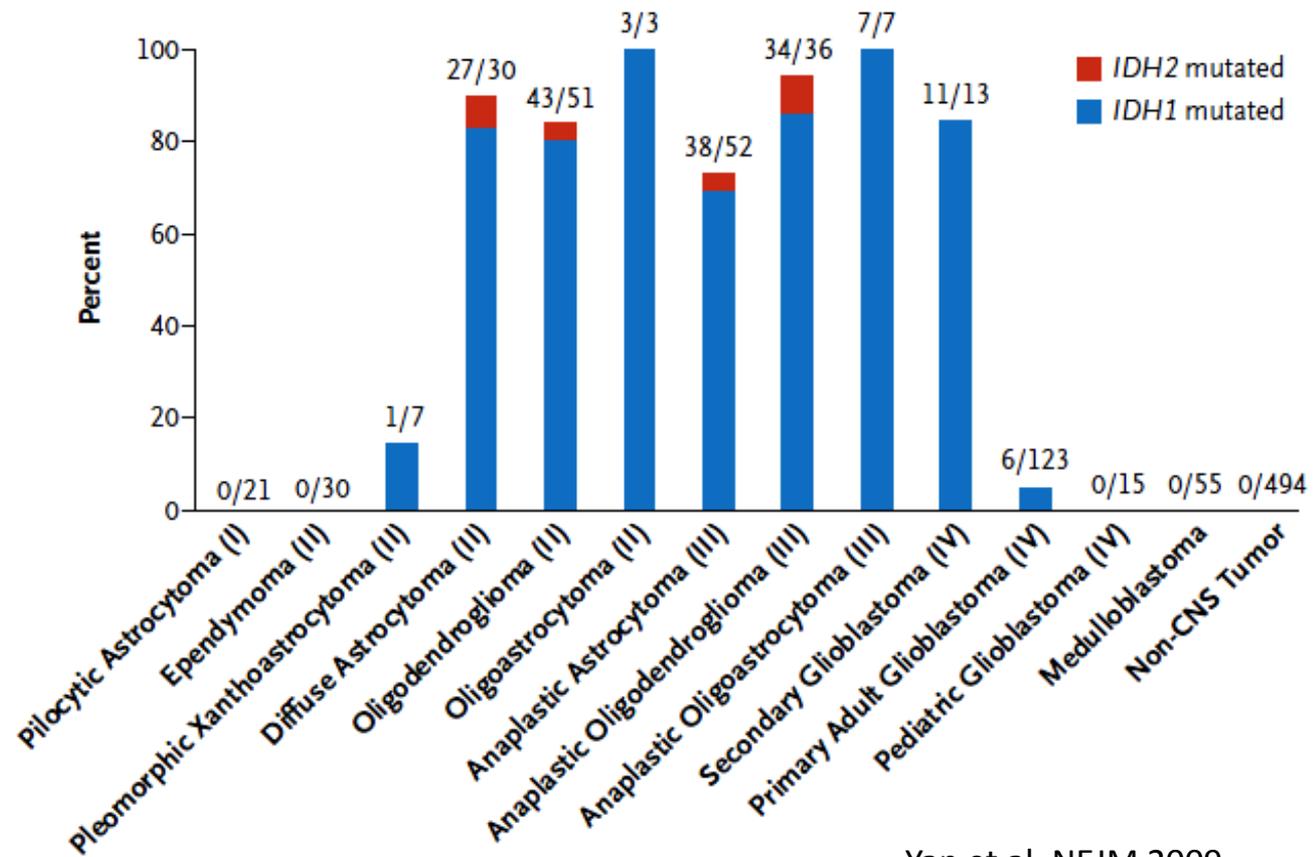
びまん性星細胞系および乏突起膠細胞系腫瘍

□ 両腫瘍型に共通してIDH変異が認められる

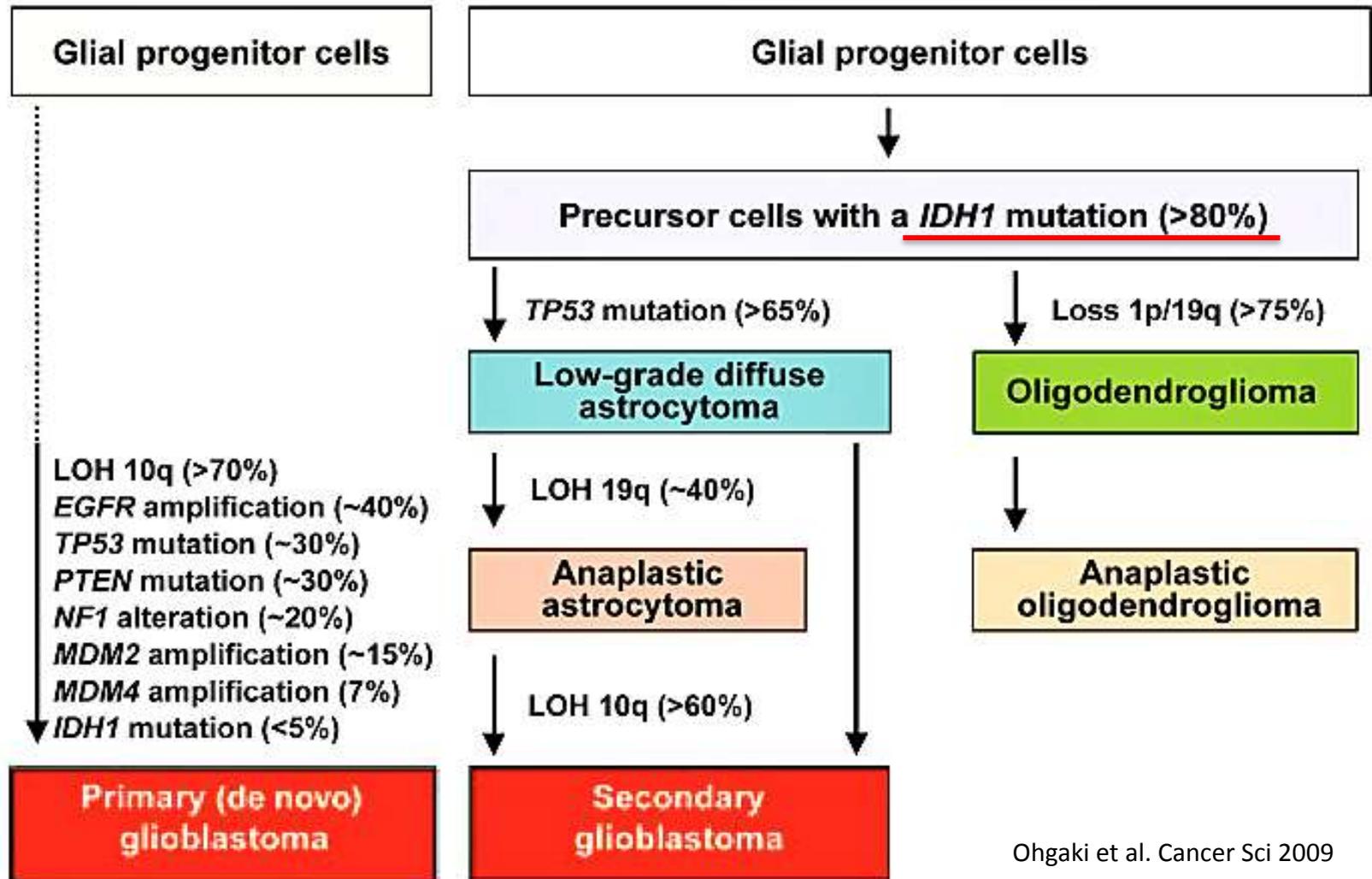
A Mutations

	R172G	GGG	N=2		
	R172M	ATG	N=3		
	R172K	AAG	N=4		
		↑			
IDH2	ATT	GGC	AGG	CAC	GCC
	I170	G171	R172	H173	A174
IDH1	I130	G131	R132	H133	A134
	ATA	GGT	CGT	CAT	GCT
		↓			
	R132H	CAT	N=142		
	R132C	TGT	N=7		
	R132L	CTT	N=7		
	R132S	AGT	N=4		
	R132G	GGT	N=1		

B Frequency of Mutations



びまん性膠腫の発生機構



2016WHO腦腫瘍分類

Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant

Diffuse astrocytoma, IDH-wildtype

Diffuse astrocytoma, NOS

Anaplastic astrocytoma, IDH-mutant

Anaplastic astrocytoma, IDH-wildtype

Anaplastic astrocytoma, NOS

Glioblastoma, IDH-wildtype

Glioblastoma, IDH-mutant

Glioblastoma, NOS

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

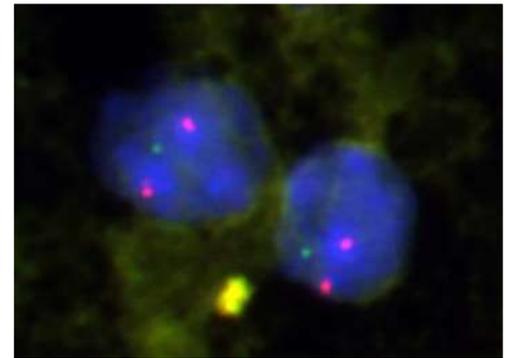
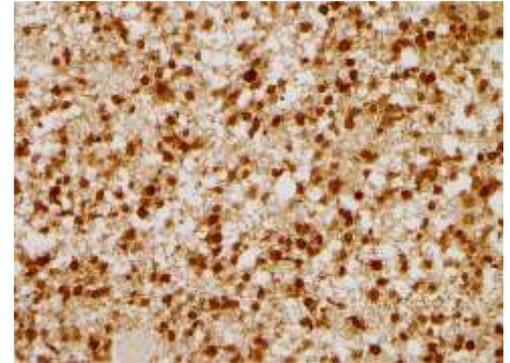
Oligodendroglioma, NOS

Anaplastic oligodendroglioma, IDH-mutant and 1p/19q codeleted

Anaplastic oligodendroglioma, NOS

今後のびまん性膠腫の診断

- IDH変異の確認
 - IDH1^{R132H}免疫染色
 - シークエンス
 - その他(HRMなど)
- 1p/19q欠失の確認
 - FISH
 - LOH解析(Microsatellite)
 - Array CGH
 - その他

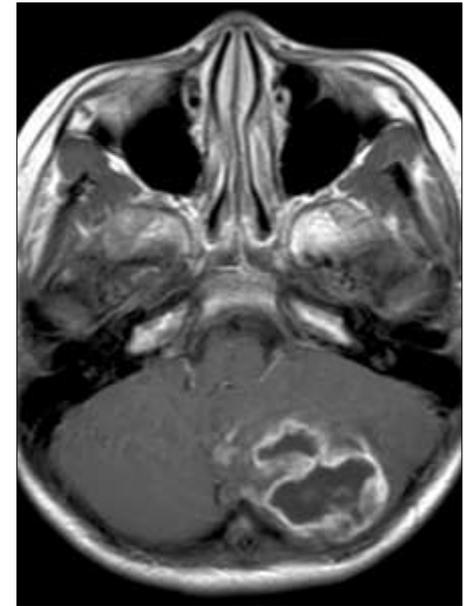


その他の星細胞系腫瘍

- Pilocytic astrocytoma
 - Pilomyxoid astrocytoma
- Subependymal giant cell astrocytoma
- Pleomorphic xanthoastrocytoma
- Anaplastic pleomorphic xanthoastrocytoma

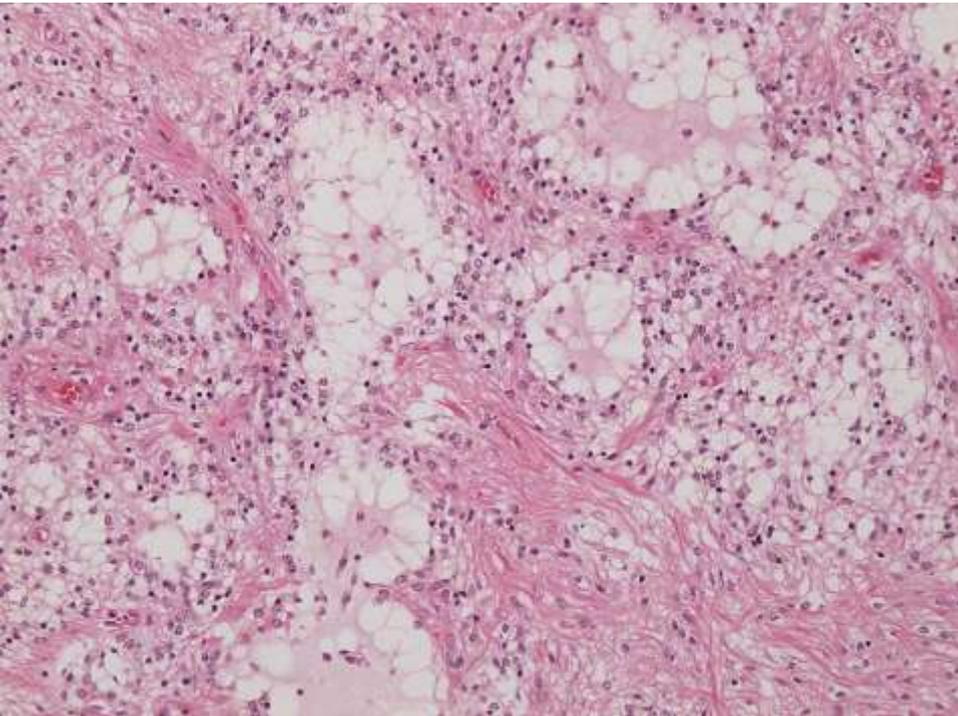
毛様細胞性星細胞腫 pilocytic astrocytoma

- 境界明瞭な良性星細胞性腫瘍
- MAPK pathwayの遺伝子異常 (*BRAF*, etc.)
- 小児、若年成人
- 小脳、視神経、視床下部など
- Grade I

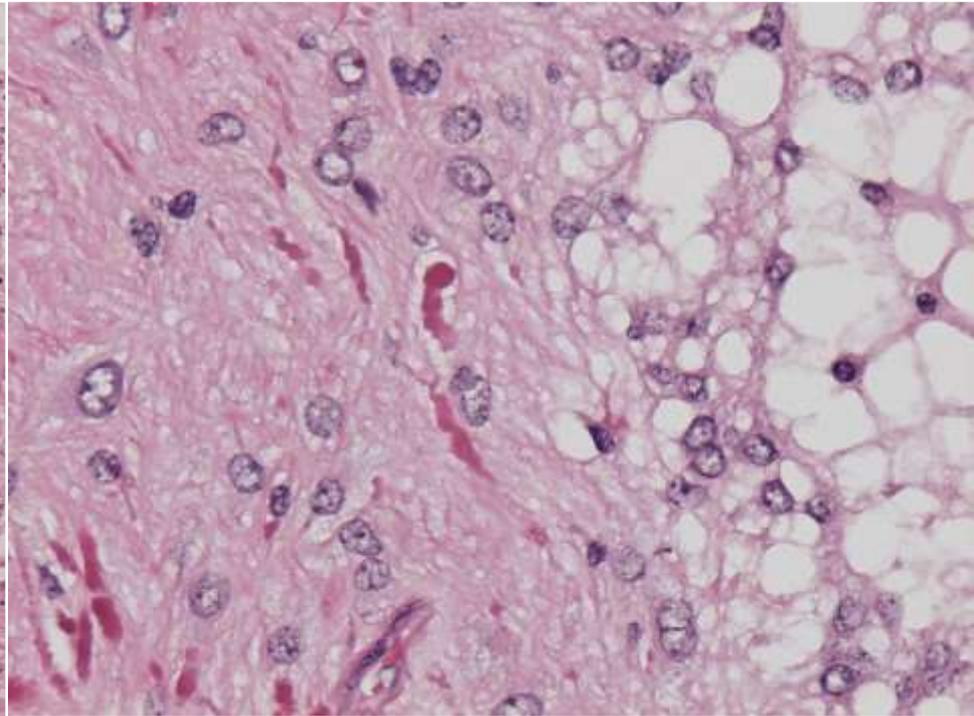


毛樣細胞性星細胞腫 pilocytic astrocytoma

Biphasic pattern

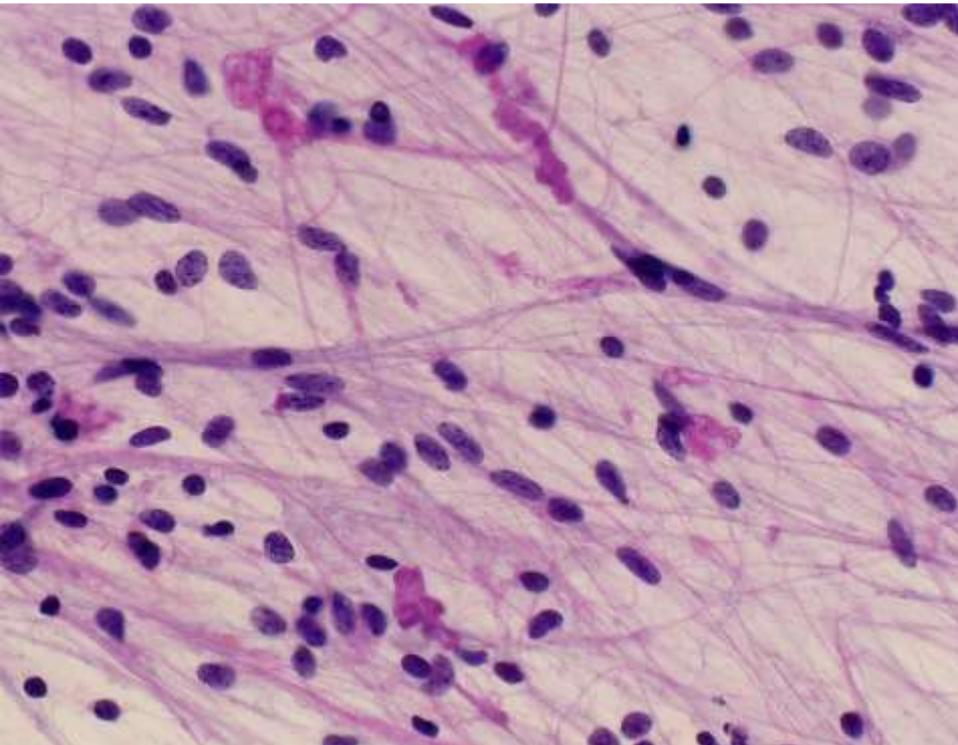


Rosenthal fibers

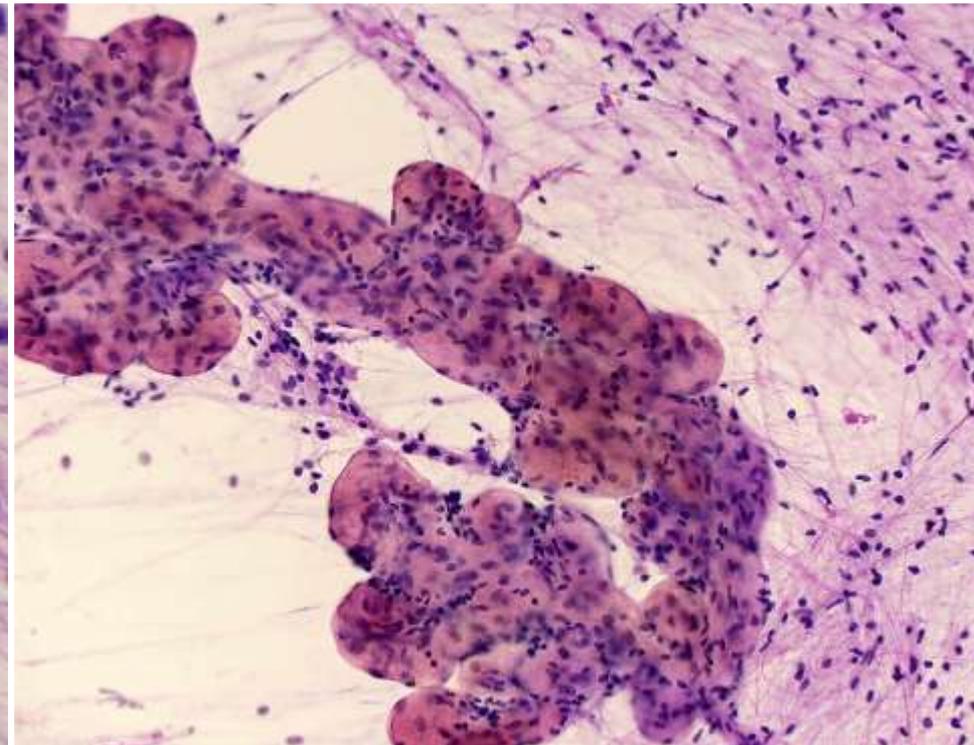


毛樣細胞性星細胞腫 pilocytic astrocytoma

毛髮樣細胞質突起、Rosenthal線維

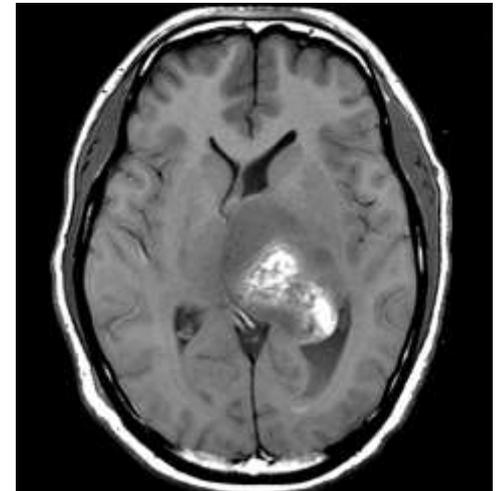


糸球體樣血管網



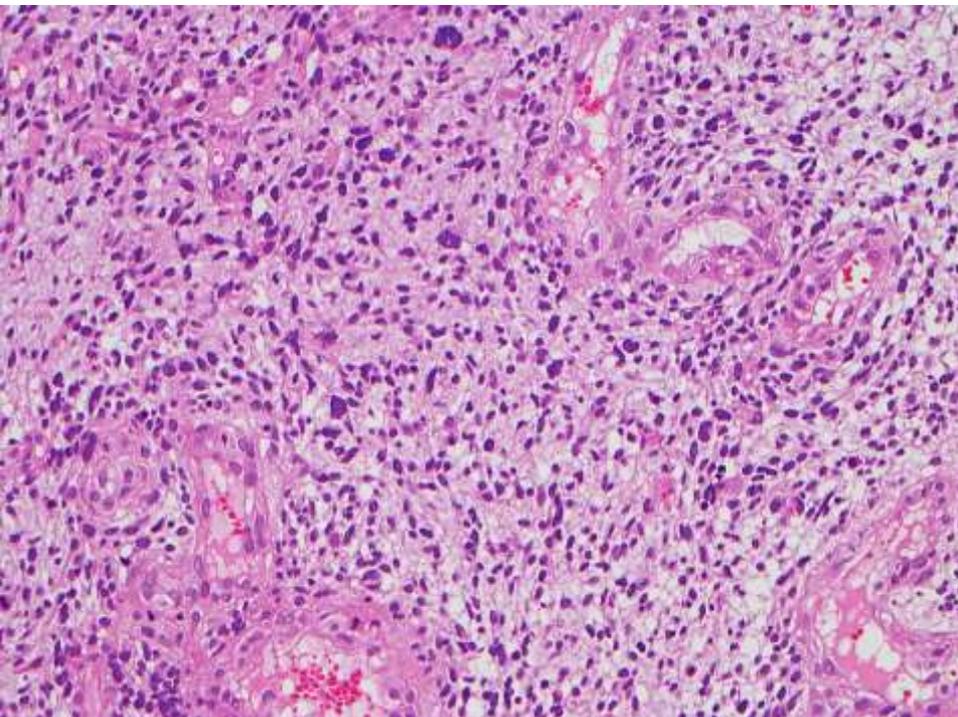
Diffuse midline glioma, H3 K27M-mutant

- 正中部に発生する高悪性度の浸潤性星細胞系腫瘍で、*H3F3A*あるいは*HIST1H3B/C* K27M変異を有している
- 主に小児；正中部（橋、視床、脊髄など）に発生
- *H3F3A* K27M > *HIST1H3B/C* K27M
- WHO grade IV、予後不良

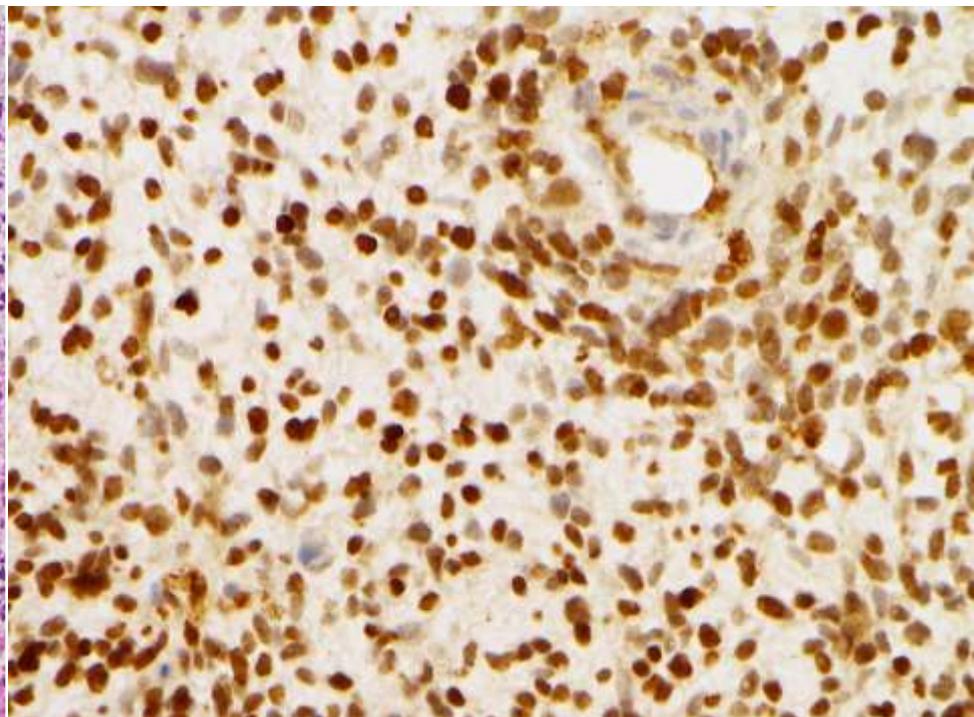


Diffuse midline glioma, H3 K27M-mutant

Glioblastoma

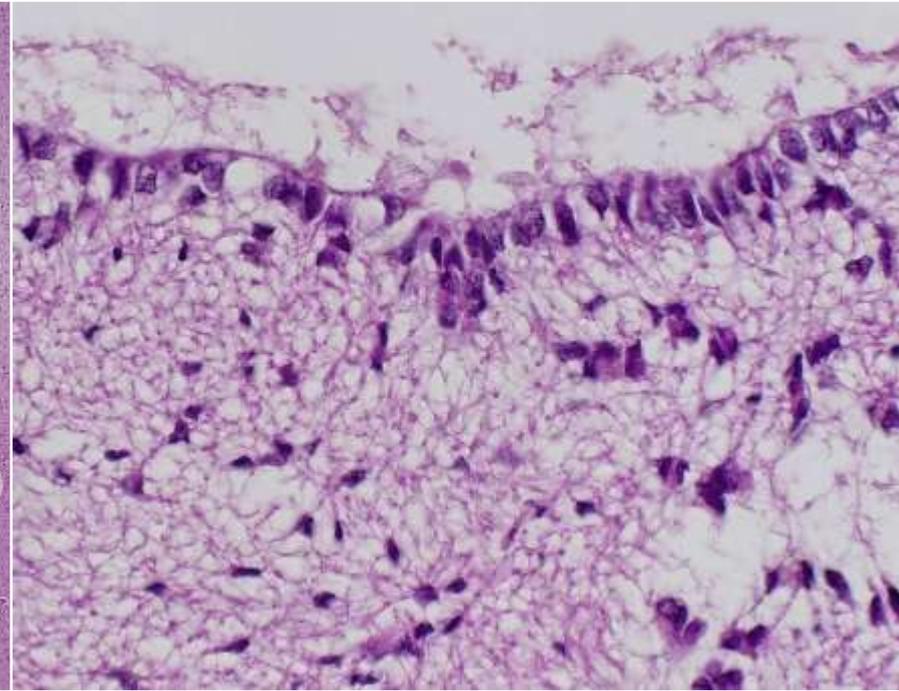
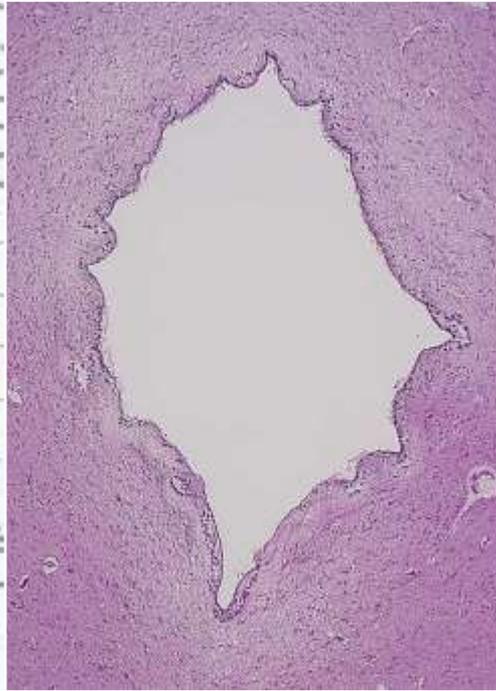
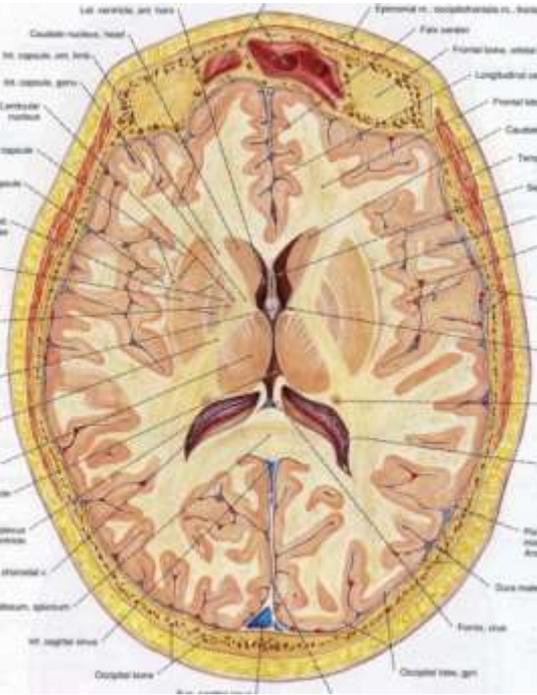


H3 K27M



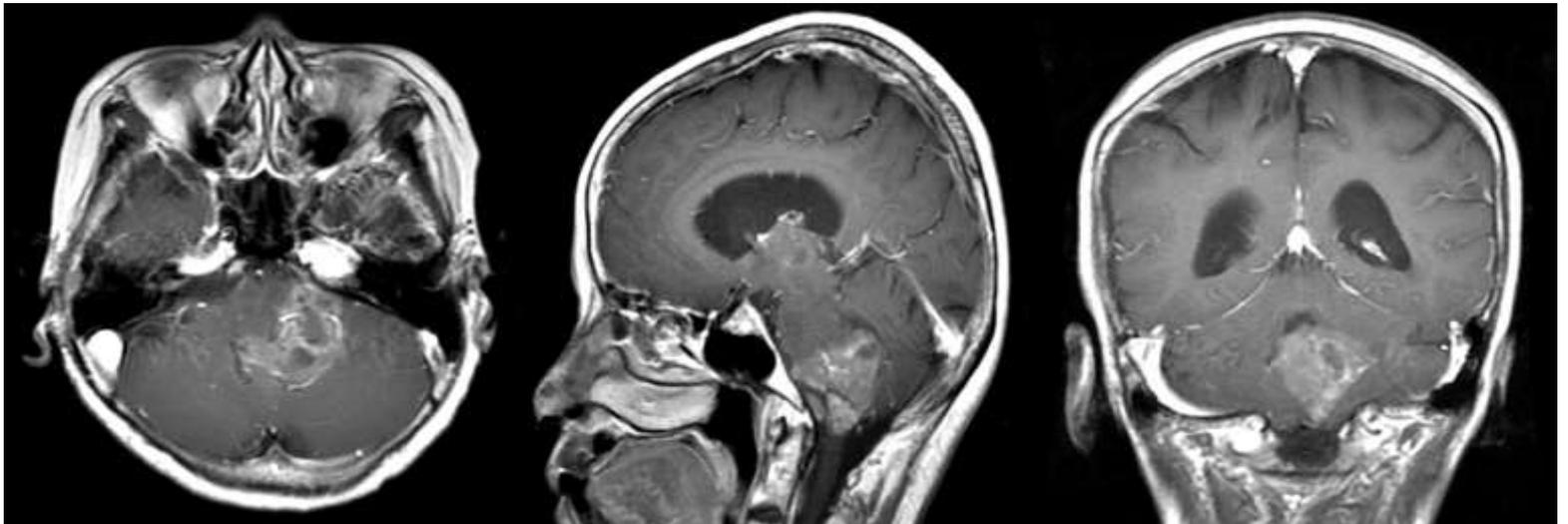
上衣腫 ependymoma

腦室上衣細胞



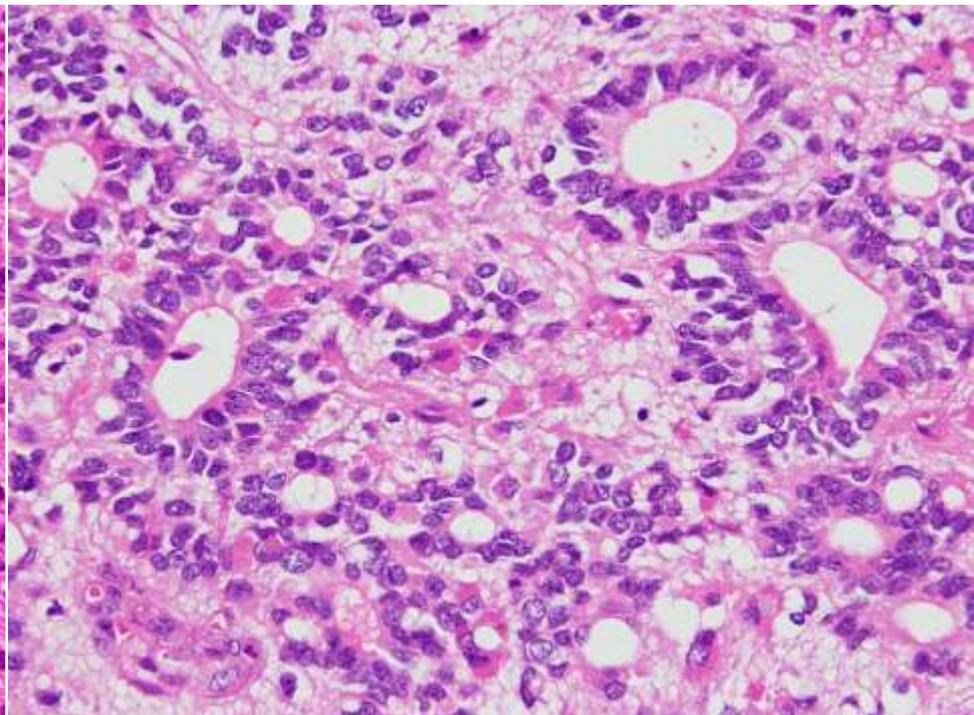
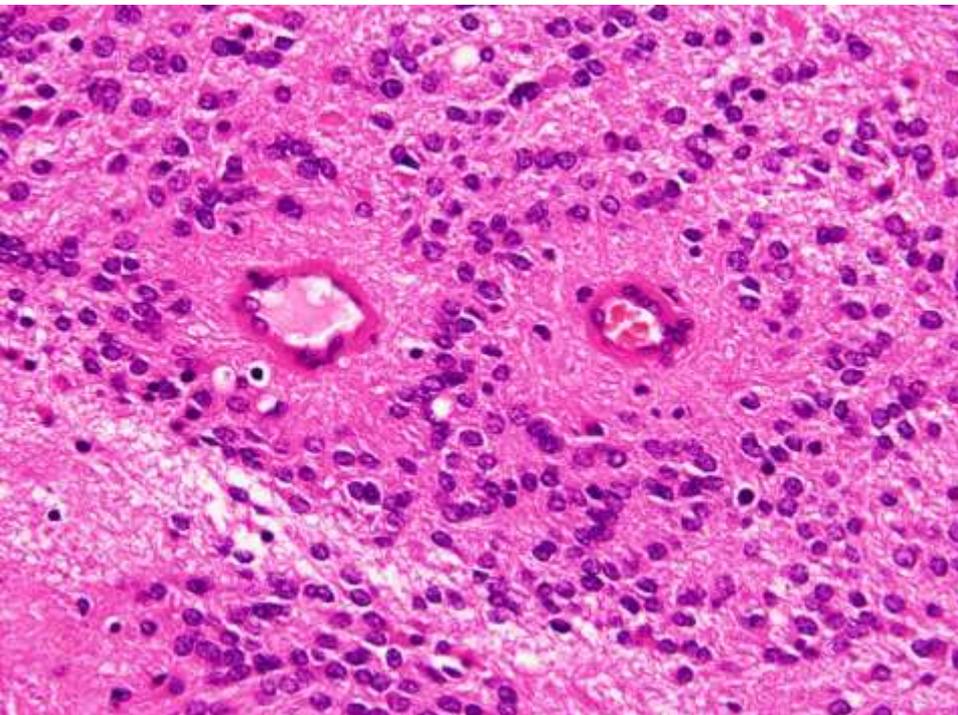
上衣腫 ependymoma

- 上衣細胞への分化を示す限局性腫瘍
- 後頭蓋窩 (60%, 小児), テント上 (30%), 脊髄 (10%成人)
- 境界明瞭、増強効果、嚢胞、出血、石灰化



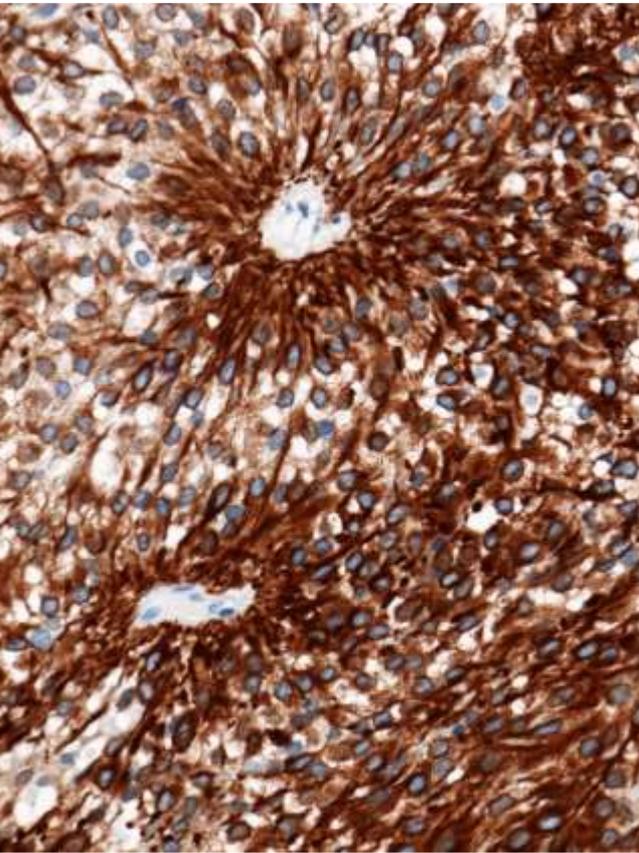
上衣腫 ependymoma

- 血管周囲偽ロゼット(無核帯)、上衣性ロゼット

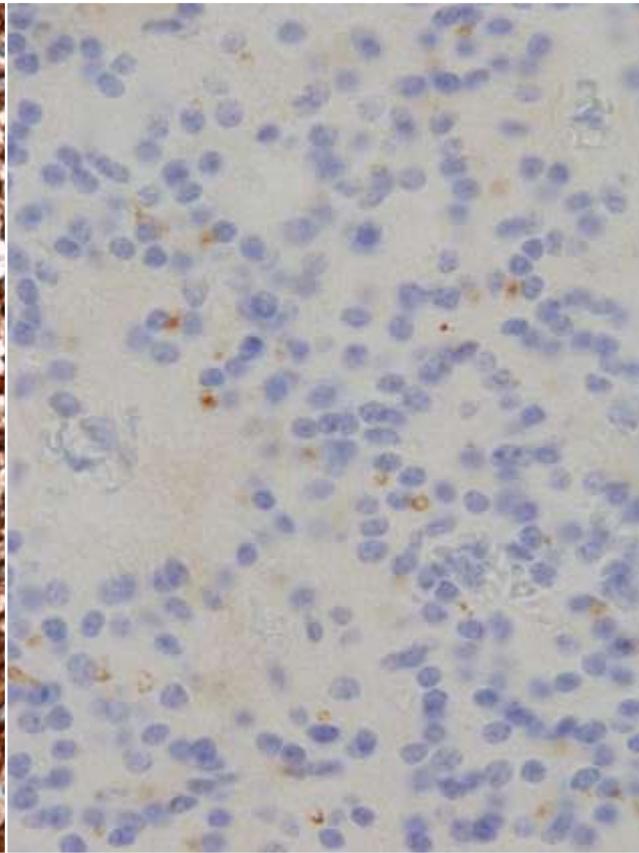


上衣腫 ependymoma

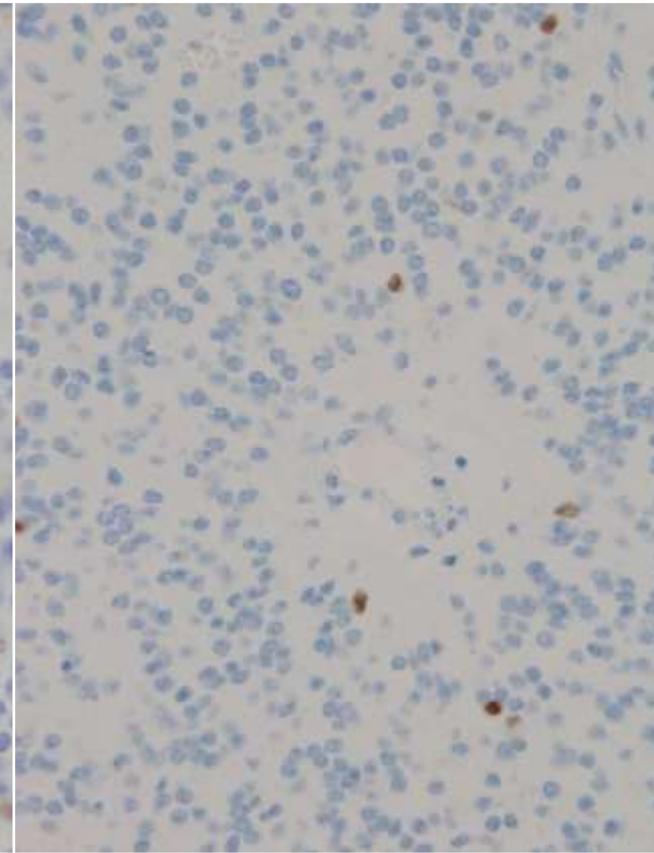
GFAP



EMA

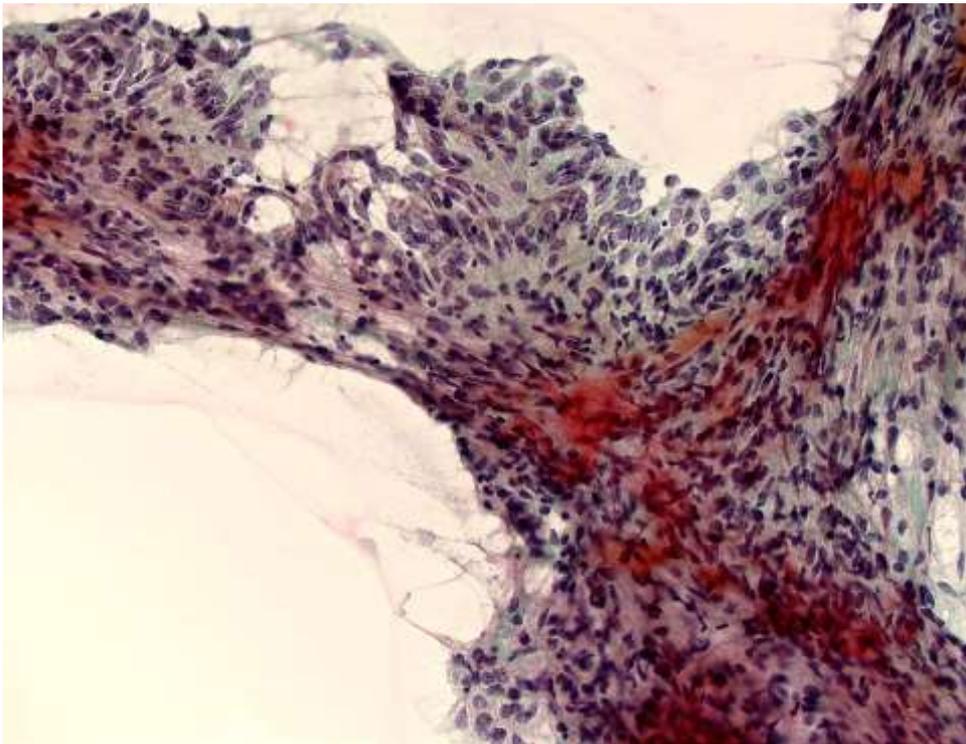


Olig2

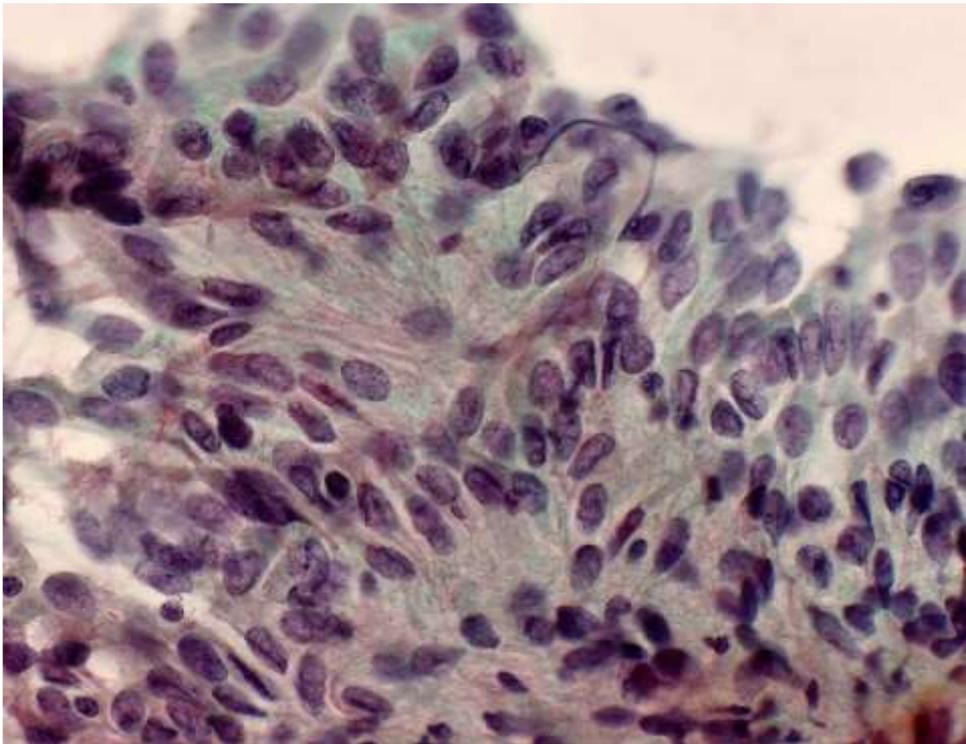


上衣腫 ependymoma

結合性



細胞質突起、ロゼット様配列



粘液乳頭状上衣腫

Myxopapillary ependymoma

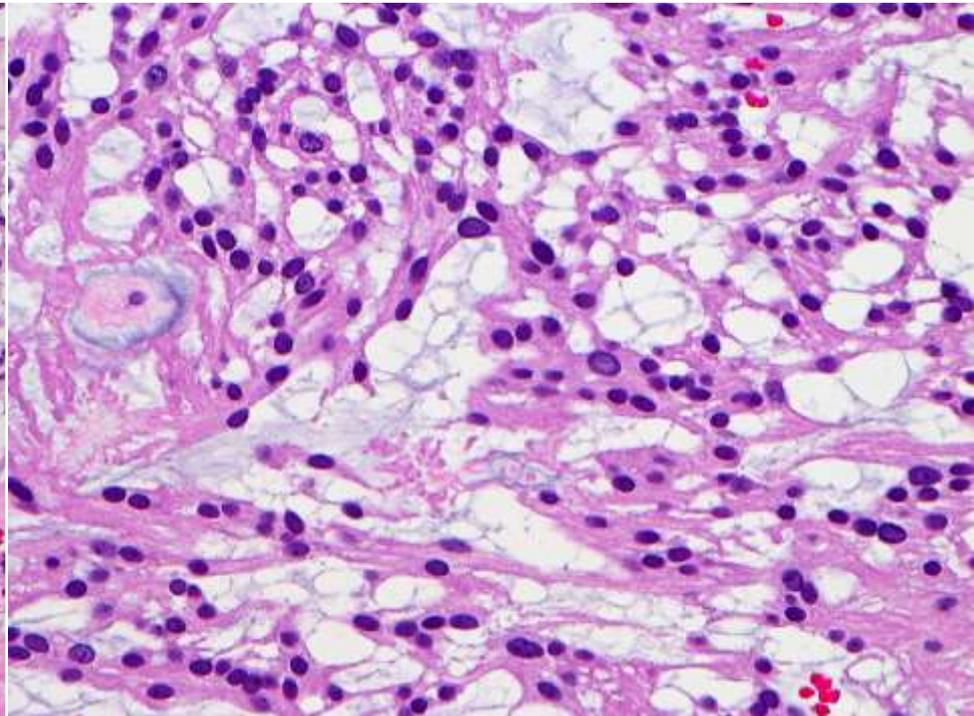
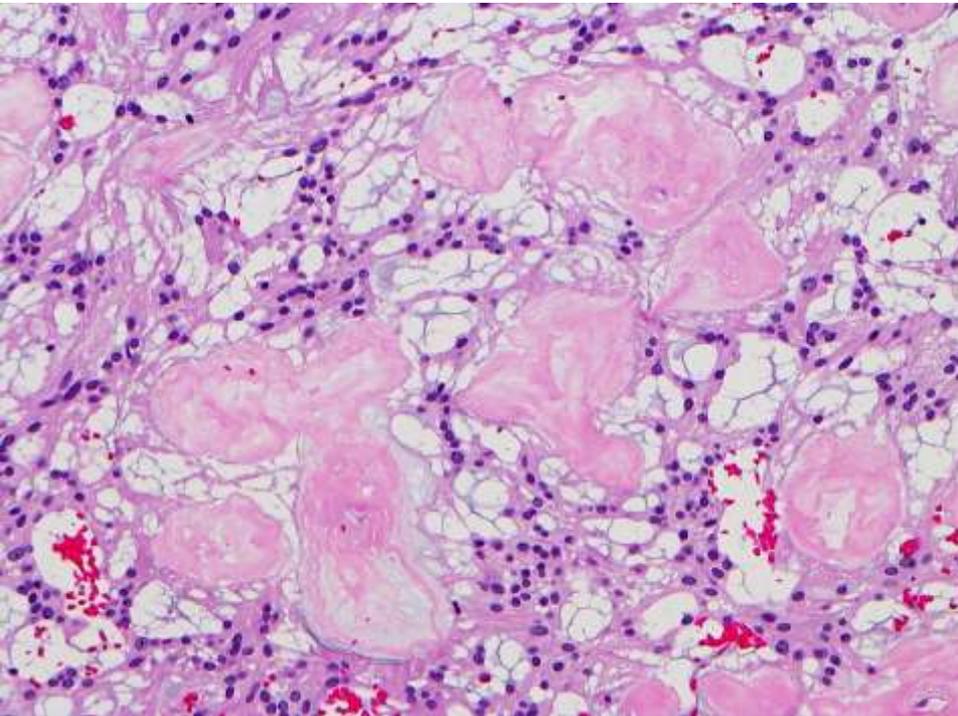
- 脊髓馬尾、円錐部に発生する上衣性腫瘍
- 境界明瞭、増強効果
- 若年成人
- Grade I



粘液乳頭狀上衣腫

Myxopapillary ependymoma

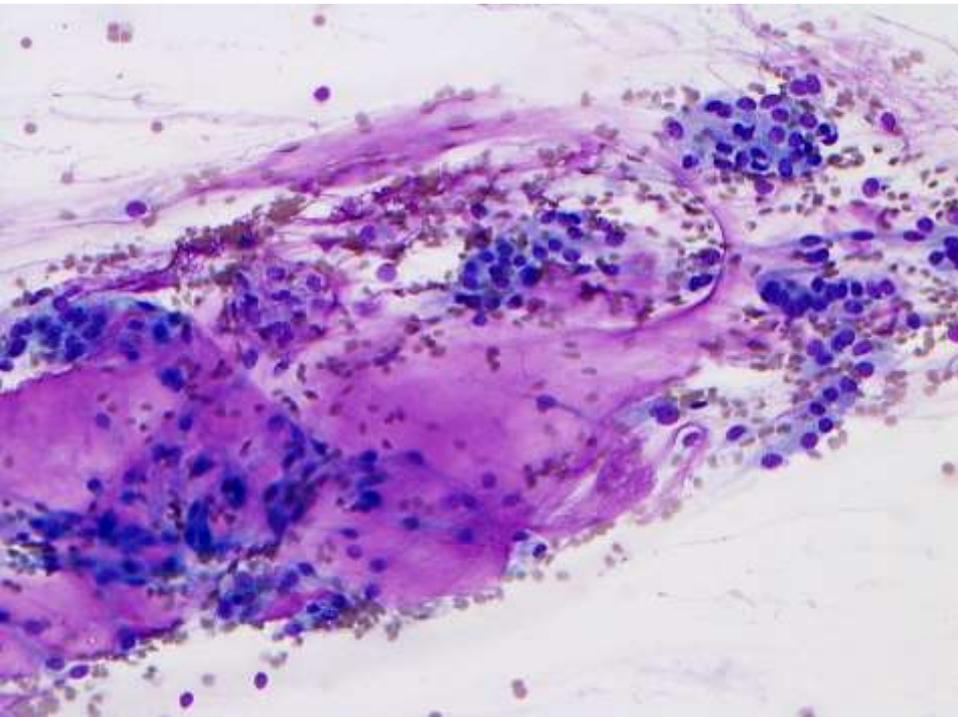
線維粘液性基質



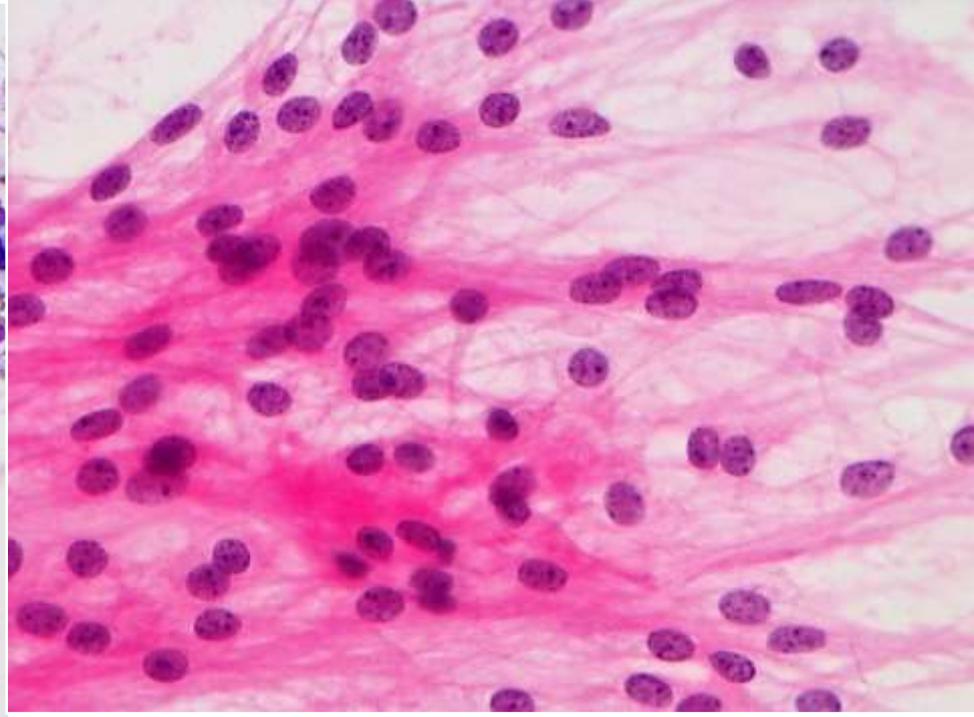
粘液乳頭狀上衣腫

Myxopapillary ependymoma

粘液狀基質、細胞集塊



線維狀突起



上衣系腫瘍 ependymal tumors

2007 4th edition

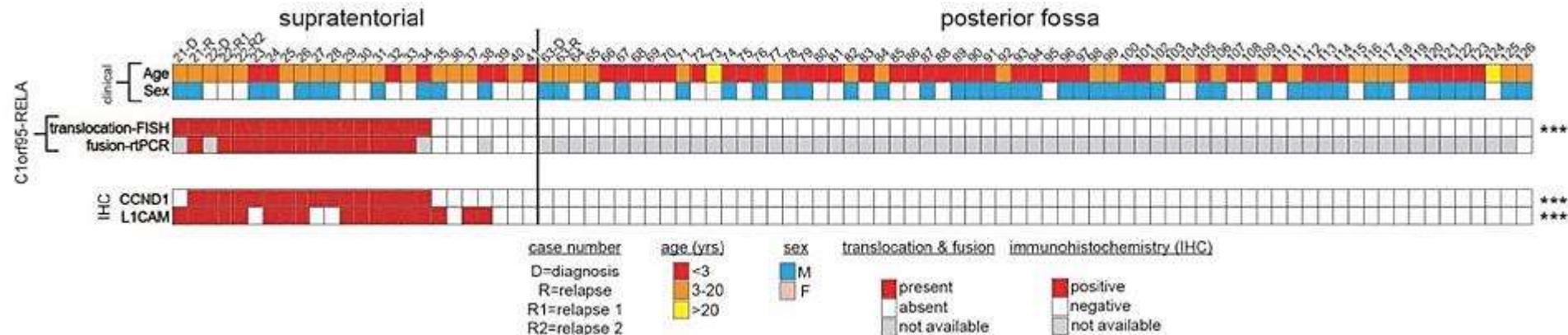
- Subependymoma
- Myxopapillary ependymoma
- Ependymoma
 - Cellular
 - Papillary
 - Clear cell
 - Tanycytic
- Anaplastic ependymoma

2016 update of 4th +

- Subependymoma
- Myxopapillary ependymoma
- Ependymoma
 - Papillary
 - Clear cell
 - Tanycytic
- Ependymoma, RELA fusion–positive
- Anaplastic ependymoma

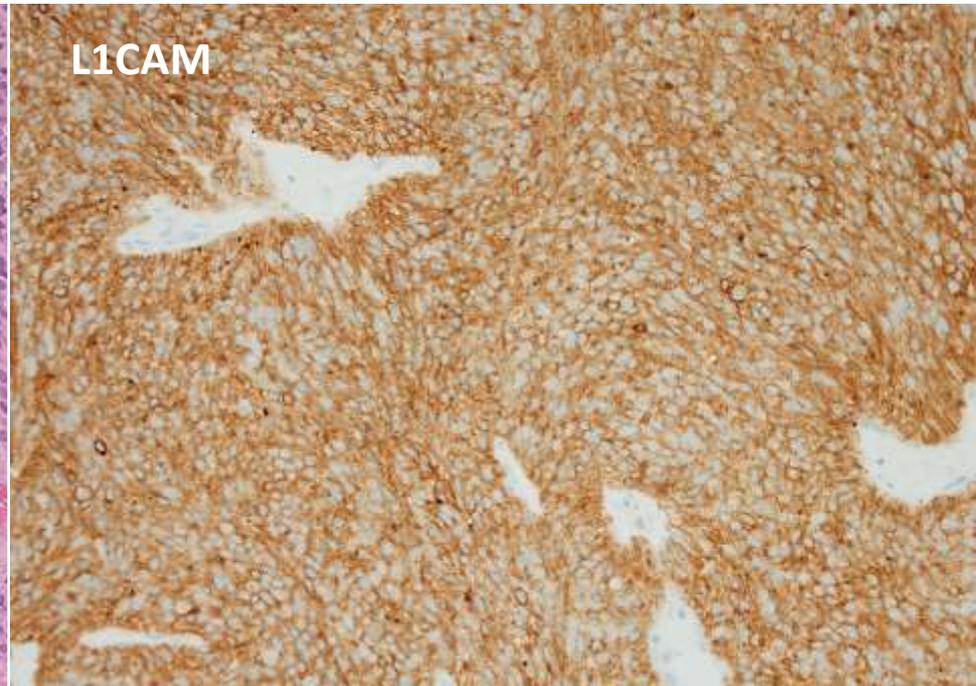
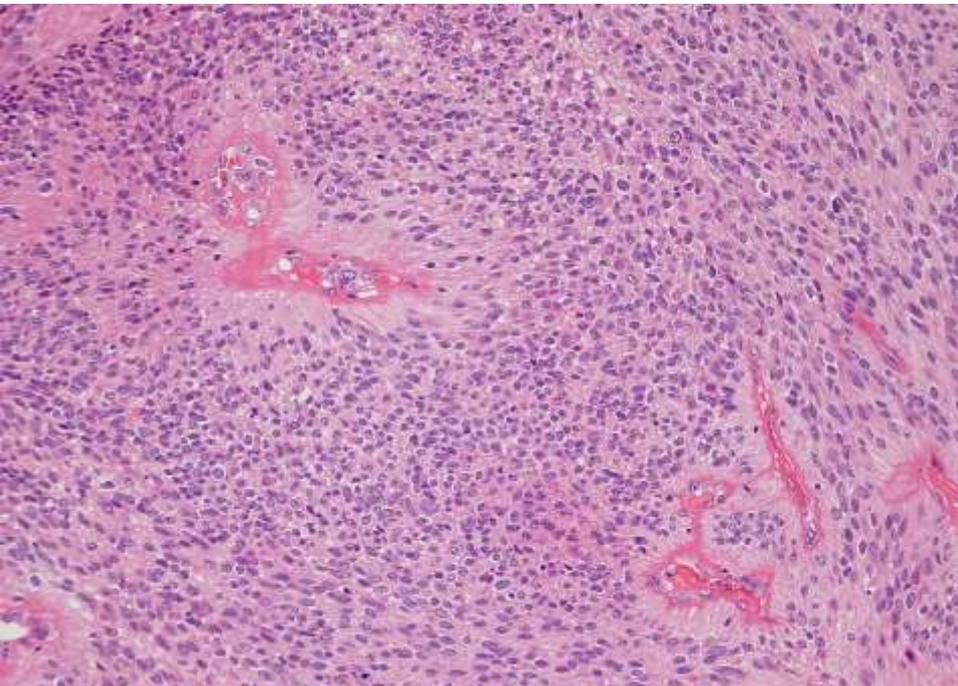
C11orf95-RELA fusions drive oncogenic NF- κ B signalling in ependymoma

Matthew Parker^{1,2*}, Kumarasamypet M. Mohankumar^{3*}, Chandanamali Punchihewa^{4*}, Ricardo Weinlich^{5*}, James D. Dalton^{1,4}, Yongjin Li^{1,2}, Ryan Lee⁴, Ruth G. Tatevossian^{1,4}, Timothy N. Phoenix³, Radhika Thiruvankatam³, Elsie White³, Bo Tang^{1,4}, Wilda Orisme^{1,4}, Kirti Gupta⁴, Michael Rusch², Xiang Chen², Yuxin Li^{2,6}, Panduka Nagahawhatte², Erin Hedlund², David Finkelstein², Gang Wu², Sheila Shurtleff⁴, John Easton^{1,4}, Kristy Boggs¹, Donald Yergeau¹, Bhavin Vadodaria¹, Heather L. Mulder¹, Jared Becksfort², Pankaj Gupta², Robert Huether⁶, Jing Ma¹, Guangchun Song¹, Amar Gajjar^{1,7}, Thomas Merchant⁸, Frederick Boop⁹, Amy A. Smith¹⁰, Li Ding^{1,11,12}, Charles Lu^{1,11}, Kerri Ochoa^{1,11,12}, David Zhao^{1,2}, Robert S. Fulton^{1,11}, Lucinda L. Fulton^{1,11,12}, Elaine R. Mardis^{1,11,12,13}, Richard K. Wilson^{1,11,12,13}, James R. Downing^{1,4}, Douglas R. Green⁵, Jinghui Zhang^{1,2}, David W. Ellison^{1,4} & Richard J. Gilbertson^{1,3}



Ependymoma, *RELA* fusion-positive

- 小児 supratentorial ependymoma の70%を占める
- 免疫染色: L1CAM の発現が相関
- *C11orf95-RELA* (chromothripsis 染色体破碎)
- 予後不良



胎兒性腫瘍 embryonal tumors

2007 WHO

- Medulloblastoma
- CNS PNET
- Atypical teratoid/rhabdoid tumor

2016 WHO

- Medulloblastoma, genetically defined
- Medulloblastoma, histologically defined
- Embryonal tumor with multilayered rosettes
- CNS embryonal tumor, NOS
- Atypical teratoid/rhabdoid tumor

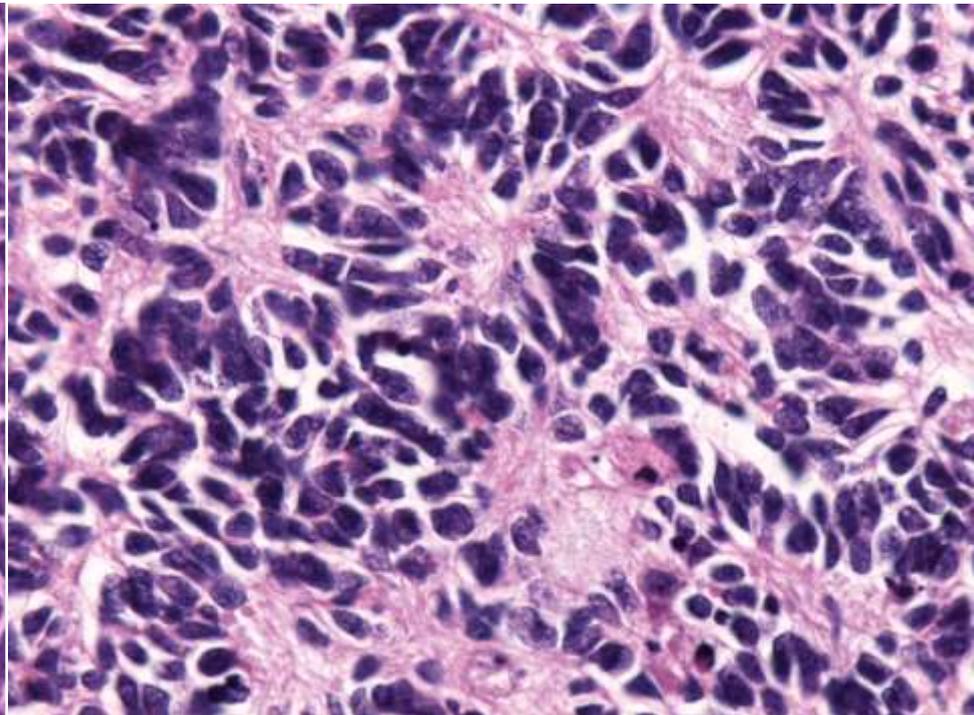
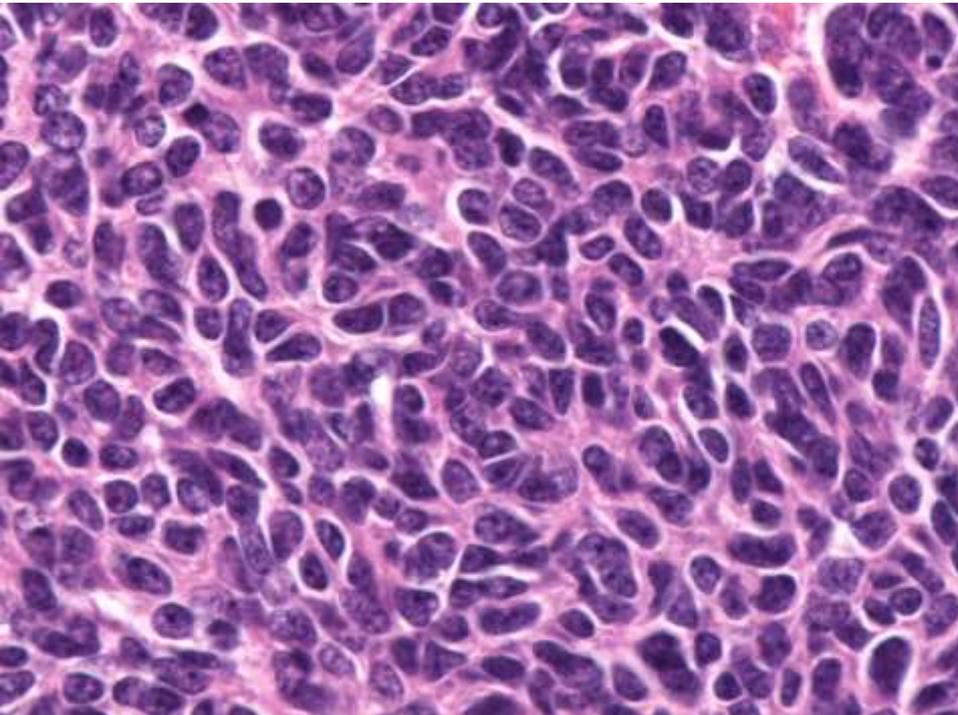
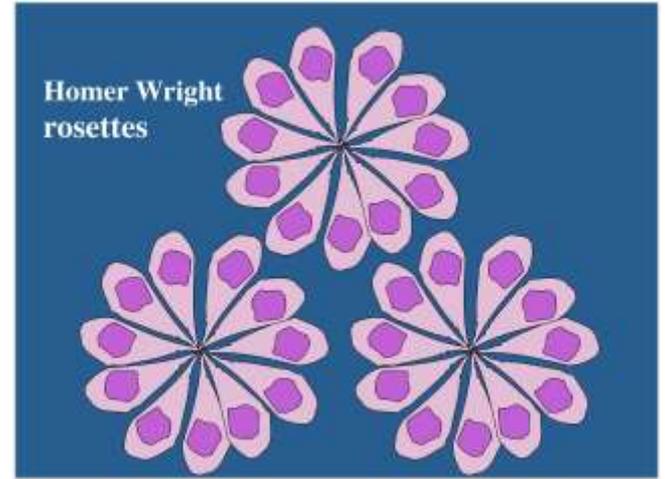
髓芽腫 medulloblastoma

- 小児の小脳に発生する高悪性度の未熟な小円形細胞性腫瘍
- 小児(平均9歳)
- 小脳(虫部>半球)、脳幹背部
- しばしば播種する
- Grade IV



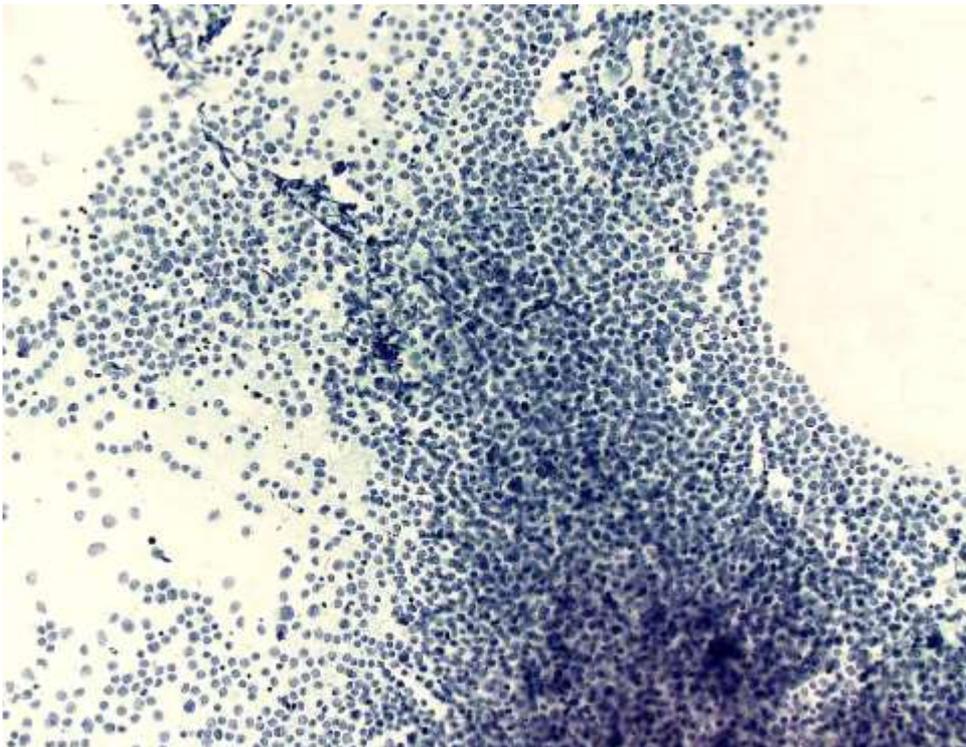
髓芽腫

- Homer Wright型ロゼット

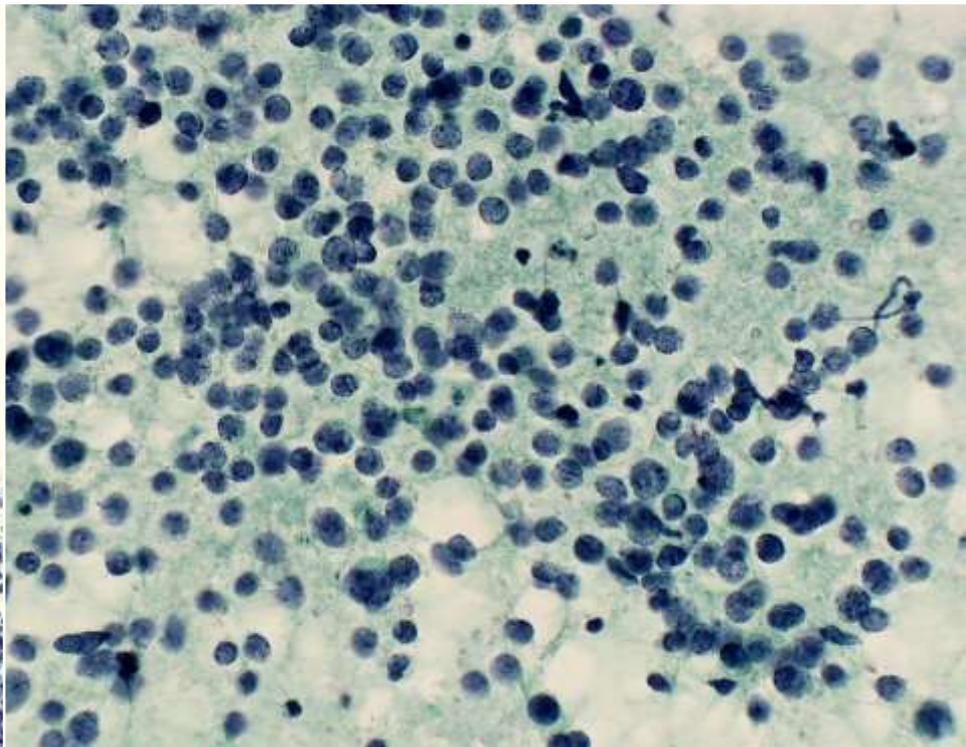


髓芽腫 medulloblastoma

富細胞性腫瘍



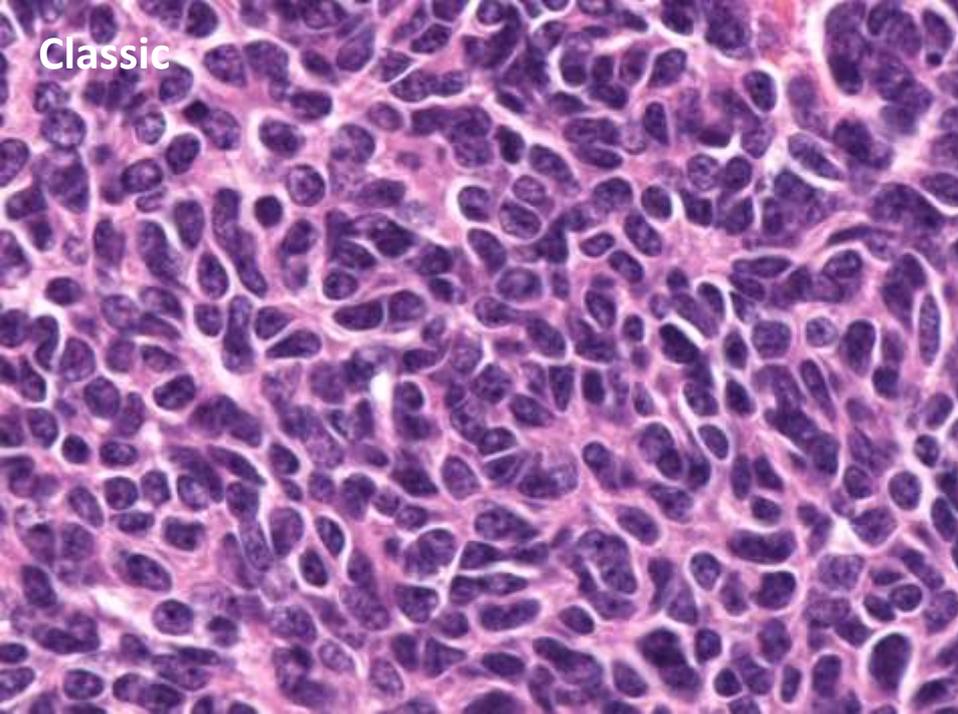
N/Cの高い未熟細胞



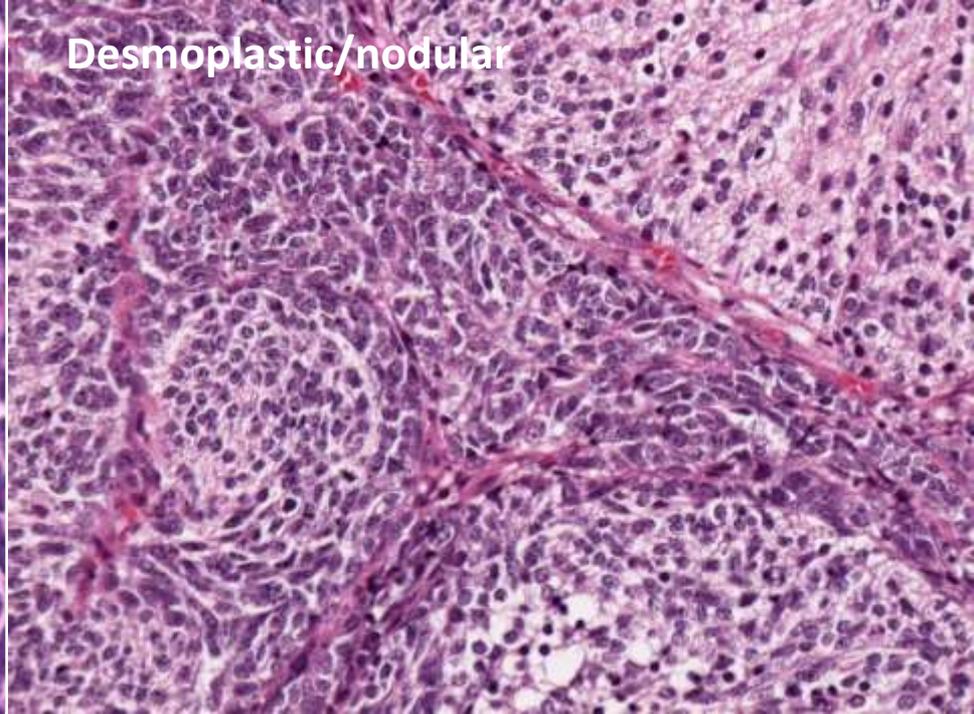
髓芽腫の亜型

- Classic
- Desmoplastic/nodular
- Medulloblastoma with extensive nodularity
- Large cell
- Anaplastic

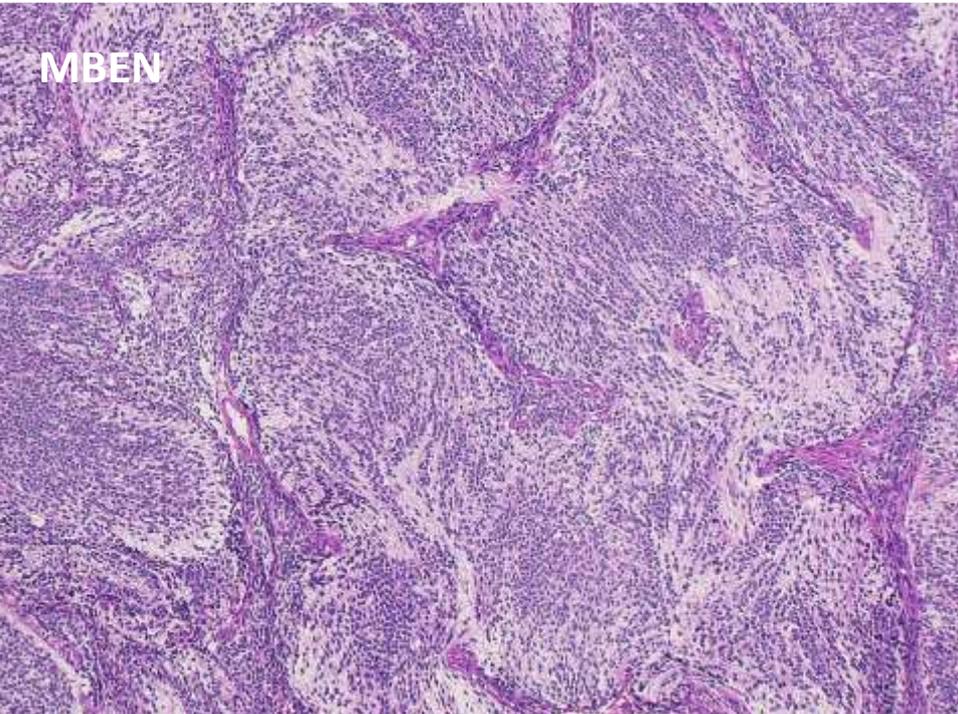
Classic



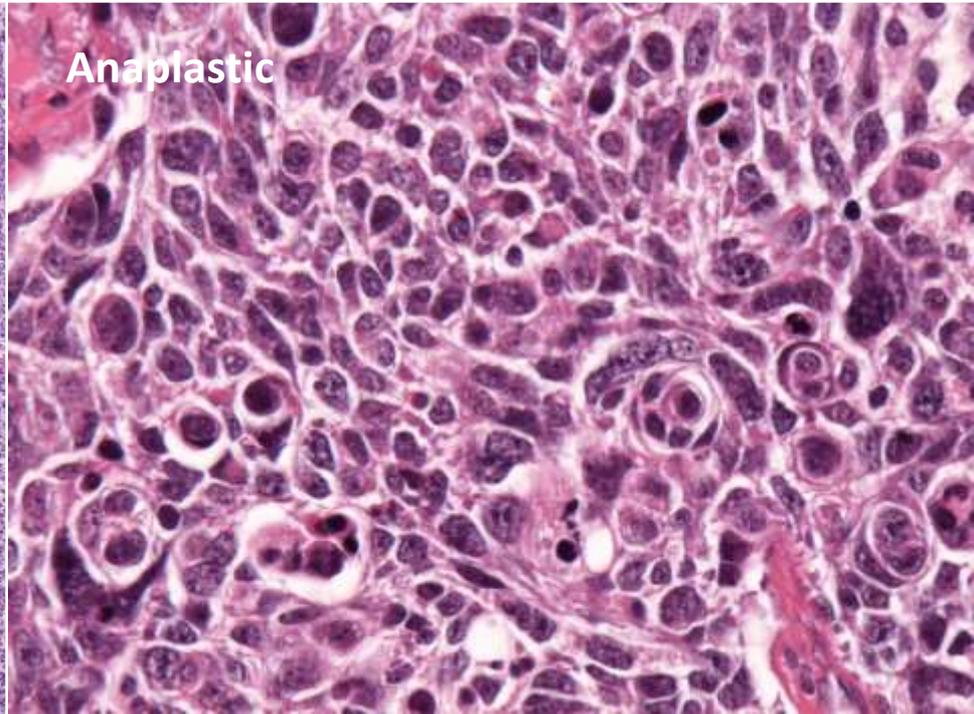
Desmoplastic/nodular



MBEN



Anaplastic



髓芽腫 Medulloblastoma

2007 4th edition

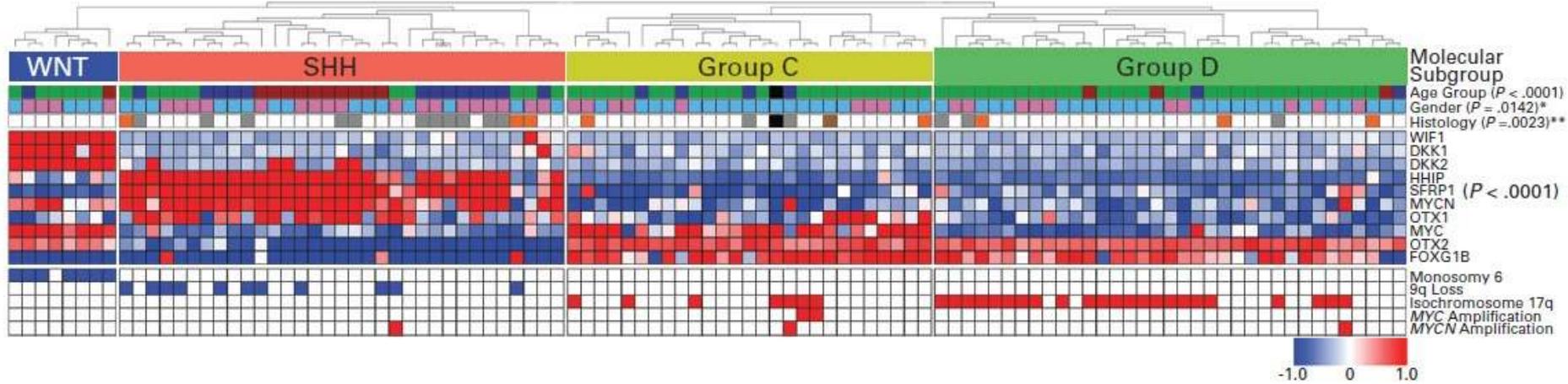
- Medulloblastoma
 - Classic
 - Desmoplastic/nodular
 - Medulloblastoma with extensive nodularity
 - Anaplastic
 - Large cell

2016 update of 4th edition

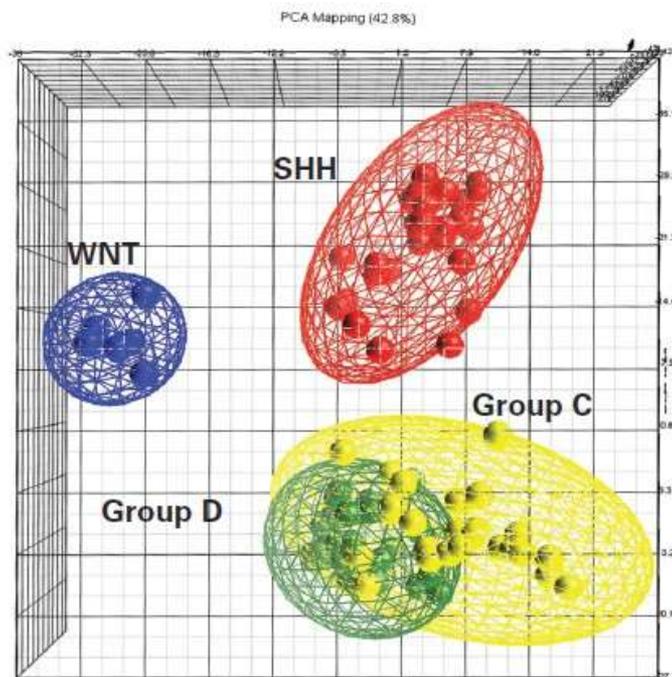
- Medulloblastoma, genetically defined
 - Medulloblastoma, WNT activated
 - Medulloblastoma, SHH activated, TP53 mutated
 - Medulloblastoma, SHH activated, TP53 wild-type
 - Medulloblastoma, non-WNT/non-SHH (group 3 and group 4)
- Medulloblastoma, histologically defined
 - Medulloblastoma, classic
 - Desmoplastic/nodular medulloblastoma
 - Medulloblastoma with extensive nodularity
 - Medulloblastoma, large cell/anaplastic

Gene expression profiling of medulloblastoma

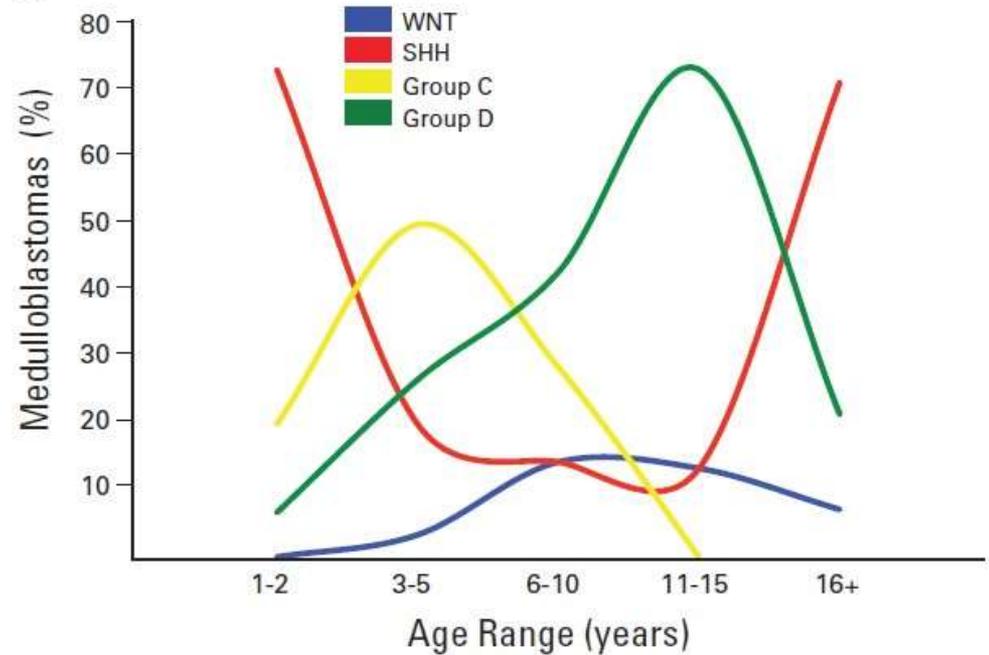
A



B



C



髓芽腫の分子分類と臨床相関

遺伝学的分類	組織学的分類	臨床相関
髓芽腫, WNT活性化	古典型(大多数)	低悪性度
	大細胞・退形成性(稀)	悪性度不明
髓芽腫, SHH活性化およびTP53変異	古典型(稀)	稀、高悪性度
	大細胞・退形成性	高悪性度、小児に好発
	線維形成結節性(稀)	悪性度不明
髓芽腫, SHH活性化およびTP53野生型	古典型	中悪性度
	大細胞・退形成	悪性度不明
	線維形成結節性	低悪性度(乳児)
	高度結節性	低悪性度、乳児に好発
髓芽腫, 非WNT/非SHH, 3群	古典型	中悪性度
	大細胞・退形成性	高悪性度
髓芽腫, 非WNT/非SHH, 4群	古典型(大多数)	中悪性度
	大細胞・退形成性(稀)	悪性度不明

Other embryonal tumors

2007 4th edition

- CNS primitive neuroectodermal tumor
 - CNS neuroblastoma
 - CNS ganglioneuroblastoma
 - Medulloepithelioma
 - Ependymoblastoma
- Atypical teratoid/rhabdoid tumor

2016 update of 4th +

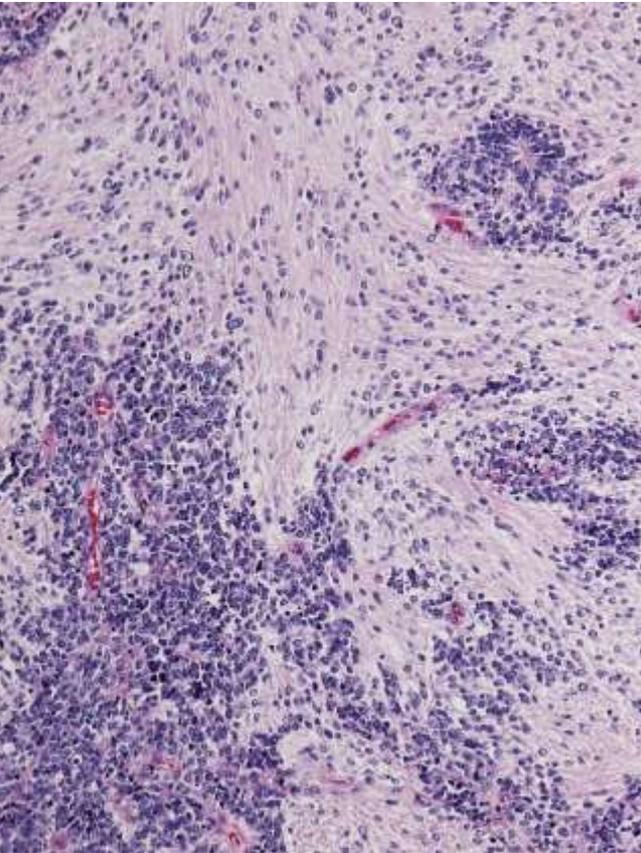
- Embryonal tumour with multilayered rosettes, C19MC altered
- Embryonal tumour with multilayered rosettes, NOS
- CNS embryonal tumour, NOS
 - CNS neuroblastoma
 - CNS ganglioneuroblastoma
- Atypical teratoid/rhabdoid tumour
- CNS embryonal tumour with rhabdoid features

Embryonal tumor with multilayered rosettes, C19MC-altered

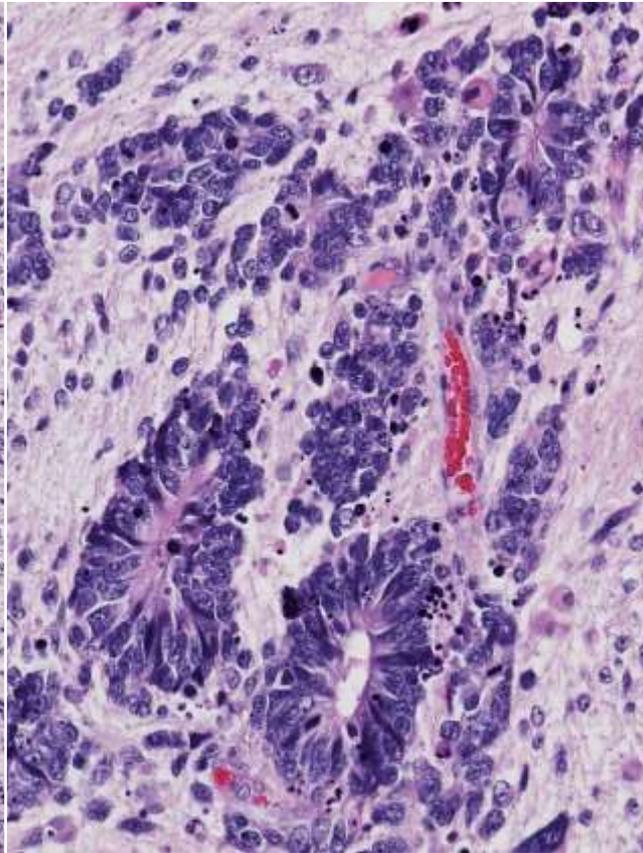
- 多層性ロゼットを特徴とする高悪性度の胎児性腫瘍で、C19MC locus の異常を有する
- Embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, medulloepitheliomaの一部
- 乳幼児；大脳半球、脳幹部、小脳など
- 多層性の真正ロゼット、未熟な腫瘍細胞、豊富な神経網
- LIN28A: ETMRの有用な免疫染色マーカー
- 高悪性度腫瘍

Embryonal tumor with multilayered rosettes, C19MC-altered

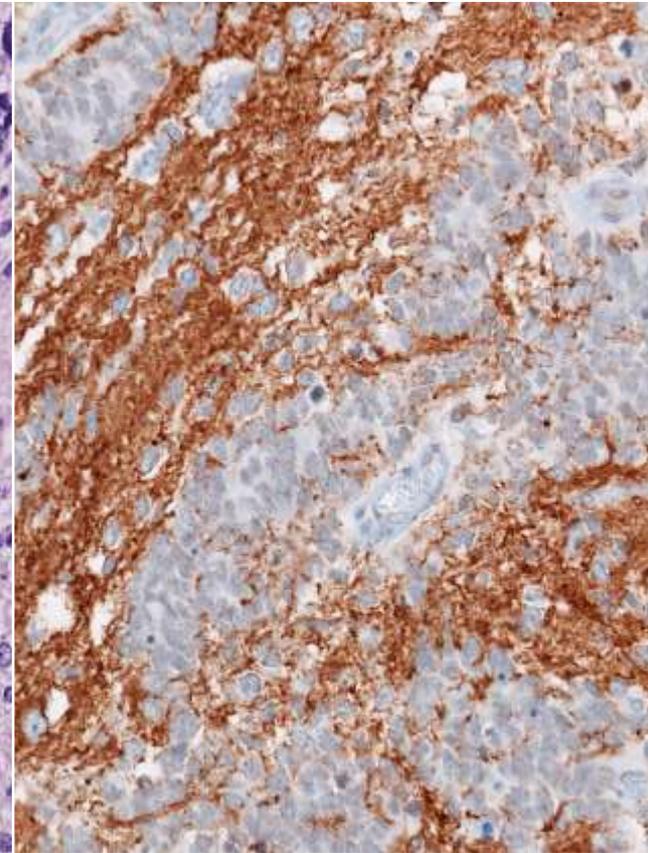
Abundant neuropil



Ependymoblastic rosettes



Synaptophysin

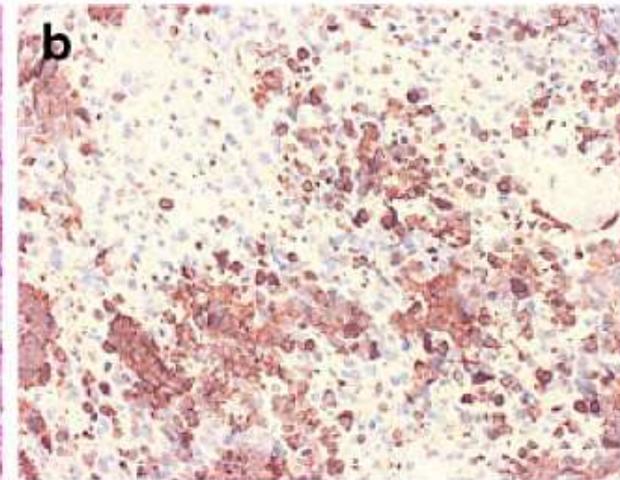
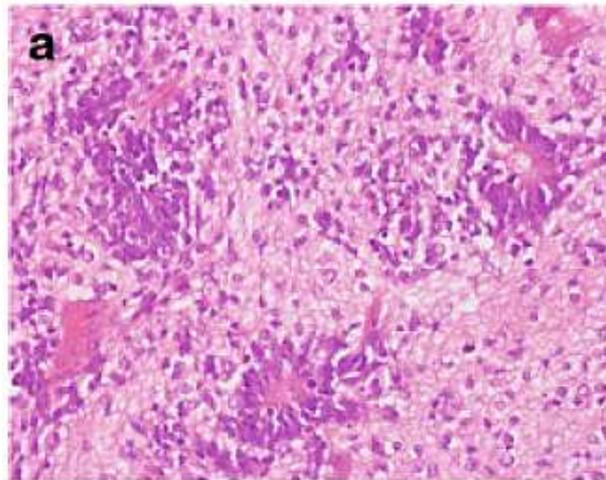
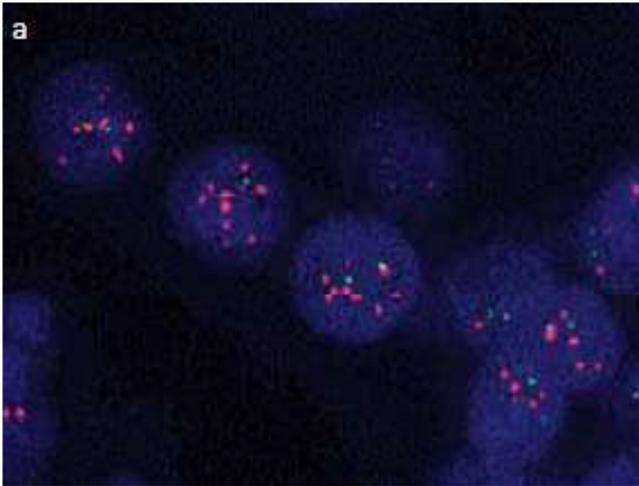


Embryonal tumor with multilayered rosettes, C19MC-altered

19q13.42 amplification

ETMR

LIN28A



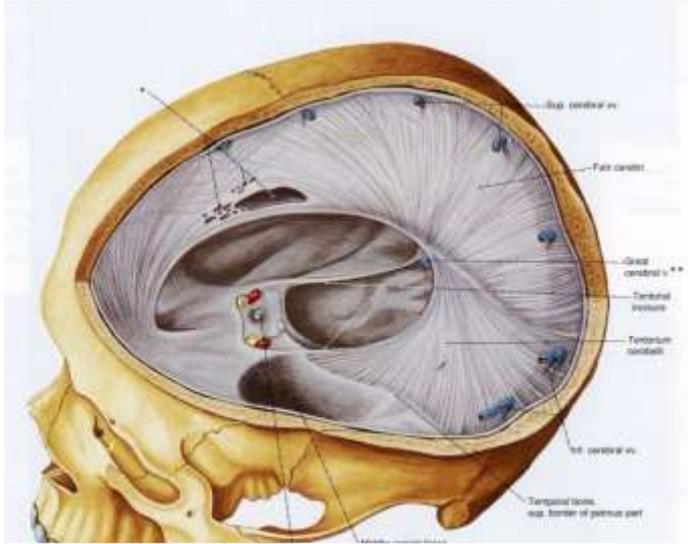
Nobusawa et al. Brain Pathol 2012

Korshunov et al. Acta Neuropathol 2012

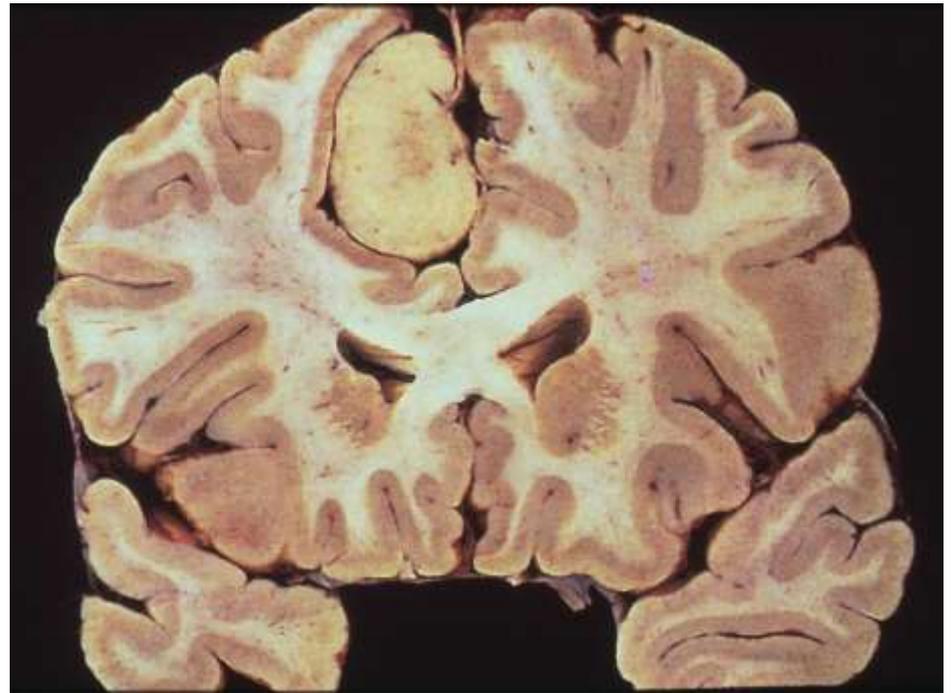
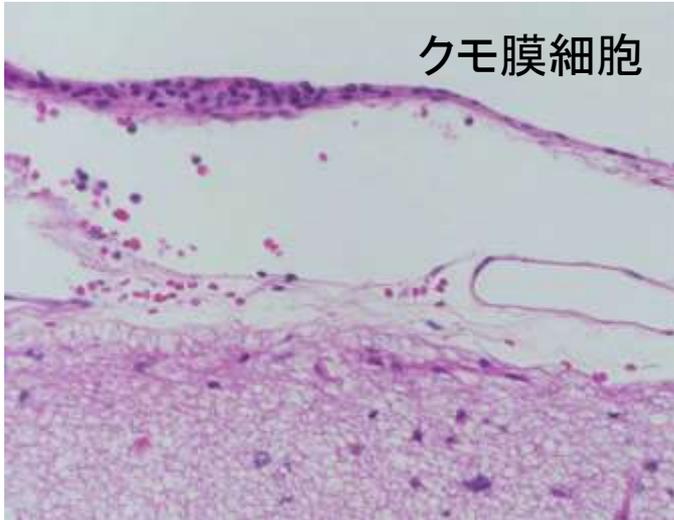
脳の外 of 腫瘍

- 髄膜腫 meningioma
- 聴神経腫 acoustic neurinoma
(シュワン細胞腫 schwannoma)

髄膜腫 meningioma



髄膜から発生する脳実質の外の腫瘍



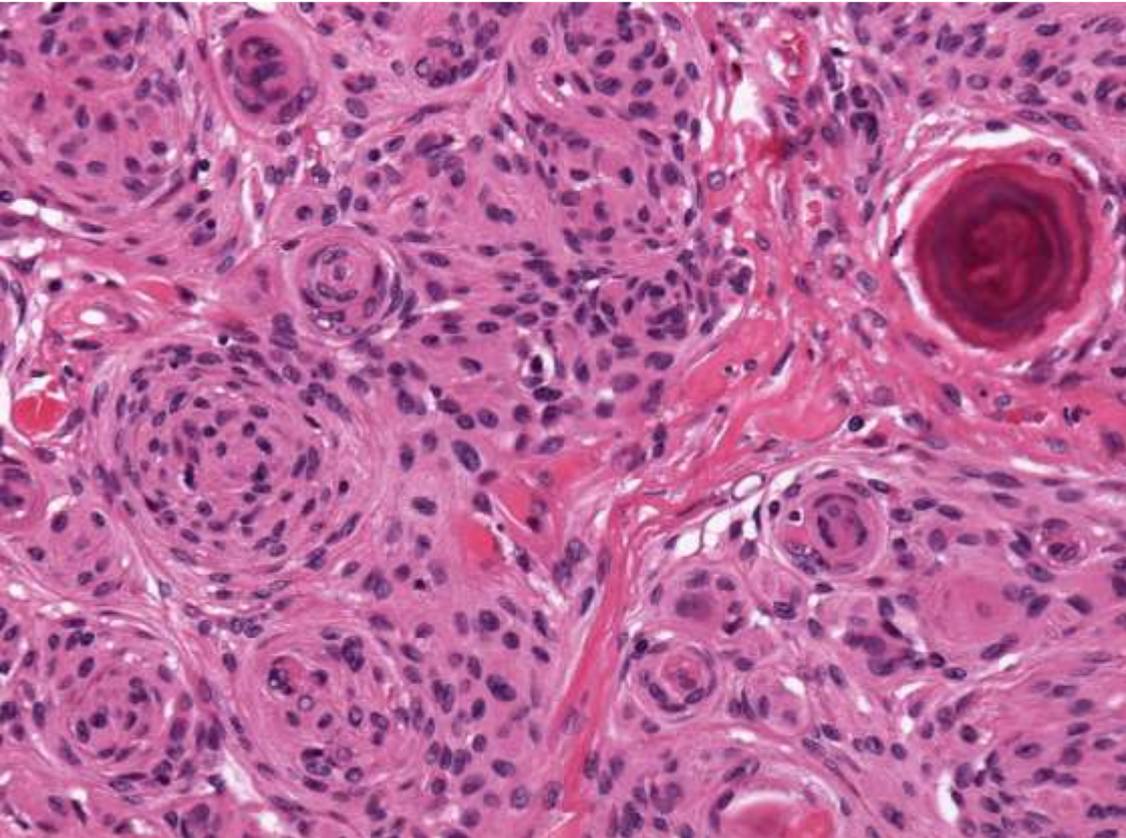
髄膜腫 meningioma

- 髄膜から発生した脳外の腫瘍
- 中年女性に好発
- 渦巻き状配列、砂粒体(石灰化)
- 家族性に発生することがある
 - 神経線維腫症2型(多発性)
- 大部分はgrade I(良性)



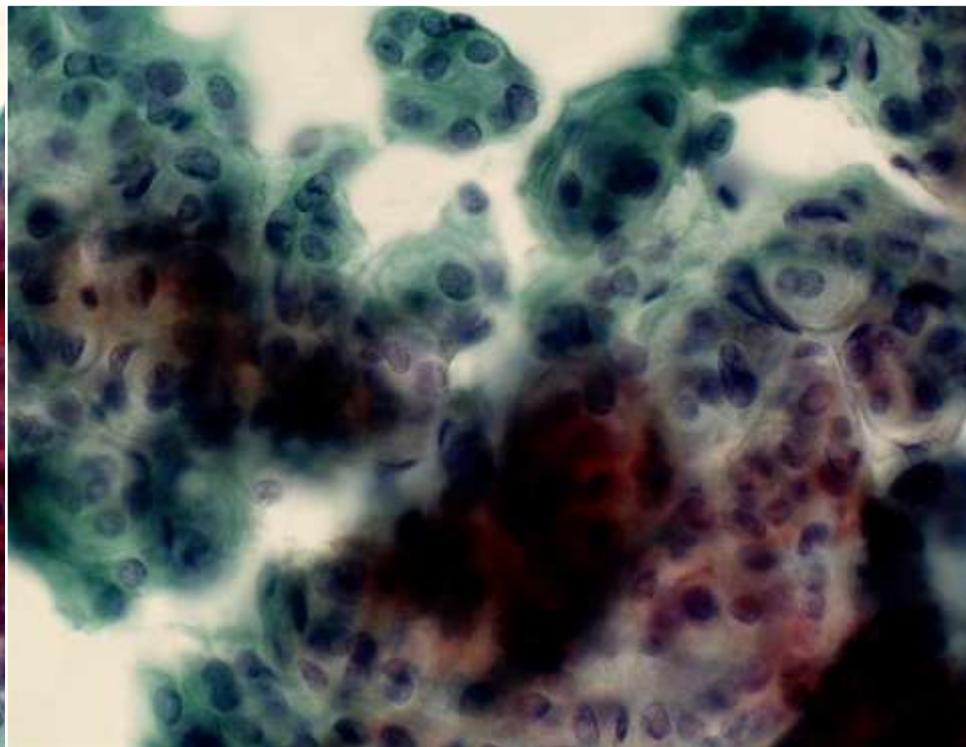
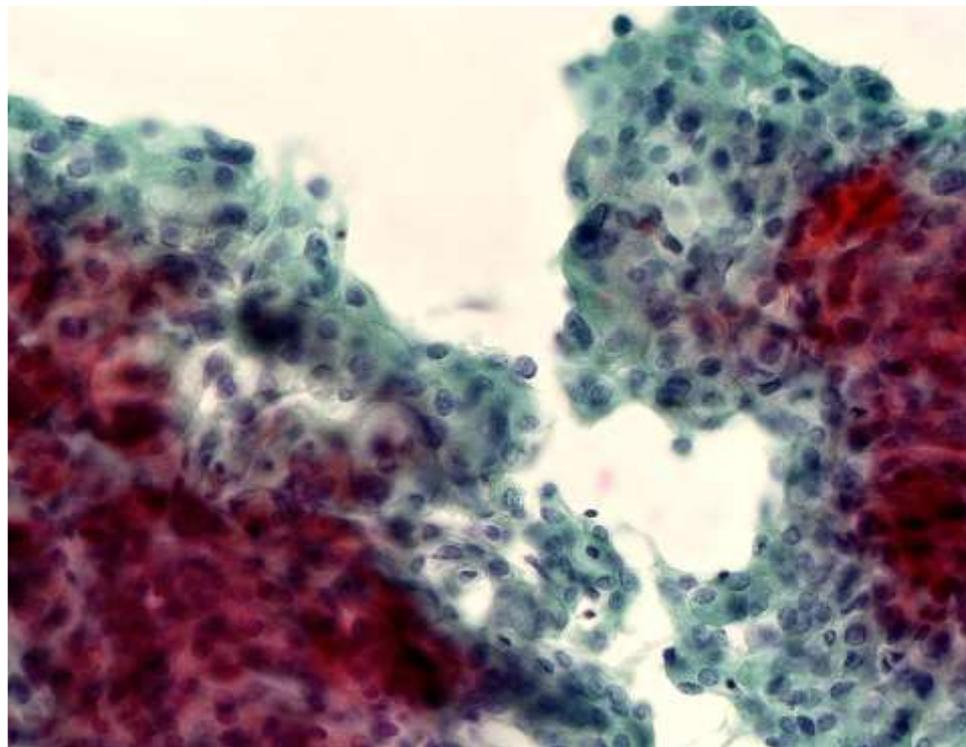
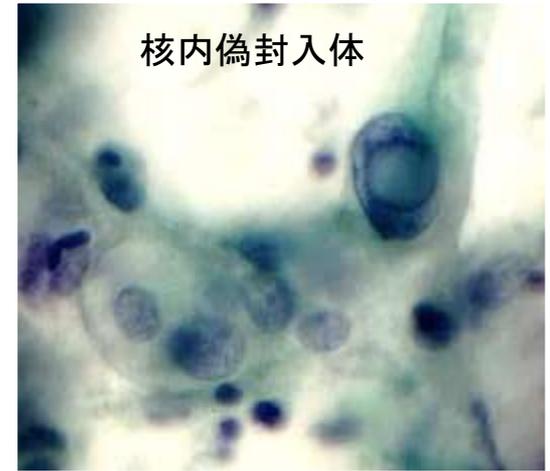
髄膜腫 meningioma

玉ねぎ様構造、砂粒体



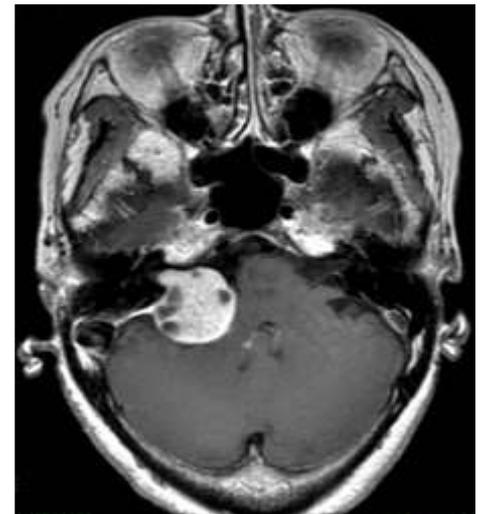
髄膜腫 meningioma

結合性、玉ねぎ様構造



聴神経腫（シュワン細胞腫）

- 末梢神経（シュワン細胞）の腫瘍
- 第8脳神経（聴神経）から発生
- 家族性に発生することがある
 - 神経線維腫症2型（両側性）
- 良性腫瘍

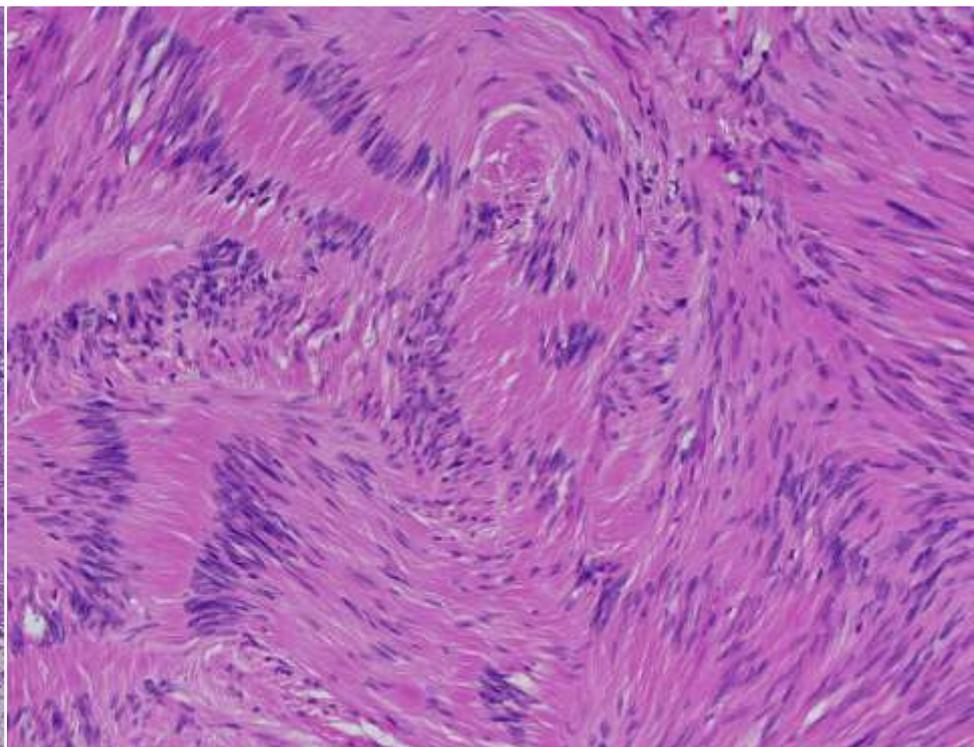
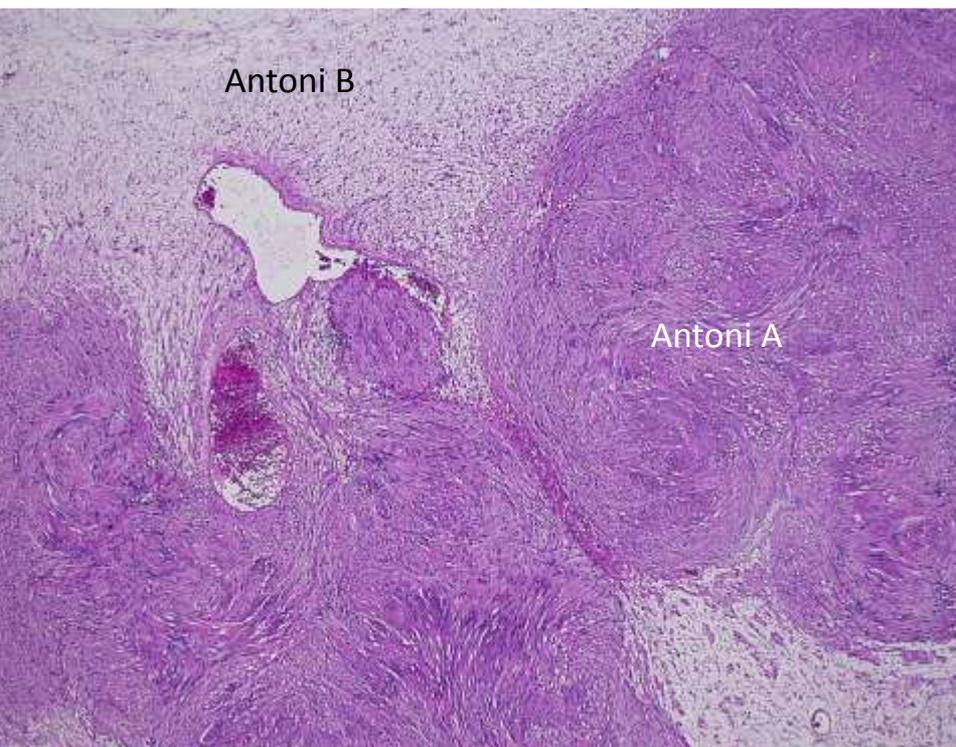


シュワン細胞腫



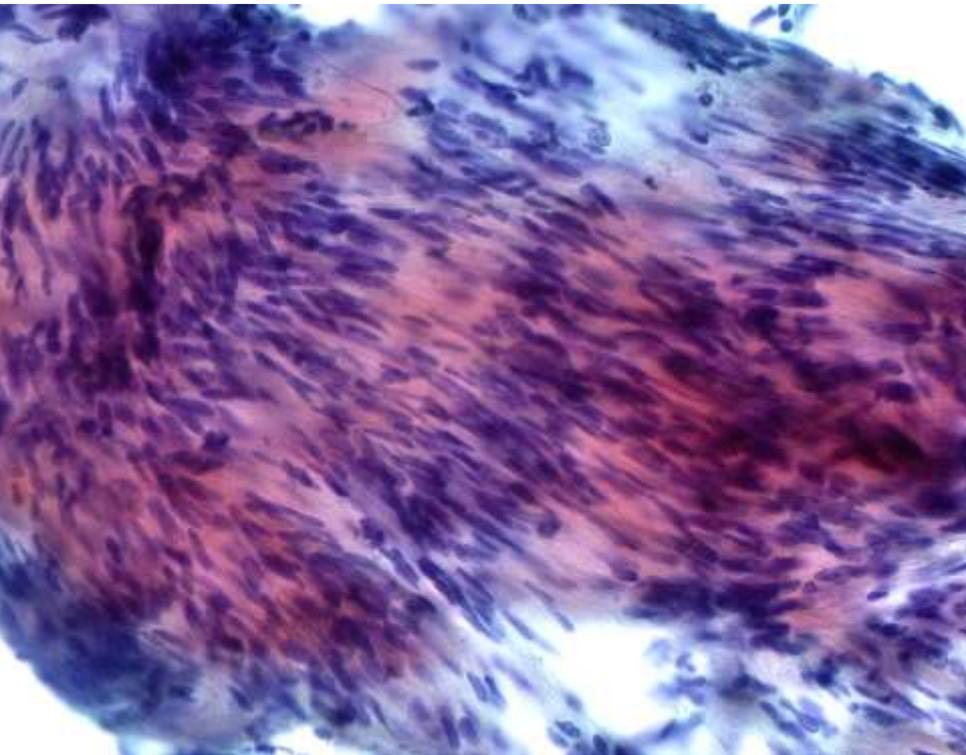
Antoni A, B pattern

核の柵状配列

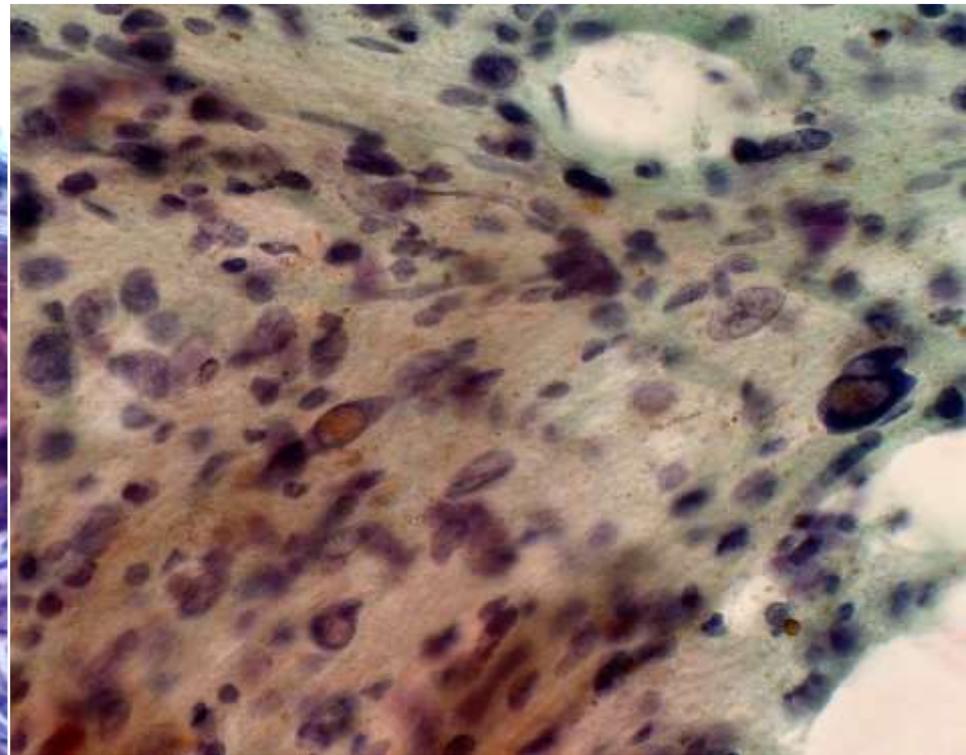


シュワン細胞腫 schwannoma

核の柵状配列



多形性、ヘモジデリン



2016WHO脳腫瘍分類の変更点

- 表現型に加えて分子型を合わせた統合分類になった
 - Diffuse astrocytoma, IDH-mutant
 - Oligodendroglioma, IDH-mutant and 1p/19q codeleted
- びまん性神経膠腫の枠組みが変わった
 - 星細胞系腫瘍と乏突起膠細胞系腫瘍が同一群に入れられた
- 髄芽腫に分子分類が加えられた
 - WNT, SHH, non-WNT/non-SHH
- 遺伝子異常で定義づけられた新しい腫瘍概念の導入
 - Ependymoma, RELA fusion-positive
 - Embryonal tumor with multilayered rosettes, C19MC-altered

脳腫瘍の細胞診

- 脳腫瘍の術中迅速診断に有用
- 長所
 - 少量の材料で、迅速かつ容易に作製できる
 - 細胞形態の保持に優れている
- 短所
 - 組織構築に関する情報は少ない
 - 採取部位が適切でないと診断を誤る
- 臨床および画像情報を参考にすることが重要である

脳腫瘍細胞診の特徴

腫瘍型	細胞所見の特徴
星細胞腫	線維状突起、豊かな細胞質
膠芽腫	異型性、多形性、分裂像、壊死、微小血管増殖
毛様細胞性星細胞腫	毛髪様の突起、Rosenthal線維
乏突起膠腫	単調な円形核、突起は乏しい、樹枝状血管網
上衣腫	結合性、ロゼット形成
髓芽腫	裸核状の細胞、クロマチン濃染核
髓膜腫	結合性、タマネギ状構造、砂粒体、核内封入体