REVIEW



Magnetic resonance imaging findings of mixed neuronal–glial tumors with pathologic correlation: a review

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Abstract

Mixed neuronal–glial tumors are rare, and MRI diagnosis of them presents a challenge. In this review, we discuss the MRI findings of ganglioglioma, anaplastic ganglioglioma, desmoplastic infantile ganglioglioma, papillary glioneuronal tumor, rosette-forming glioneuronal tumor, and primary diffuse leptomeningeal glioneuronal tumor with clinicopathologic correlation. There is overlap of imaging features both with each other and some other tumors, which complicates diagnosis. The combination of imaging findings and the age, location, and appropriate clinical picture should allow the radiologist and the clinicians to raise a provisional diagnosis of a mixed neuronal glial tumor, and guide patient management.

Keywords Mixed neuronal–glial tumor \cdot Ganglioglioma \cdot Anaplastic ganglioglioma \cdot Desmoplastic infantile ganglioglioma \cdot Papillary glioneuronal tumor \cdot Rosette-forming glioneuronal tumor \cdot Diffuse leptomeningeal glioneuronal tumor \cdot Magnetic resonance imaging

Introduction

The classification of primary brain tumors has been changed by the World Health Organization (WHO) in 2016 [1]. Regarding this classification, mixed neuronal–glial tumors (MNGT) include ganglioglioma, anaplastic ganglioglioma, desmoplastic infantile ganglioglioma/astrocytoma (DIG/A), papillary glioneuronal tumor (PGNT), rosette-forming glioneuronal tumor (RF-GNT) and primary diffuse leptomeningeal glioneuronal tumor (PDL-GNT). Although gangliocytomas, dysembryoplastic neuroepithelial tumors (DNETs) and neurocytomas may display some glial differentiation, these tumors are generally not considered as glial neoplasms and

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are not included in this study. Desmoplastic infantile astrocytoma, which is characterized by prominent desmoplasia with neoplastic glial cells, but without neuronal component is also excluded. Recent studies have shown that these rare tumors may have characteristic magnetic resonance imaging (MRI) features that may permit a confident non-invasive preoperative diagnosis. Our aim is to discuss and demonstrate the common and distinctive characteristics of MNGTs on MR imaging with a clinical–pathological correlation.

Ganglioglioma

Ganglioglioma is a rare WHO grade I tumor, occurring mostly in the pediatric population, but also in young adults. The most common clinical presentation is refractory complex partial epilepsy, but the clinical symptoms of gangliogliomas may vary due to tumor size and site. The histopathologic criteria include mature neoplastic astrocytes and atypical large binucleate neurons with prominent nucleoli in varying proportions. The lesions may be iso- to hypointense and hyperintense on T1- and T2-weighted MRI, respectively. The tumor may usually appear as a solid-cystic mass, or may entirely be a solid mass. Contrast enhancement can be either a nodular rim or a solid enhancement pattern. Unenhancement may also occur. Presence of calcifications is usually



extensive (Fig. 1). They often involve temporal lobes, and occur less commonly in the frontal and parietal lobes [2]. However, they may occur anywhere of the neural axis, including extra axial sites and the cerebellum. Ipsilateral cerebellar cortical atrophy may be seen in patients with solid infratentorial gangliogliomas as a distinctive feature [3]. Multiple gangliogliomas of the optic pathway may also exist [4]. The main MRI differential diagnosis includes pilocytic astrocytoma, pleomorphic xantoastrocytoma, and hemangioblastoma. Pilocytic astrocytoma and hemangioblastoma typically occur in the cerebellum, whereas the overwhelming majority of pleomorphic xantoastrocytoma arises from the supratentorial brain. With the typical location and appearance of a well-delineated cerebellar cystic mass with mural nodule, the diagnosis of pilocytic astrocytoma and hemangioblastoma is easy. However, when located in the supratentorial region, they share the typical appearance of a supratentorial cystic mass with enhancing mural nodule, making the differential diagnosis difficult. The differential diagnosis with pleomorphic xantoastrocytoma may further be very difficult, both radiologically and pathologically. Pleomorphic xanthoastrocytomas favor a peripheral location, suggesting that they arise from subpial astrocytes. They may scallop and/or erode the inner table of the calvarium. Most are heterogeneous, and the solid peripheral portions of the tumor are isointense on T2-weighted MR images. They **∢Fig. 1** Ganglioglioma in the suprasellar region in a 61-yearold female with headache and visual field defects (a-c). Sagittal T2-weighted MRI (a) reveals a heterogeneous solid mass (black star) with internal cystic components (arrow) in the suprasellar region involving hypothalamus and optic chiasma. Sagittal contrastenhanced MRI (b) shows heterogeneous slightly enhancing solid component (arrow). Photomicrograph (original magnification, ×200; hematoxylin-eosin stain) (c) reveals pleomorphic neoplastic ganglion cells (arrow) and a fibrillary astrocytic component (arrowheads). Ganglioglioma in the right cerebral hemisphere in a 10-year-old boy with headache and seizure $(\mathbf{d}-\mathbf{f})$. Axial T2-weighted MRI (\mathbf{d}) reveals a heterogeneous high signal intensity mass (arrow). Axial contrastenhanced T1-weighted MRI (e) reveals complete homogeneous and intense enhancement of the solid portion of the tumor (arrow) and unenhancing cystic component (arrowhead). MR spectroscopy (f) of the lesion reveals a raised choline peak and choline-creatine ratio with decreased N-acetyl aspartate peak. Ganglioglioma in the right hippocampus in a 23-year-old female with intractable seizure (g, h). Coronal T1 inversion recovery image (g) reveals an isointense solid mass (arrowhead) with peripheral cystic components (arrows) in the right hippocampus. Axial contrast-enhanced T1-weighted 3D gradient echo image reveals (h) complete inhomogeneous slight enhancement in the solid portion of the tumor (arrowhead). There is no contrast enhancement in the peripheral cystic components. The tumor shows no surrounding edema. Infratentorial ganglioglioma in a 35-year-old female with, headache, vertigo, and imbalance (i). Coronal contrast-enhanced T1-weighted MRI shows left cerebellar mass with multiple solid-cystic components. The solid components show both intense (thick arrow) and slight enhancement (thin arrow). There is no enhancement in the cystic components (arrowheads), suggesting the diagnosis of WHO grade 1 tumor. Multiple ganglioglioma of the optic pathway in a 19-year-old boy with headache and progressive visual disturbance particularly in his right eye (j-l). Axial T2-weighted MRI (j) reveals a solid tumor in the optic chiasm (arrowhead) and another solid-cystic tumor in the medial surface of right temporal lobe (arrowheads). Axial contrast-enhanced T1-weighted MRI (k) reveals partial intensely enhancing solid component (arrow) in the right temporal lobe tumor. There is no enhancement in the solid tumor of the optic chiasm (arrowhead). Unenhanced coronal CT scan (I) reveals heavy calcification in the tumor like a craniopharyngioma. This type of calcification is more common in ganglioglioma rather than pilocytic astrocytoma

may characteristically abut the meninges, and usually show intense enhancement with gadolinium, which is described as "meningocerebral" [5]. The transformation into, or coexistance with ganglioglioma may rarely exist [6]. The differential diagnosis of gangliogliomas should also be made with cortical dysplasia, DNETs, and diffuse gliomas in a young epileptic patient with a cortical lesion, especially in the temporal lobes. The presence of minimal mass effect and surrounding edema in gangliogliomas is important to differentiate them from more aggressive contrast-enhancing tumors. Since gangliogliomas have a potential anaplastic transformation, multimodal MRI is required to distinguish them from mimics such as DNETs and local cortical dysplasias. Relative cerebral blood volume, relative cerebral blood flow and choline are higher in gangliogliomas and the creatine is lower [7]. The BRAF V600E mutation is a helpful diagnostic marker in ganglioglioma, even if some of its differential diagnoses such as DNETs can also exhibit this mutation [8–10]. Meanwhile, the association of cortical dysplasia and ganglioglioma should not be forgotten in the radiologic evaluation of patients with seizure, due to its specific treatment considerations. Thus, it is important to detect abnormal sulcal and/or gyral pattern, cortical thickening, blurred gray matter–white matter junction, abnormal white matter signal, abnormal gray matter signal, transmantle (down to the ventricles) subcortical signal changes, and localized cortical volume loss for the diagnosis of cortical dysplasia surrounding the ganglioglioma [11]. Surgical excision is considered the standard of care.

Anaplastic ganglioglioma

Anaplastic ganglioglioma, the WHO grade III variant, is a rare and malignant form of ganglioglioma. They occur in children and young adults with severe neurologic symptoms such as symptoms of elevated pressure and hemiplegia due to its aggressive nature. Survival is very poor. Contrarily to the grade I ganglioglioma, anaplastic gangliogliomas do not show a predilection for the temporal lobes, but are evenly distributed among the cerebral hemispheric lobes and the spinal cords [12]. It may occur either de novo or following malignant transformation of a WHO grade I ganglioglioma. Mitotic activity, increased cellularity, microvascular proliferation and necrosis are the main pathologic findings of the disease. On MRI, tumors are typically isointense or hypointense on T1-weighted sequences, hyperintense on T2-weighted sequences. Contrast enhancement of the solid and cystic components is irregular, and the course of the tumor is characterized by a local recurrence or leptomeningeal spread, which correlates with its malignant histopathologic features (Fig. 2). The advanced imaging studies such as functional imaging, perfusion and diffusion images are of great help to demonstrate its aggressive nature. The main differential diagnosis of the disease includes anaplastic gliomas [13]. The combination of a gross total resection, adjuvant radiation and chemotherapy is the preferred treatment choice to improve the outcome of these patients. Since BRAF V600E mutation is present in 39% of anaplastic gangliogliomas, anti-BRAF inhibitors can also be a useful adjuvant therapy [14, 15].

Desmoplastic infantile ganglioglioma

DIGs are usually seen in newborns or infants primarily presenting in the first 18 months of life as large cystic-solid tumors. It usually causes macrocrania, epilepsy, and focal neurologic signs. The histopathology of the desmoplastic infantile ganglioglioma differs from the desmoplastic infantile astrocytoma by the presence of a neural component



Fig.2 Anaplastic ganglioglioma in a 8-year-old boy with headache, hemiplegia and symptoms of intracranial pressure elevation. **a** Axial susceptibility-weighted MR image reveals a tumor in the left thalamus with punctate foci of diminished signals (arrows) compatible with hemorrhagic deposits. **b** Axial T2-weighted MRI reveals a heterogeneous high signal intensity mass with solid (arrowhead) and cystic components (arrows). **c** Axial contrast-enhanced MR image reveals intense irregular enhancement of the solid (arrow) and cystic

with glial differentiation, but they have similar clinical and neuroimaging findings. Histologically, the most prominent feature of the tumor is desmoplasia and spindle cells in a storiform or whorled pattern. The tumor shows heterogeneous signals on T2-weighted images, and demonstrates hypointensity of the cystic component and isointensity of the solid component on T1-weighted images. The solid part of the tumor enhances on contrast-enhanced images. They are typically supratentorial tumors involving more than one lobe, although atypical appearances may exist. The involvement of the superficial cerebral cortex and leptomeninges with an attachment to the dura via a desmoplastic reaction is its distinctive MRI feature, but it may appear as a small tumor (Fig. 3) [16]. The tumor may show very high cholin/ NAA level, high perfusion and low ADC values on advanced MRI. The differential diagnosis of primary infantile CNS neoplasms with similar radiologic appearance includes CNS embryonal tumor, atypical teratoid rhabdoid tumor, choroid plexus carcinomas, and supratentorial ependymomas [17]. Chromosomal gains affecting the region harboring the BRAF protein have been described in the desmoplastic area of some DIG/As [16]. Its prognosis is usually good after complete surgical removal, and rarely requires a chemotherapy or radiotherapy.

(arrowheads) components. **d** Axial contrast-enhanced T1-weighted MR image obtained 6 months after the partial resection of the tumor followed by radiation therapy demonstrates diffuse leptomeningeal spread (arrows). **e** Photomicrograph (original magnification, $\times 200$; hematoxylin–eosin stain) reveals atypical glial cells and binucleated neoplastic neurons (arrowhead) with a large necrotic zone (arrows). **f** Photomicrograph (original magnification, $\times 400$; Ki-67) reveals the anaplastic ganglioglioma with a high proliferation index (18%)

Papillary glioneuronal tumor

PGNT was first recognized in the 2007 WHO classification of CNS tumors as a distinct tumor entity and was assigned as WHO grade I neoplasm in the 2016 update. Histopathologically, it is characterized by the presence of GFAP-positive small cuboidal cells lining hyalinized vascular pseudopapillae and synaptophysin and/or NeuNpositive interpapillary neuronal elements. They predominantly locate in the cerebral hemispheres adjacent to the ventricle suggesting a possible origin from the germinal zone of subependymal plate, or more superficially extending to the cortex and the white matter. They are usually seen as a well-defined contrast-enhancing cystic-solid mass, or pure solid or cystic. Solid components of the tumor are iso/hypointense on T1-weighted MRI, hyperintense on T2/FLAIR images and show diffuse, patchy or rimming enhancement. Cystic components may also show ring enhancement. The presence of prominent septations within the cystic component formed by long pseudopapillae traversing the cyst is a distinctive imaging feature (Fig. 4) [18, 19]. The SLC44A1 (solute carrier family 44, member 1)-PRKCA (protein kinase C alpha) fusion gene has been shown to be associated with PGNT and almost



Fig. 3 Desmoplastic infantile ganglioglioma in a 1-year-old male with seizure. **a** Axial T2-weighted image reveals a heterogeneous mixed signal intensity mass (arrow) in the left hippocampus. **b** Axial contrast-enhanced T1-weighted image reveals heterogeneous intense (arrow) and slight enhancement (arrowhead). There is involvement of the superficial cerebral cortex and leptomeninges with attachment to the dura—a distinctive imaging feature—(arrow) without surrounding edema. **c** Photomicrograph (original magnification, $\times 200$;

pathognomonic of this diagnosis [20]. The main differential diagnosis includes ganglioglioma.

Rosette-forming glioneuronal tumor

RGNTs have been recently identified as an unusual variant of MNGTs, and they were first categorized as a novel tumor of the fourth ventricle in the 2007 WHO classification of CNS tumors. This slow growing WHO grade I tumor occurs typically in the midline of the posterior fossa and is commonly located in the fourth ventricle, but rare locations such as cerebellar hemispheres, thalamus and pineal regions, optic chiasma and spinal cord may exist. The characteristic histopathologic appearance is neurocytic rosettes/ perivascular pseudorosettes and glial elements that resemble a pilocytic astrocytoma. Given their location, most of them present with symptoms of obstructive hydrocephalus, headache, and ataxia. They are usually well-defined solidcystic tumors, but can be entirely solid or cystic on imaging. Peripheral heterogeneous enhancement is common on contrast-enhanced studies (Fig. 5). There is no evidence of hematoxylin–eosin stain) reveals fibroblast like spindle cells (yellow star) intermixed with predominant neoplastic astrocytes and neuronal component (black star). **d** Photomicrograph (original magnification, \times 100; Reticulin) reveals the prominent desmoplastic component (red star). **e** Photomicrograph (original magnification, \times 200; GFAP) reveals neoplastic astrocytes arranged in fascicles (red arrow). **f** Right photomicrograph (original magnification, \times 400; synaptophysin) reveals scattered neoplastic ganglion cells (black arrows)

restricted diffusion on diffusion-weighted imaging. On magnetic resonance spectroscopy, they usually show a slightly elevated choline value and reduced *N*-acetylaspartate (NAA) value, without lipid and lactate peaks. Intratumoral hemorrhage is frequent. Cerebrospinal fluid dissemination is a feature of the tumor [21, 22]. The molecular features of RGNTs have not yet been well elucidated [22]. The differential diagnosis may include dysembryoplastic neuroepithelial tumor, pilocytic astrocytoma, medulloblastoma, ependymoma, choroid plexus papilloma, embryonal tumor with multilayered rosettes, and metastases.

Primary diffuse leptomeningeal glioneuronal tumor

PDL-GNT is a very rare and only recently described tumor without assigning a grade. Histologically, they are composed of sheets of monotonous rounded glial cells similar to oligodendroglioma with an additional neuronal component. This morphology is commonly combined with *BRAF* fusions and deletions of chromosome arm 1p, either alone



Fig. 4 Papillary glioneuronal tumors in a 32-year-old female with headache (**a**–**c**), and in a 17-year-old male with headache (**d**, **e**). **a** Axial FLAIR image reveals a hyperintense mass (arrow) adjacent to the left trigon. **b** Axial contrast-enhanced T1-weighted MR image reveals an intense nodular enhancement inside the tumor (arrow) with an unenhancing cystic component (arrowhead). **c** Photomicrograph (original magnification, ×400; hematoxylin–eosin stain) reveals a biphasic tumor characterized by hyalinized vascular pseudopapillary structures surrounded by a single layer of glial cells and inter-

papillary gangliocytic cells displaying round nuclei (arrow). **d** Axial T2-weighted MR image reveals a heterogeneous hyperintense solid (star)-cystic (diamond card) mass with surrounding severe edema in the right frontal lobe. **e** Axial contrast-enhanced T1-weighted MR image reveals homogeneous intense enhancement of the solid component and peripheral enhancement of the cystic part. There are prominent septations within the cystic component formed by long pseudopapillae traversing the cyst—a distinctive imaging feature



Fig.5 A rosette-forming glioneuronal tumor in a 12-year-old female with headache and vertigo. **a** Axial T2-weighted MR image (**a**) reveals a cystic midline mass in the vermis. **b** Sagittal contrast-enhanced T1-weighted MR image reveals peripheral enhancement of

the tumor (arrow). **c** Photomicrograph (original magnification, \times 400; hematoxylin–eosin stain) reveals tumor cells forming numerous neurocytic rosettes (arrows) with central pink neuropil-like cores. These tumor cells have uniform small round nuclei and clear cytoplasm

or occasionally combined with 19q. However, in contrast to oligodendrogliomas, these tumors do not have IDH mutations [1]. On MRI, the tumor presents as a diffuse, enhancing plaque-like subarachnoid tumor associated with cystic lesions, a distinctive feature, predominantly along the spinal cord, the basal cisterns and interhemispheric fissure of children and adolescents with or without obvious intraparenchymal tumor. Even though they are histologically benign, they can show aggressive behavior due to tendency of involvement of wide area of the leptomeninges and common development around the brainstem, resulting in difficulty in surgical intervention (Fig. 6) [1, 23]. The main differential



Fig. 6 Primary diffuse leptomeningeal glioneuronal tumor in a 22-year-old male who had been diagnosed as clear cell ependymoma presented with headache and seizure. Axial T2-weighted (a) and contrast-enhanced T1-weighted MR images (b) show a superficial cortical recurrent tumor with a homogeneous enhancing solid component (arrows). c Photomicrograph (original magnification, $\times 100$; hematoxylin–eosin stain) reveals oligodendroglial-like tumor cells (white arrows) invading leptomeninges (black arrows), consistent with the diagnosis of PDL-GNT. Cranial axial T2- weighted (d),

diagnosis of the PDL-GNT includes tuberculous meningitis, chronic infectious meningitis, subacute or acute meningitis, autoimmune and inflammatory diseases, and other tumors with secondary malignant dissemination such as primary DL-glioma/gliomatosis [23].

Conclusion

The MRI appearance of MNGTs is very variable, but a solid-cystic mass or solid mass with internal cystic components is the main common finding. Presence of enhancing or non-enhancing solid component with a usual non-enhancing cystic component on postcontrast imaging should raise the most likely diagnosis towards the WHO grade 1 MNGTs. Age, location, and some distinctive MRI features may further help the development of a differential diagnosis. The occurence in newborn infants with an attachment to the dura, located in the midline of the posterior fossa, located in the cerebral hemispheres adjacent to the ventricle are the distinctive features for DIG, RF-GNT, and PGNT, respectively. The presence of prominent septations within the cystic component is a distinctive MR

axial contrast-enhanced T1-weighted (e), and cervical spine (f) sagittal contrast-enhanced T1-weighted MR images obtained 15 months after the surgical removal of the tumor show repeated superficial tumor recurrence with hemorrhagic cystic components (arrowheads and star), enhancing solid components (arrows) and spinal leptomeningeal metastases (arrows). This patient received surgical resection for spinal leptomeningeal metastases, and gamma-knife surgery treatment followed by surgical resection for cranial recurrence tumor, and still in a follow-up period

imaging feature for PGNT. Enhancing plaque-like subarachnoid tumor associated with cystic lesions is a unique MRI finding for DLGNT. Familiarity with the common and distinctive imaging findings in these rare tumors may improve diagnostic accuracy and patient management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures in this study were in accordance with national and international ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the review.

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