Markers and Immunoprofile of Central Nervous System Tumors

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27.1 Diagnostic Antibody Panel for Tumors of the Central Nervous System

GFAP, MAP2, NeuN, Olig-2, neurofilaments, synaptophysin, pan-cytokeratin, Ki-67.

Glial fibrillary acidic protein (GFAP)		
Expression pattern: cytoplasmic		
Main diagnostic use	Expression in other tumors	Expression in normal cells
CNS tumors (astrocytoma, glioblastoma, oligodendroglioma, medulloblastoma, ependymoma), retinoblastoma, neurilemoma, neurothekeoma, MPNST	Salivary gland tumors (myoepithelial tumors, basal cell adenoma/carcinoma, pleomorphic adenoma), neuroblastoma, osteosarcoma, chondrosarcoma	Astrocytes, subset of CNS ependymal cells, cells of choroid plexus, Schwann cells, Kupffer cells, myoepithelial cells, chondrocytes
Positive control: brain tissue		

Diagnostic Approach Glial fibrillary acidic protein (GFAP) is a member of class III of intermediate filament proteins. GFAP is mainly expressed in neuroglia including astrocytes and ependymal cells. Lower expression levels are found in Schwann cells, paraganglial cells, enteric glial cells, Kupffer cells of the liver, osteocytes, chondrocytes, and myoepithelial cells. GFAP is a

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marker of neoplastic glial cells and glial differentiation. Lower GFAP expression level is also found in neurilemoma and neuroblastoma.

Diagnostic Pitfalls GFAP is an important marker to discriminate between primary brain and metastatic tumors; however, it can be expressed in non-glial tumors such as myoepithelioma and myoepithelial component of different types of salivary gland tumors, osteosarcoma, chondrosarcoma, and angiosarcoma.

Microtubule-Associated Protein 2 (MAP2): MAP2 is one of the five members of the microtubule-associated protein family. This protein is a neuron-specific cytoskeletal protein found in three isoforms a, b, and c expressed in neurons and reactive astrocytes. MAP2 labels the cytoplasm of the neuronal cell body and basal dendrites and is considered as an early marker for neuronal differentiation. In immunohistochemistry, MAP2 is used as a marker of neuronal differentiation. Positive stain is found in glial tumors, medulloblastoma, neuroblastoma, pulmonary neuroendocrine tumors, a subset of melanomas, and some carcinoma types (mainly thyroid and prostate).

Neuronal Nuclear Antigen (NeuN): NeuN (also known as FOX-3 protein) is a low molecular weight protein localized in the nuclei and cytoplasm of most neuronal cells of the central and peripheral nervous system and tumors derived from these cells. NeuN is a marker for central neurocytoma and gangliogliomas. The majority of PNETs of the CNS and medulloblastoma are also NeuN positive. Less than 5% of astrocytic and oligodendroglial tumors show NeuN expression.

Oligodendrocyte Lineage Transcription Factor 2 (Olig-2): Olig-2 is a transcription factor involved in the regulation of neuroectodermal progenitor cells and development of oligodendrocytes and motoneurons. Normally, Olig-2 is strongly expressed in oligodendroglial cells and oligodendroglioma. Weak to moderate Olig-2 expression is also found in all other gliomas including glioblastoma. Olig-2 expression is also reported in neuroendocrine carcinomas and in a small subset of central neurocytoma and supratentorial ependymoma.

27.2 Diagnostic Antibody Panel for Meningeal Tumors

S100, podoplanin, nestin, claudin-1, pan-cytokeratin, EMA, CEA, vimentin, Ki-67.

Characteristic for meningeal tumors is the co-expression of EMA, pan-cytokeratin, and S100. Other markers such as podoplanin (D2 40) are useful to confirm the diagnosis mainly in aggressive tumor types such as atypical and anaplastic meningioma (Fig. 27.1). For the assessment of tumor grade, the estimation of Ki-67 proliferation index is essential. The CEA expression is characteristic for the pseudopsammoma bodies found in secretory meningioma (Fig. 27.2).

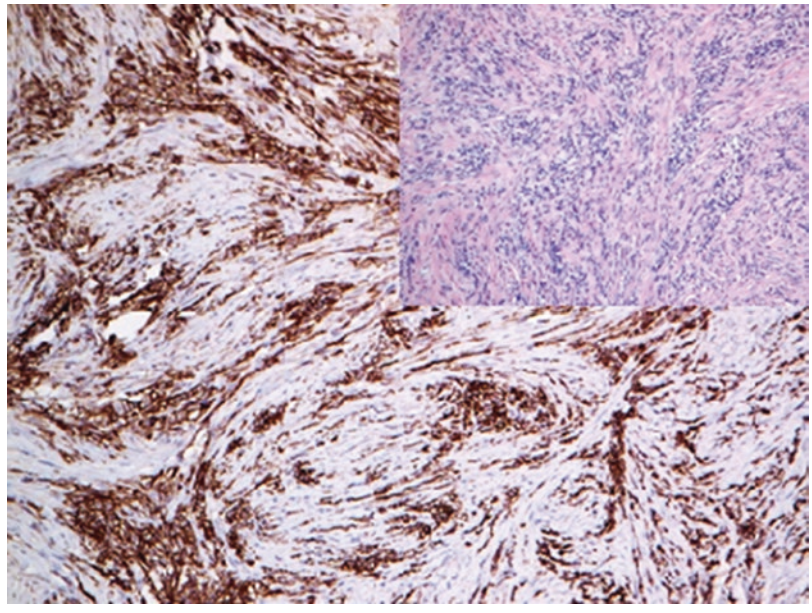

Fig. 27.1 Strong podoplanin (D2-40) expression in anaplastic meningioma

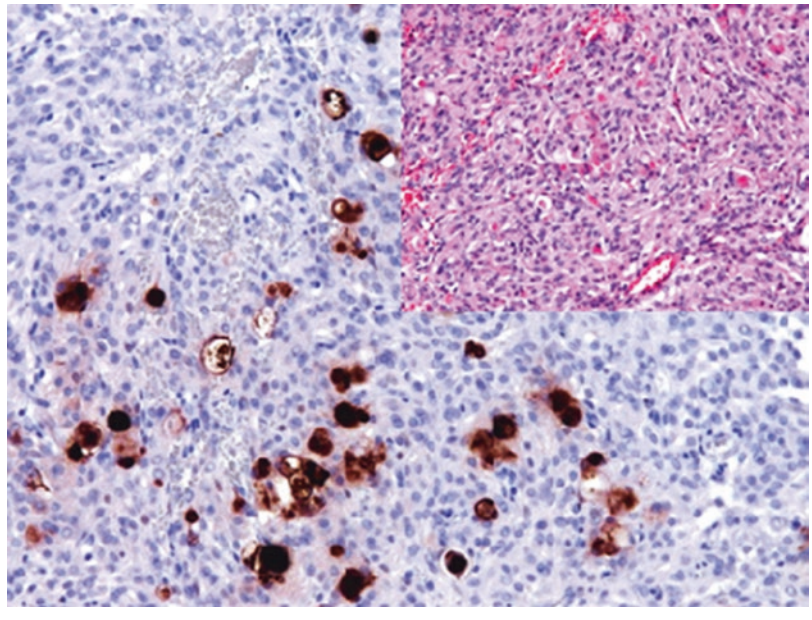

Fig. 27.2 Secretory meningioma with CEA-positive pseudopsammoma bodies

Immunoprofile of central nervous system tumors				
Tumor type	+ in >90% (+)	+ in 50–90% (±)	+ in 10–50% (∓)	+ in <10% (−)
A. Astrocytic tumors				
– Pilocytic astrocytoma (grade I) – Diffuse astrocytoma – (grade II) – Anaplastic astrocytoma (grade III) – Glioblastoma (grade IV)	*GFAP*, S100, NSE, Olig-2, bcl-2 (only in gemistocytic astrocytoma) Proliferation index (Ki-67): Diffuse astrocytoma: <5% Anaplastic astrocytoma: 5–10% Glioblastoma: >15% (5–40%)	CD56, CD99, HER-2	Synaptophysin, pan-CK[a]	Chromogranin, CK7, CK20, neurofilaments
Diffuse midline glioma (grade IV)	CD56, Olig-2, S100	GFAP, MAP2	Synaptophysin	Chromogranin
Subependymal giant cell astrocytoma (grade I)	GFAP, S100, NSE, Olig-2			
– Pleomorphic xanthoastrocytoma (grade II) – Anaplastic pleomorphic xanthoastrocytoma (grade III)	GFAP, S100 Proliferation index (Ki-67) in grade II: <1%	Synaptophysin, neurofilaments, CD34, MAP2		
Astroblastoma	S100, vimentin	*GFAP*	EMA	
Chordoid glioma of the third ventricle (grade II)	*GFAP*, *TTF-1*, CD34	S100	EMA	
Angiocentric glioma (grade I)	*GFAP*, S100 Proliferation index (Ki-67): <5%		EMA	Synaptophysin, chromogranin
B. Oligodendroglial tumors				
Oligodendroglioma (grade II)	S100, NSE, synaptophysin, MAP-2, Olig-2, SOX-10 Proliferation index (Ki-67): <5%			Pan-CK, EMA
Anaplastic oligodendroglioma (grade III)	S100, NSE, synaptophysin, MAP-2, CD57 Proliferation index (Ki-67): >10%	GFAP, CD56, vimentin	Chromogranin, pan-CK	EMA, neurofilaments
C. Ependymal tumors				
Subependymoma (grade I)	*GFAP* Proliferation index (Ki-67): <1%	NSE, CD56, STAT-3		
Myxopapillary ependymoma (grade I)	*GFAP*, S100, vimentin	CD56, CD99	Pan-CK	

Immunoprofile of central nervous system tumors				
Ependymoma/anaplastic ependymoma (grade II/III):	*Podoplanin*, *GFAP*, S100, nestin	EMA, TTF-1[b]	Synaptophysin, CD99, pan-CK	Chromogranin
D. Tumors of the choroid plexus				
– Choroid plexus papilloma (grade I) – Atypical choroid plexus papilloma: (grade II) – Choroid plexus carcinoma (grade III)	*Podoplanin* (D2-40), pan-CK, stanniocalcin-1, Kir7.1 Proliferation index (Ki-67): Choroid plexus papilloma: <6% Choroid plexus carcinoma: >6%	Transthyretin, S100, CK7, CD44, vimentin	GFAP, EMA, synaptophysin	Chromogranin, CD56, SOX10
E. Neuronal and mixed neuronal glial tumors				
Desmoplastic infantile astrocytoma and ganglioglioma: (grade I) – Leptomeningeal component – Poorly differentiated neuroepithelial component	Vimentin *GFAP*, MAP2, vimentin Proliferation index (Ki-67): <5%	GFAP	Actin	
Dysembryoplastic neuroepithelial tumor (grade I)	*Oligodendroglia-like cells*: S100, Olig-2 Proliferation index (Ki-67): <8%	Neurofilaments, MAP2, β-tubulin	Synaptophysin	GFAP
Ganglioglioma and gangliocytoma (grade I)	*Neuronal/ganglion cells*: neurofilaments, synaptophysin, MAP2 *Astrocytic cells*: S100, GFAP Proliferation index (Ki-67): <3%	CD34	S100	GFAP, pan-CK
Central and extraventricular neurocytoma (grade II)	*Synaptophysin*, NeuN		S100, GFAP	Pan-CK, chromogranin, neurofilaments
Cerebellar liponeurocytoma (grade II) neuronal component	Synaptophysin, MAP2, NSE		GFAP	
Papillary glioneuronal tumor (grade I) perivascular cells neuronal cell component	GFAP synaptophysin, NeuN			Chromogranin
Rosette-forming glioneuronal tumor of the fourth ventricle (grade I)	*Neurocytic perivascular cells*: synaptophysin, NSE *Glial cells:* GFAP, S100	MAP-2		GFAP, S100

Immunoprofile of central nervous system tumors				
Spinal paraganglioma (grade I)	*Chief cells*: synaptophysin, chromogranin, NSE, NF *Sustentacular cells*: S100	S100 GFAP	Pan-CK	
F. Tumors of the pineal region				
Pineocytoma (grade I) and pineoblastoma (grade IV)	Synaptophysin, neurofilaments, NSE	β-tubulin, PGP9.5, chromogranin, serotonin	S100	GFAP, pan-CK
Pineal parenchyma tumor of intermediate differentiation (grade II–III)	Synaptophysin, NSE	Neurofilaments, chromogranin, S100		
Papillary tumor of the pineal region (grade II–III)	*Pan-CK*, NSE, S100, MAP2, vimentin	GFAP	Synaptophysin, chromogranin, EMA	Stanniocalcin-1, Kir7.1, neurofilaments
G. Embryonal tumors				
Medulloblastoma (grade IV)	S100, *CD56*, nestin, β-tubulin, vimentin	MAP2, NSE, synaptophysin, PGP9.5, neurofilaments, PAX-8	GFAP, bcl-2, chromogranin	CD99, Sox-2, PAX-2
Neuroblastoma (grade IV)	Synaptophysin, neurofilaments, S100, NSE, β-tubulin, vimentin	GFAP		
Embryonal tumor with multilayered rosettes (grade IV)	*Neuroepithelial cells*: nestin, vimentin *Neuropil-like areas*: synaptophysin, NeuN, neurofilaments		Pan-CK, EMA, CD99	
Medulloepithelioma (grade IV)	*Neuroepithelial neoplastic cells*: synaptophysin, neurofilaments, nestin, vimentin	Neurofilaments	Pan-CK, EMA	GFAP, NSE
Ependymoblastoma (grade (IV)	S100, vimentin	Pan-CK, GFAP		
Atypical teratoid/rhabdoid tumor (grade IV)	EMA, vimentin	sm-Actin, GFAP, neurofilaments, pan-CK		Desmin, AFP, PLAP

Immunoprofile of central nervous system tumors				
H. Meningeal tumors				
Meningioma (intra- and extracranial)	*S100*, vimentin Proliferation index (Ki-67): – Meningioma (grade I): >4% – Atypical meningioma (grade II): 6–10% – Anaplastic meningioma (grade III): >10% Progesterone receptor expression: – Meningioma (grade I): ~ 60–90% – Atypical meningioma (grade II): ~20–40% – Anaplastic meningioma (grade III): <20%	Podoplanin, nestin, claudin-1, NSE, CD141, *EMA*, *pan-CK*, CK8/18, CD99, PgR, CEA[c], ERG[d]	Osteonectin, CD34, CK7, bcl-2	*GFAP*, synaptophysin, chromogranin, CD56, CK5/6, CK20, neurofilaments

[a]Mainly found in epithelioid glioblastoma
[b]In ependymoma of the third ventricle
[c]Characteristic for secretory type meningioma
[d]Characteristic for fibrous meningioma