

Ganglioglioma and gangliocytoma: a review for pathologists

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Ganglioglioma and gangliocytoma are rare, predominantly low-grade neuroepithelial tumors that commonly present with epilepsy in children and young adults. Advances in molecular profiling have improved understanding of their pathogenesis, highlighting key roles for the mitogen-activated protein kinase/ERK signaling pathway. Diagnosis relies on a combination of clinical, radiologic, and histopathologic features, with complete surgical resection offering the best clinical outcomes. This review summarizes current knowledge on their epidemiology, etiology, clinical presentation, imaging characteristics, pathology, treatment strategies, and prognosis.

Keywords: Ganglioglioma; Seizures; Epilepsy; Neuropathology; Proto-oncogene proteins B-raf

INTRODUCTION

Ganglioglioma and gangliocytoma are rare, low-grade central nervous system (CNS) tumors that primarily affect children and young adults. Patients with these lesions often present with seizures, particularly when located in the temporal lobe. Gangliogliomas are more frequently encountered and are recognized as a leading cause of epilepsy-associated brain tumors in both pediatric and adult populations [1-3]. Gangliocytomas, while less common, share many clinical and histopathological features with gangliogliomas. Despite their relative rarity, these tumors are clinically significant due to their epileptogenic potential and generally favorable outcomes following appropriate management. This review provides a structured overview of gangliogliomas and gangliocytomas, addressing key aspects of their epidemiology, pathogenesis, clinical presentation, neuroimaging characteristics, histopathologic features, molecular properties, therapeutic approaches, and prognostic implications.

EPIDEMIOLOGY

Gangliogliomas have an estimated global incidence of 0.186 cases per 100,000 population [4]. They exhibit a slight male predominance [4-6] and account for approximately 0.4% of all CNS tumors and 1%–7% of pediatric CNS neoplasms [7,8]. These tumors predominantly affect children and young adults, with the majority of cases diagnosed before the age of 20 and a median age of 12 years, although they can occasionally present in older individuals [1]. In epilepsy surgical series, gangliogliomas represent the most frequent histopathological diagnosis among brain tumors associated with intractable epilepsy in adult and pediatric patients, accounting for approximately 40% of such cases [1-3]. Gangliocytomas are much less common, with an incidence of 0.016 cases per 100,000 population [4]. In the context of epilepsy-related surgical resections, gangliocytomas account for approximately 1%–3% of cases [1,9].

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ETIOLOGY AND PATHOPHYSIOLOGY

Gangliogliomas result from genetic alterations that activate the mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK) signaling cascade, including proteins such as MEK, ERK, RSK1, RHEB, and MSK1, which collectively promote aberrant cell proliferation and oncogenesis [10,11]. Although most gangliogliomas occur sporadically, a minority are associated with neurofibromatosis type 1 (NF1) [12]. In addition, gangliogliomas may coexist with adjacent focal cortical dysplasia (FCD), particularly FCD type III [13]. While molecular data regarding gangliocytomas remain limited, their overlapping histopathologic and clinical features with gangliogliomas suggest a shared pathophysiologic basis. Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) associated with Cowden syndrome is considered a distinct pathologic entity and will not be included in the discussion here (for comprehensive review, see Alanazi et al. [14]). To date, no definitive environmental risk factors have been identified for either tumor type.

CLINICAL FEATURES

The clinical presentation of gangliogliomas and gangliocytomas is closely linked to their anatomical location, with lesions in the temporal lobe of the cerebrum frequently associated with seizures and epilepsy. Studies have consistently reported epileptic crises as the most common initial manifestation [5,15], with an average symptom duration of 7.4 years prior to diagnosis [16]. Additional symptoms may include headache, hydrocephalus, and developmental disorders [17].

RADIOLOGY

Gangliogliomas are typically characterized on brain imaging as circumscribed, cystic masses with an avidly enhancing mural nodule. On magnetic resonance imaging, the cystic component is classically T1 hypointense and T2 hyperintense [18,19]. These tumors often exhibit minimal to no surrounding edema and lack significant mass effect, contributing to their well-delineated appearance. Calcifications are common, present in approximately 40%–50% of cases, and enhancement patterns can vary, especially in less typical presentations where the lesion may appear as a solid mass. The most frequent location is the temporal lobe, followed by the frontal, occipital, and parietal lobes; less commonly, gangliogliomas may arise in the cere-

bellum, brainstem, or spinal cord [5,18]. Additionally, areas of cortical dysplasia are often observed adjacent to the tumor [18].

PATHOLOGIC FINDINGS

Gross findings

Gangliogliomas and gangliocytomas are typically grossly well-demarcated lesions, often presenting as variably solid and cystic masses. These tumors characteristically lack areas of hemorrhage and necrosis.

Frozen section findings

Intraoperative frozen section evaluation reveals a similarly well-circumscribed mass; however, a diffuse growth pattern involving adjacent brain parenchyma may also be observed, especially at the tumor edge. On a frozen preparation, gangliogliomas exhibit a biphasic cellular composition, comprising dysplastic ganglioid cells intermixed with atypical glial elements (Fig. 1A–C), whereas gangliocytomas are predominantly composed of neuron-like cells. Additional features include variable microcalcifications (Fig. 1C), perivascular lymphocytic infiltrates, and eosinophilic granular bodies (Fig. 1B). Squash preparations of gangliogliomas demonstrate glial cells with fine, piloid-like processes and dysplastic ganglioid cells embedded within a vascular network of thin- to thick-walled vessels (Fig. 1D–F) [20].

Microscopic findings

Histologically, ganglioglioma is a biphasic tumor characterized by a variable admixture of dysmorphic ganglion-like cells and atypical glial elements, generally well-demarcated from the adjacent brain. A representative case with classic histopathologic features is presented in Fig. 2. Microscopically, the dysplastic ganglion-like cells exhibit several hallmark features, including binucleation, cytomegaly with ballooned cytoplasm, and peripheral accumulation of Nissl substance. These cells often form abnormal clusters, referred to as "kissing neurons," and lack an organized cytoarchitecture (Fig. 2C) [5,15]. The glial component comprises hyperchromatic, moderately enlarged cells that may resemble those seen in fibrillary astrocytomas, pilocytic astrocytomas, or oligodendrogliomas [5,21]. Eosinophilic granular bodies are more frequently observed than Rosenthal fibers, and additional features include dystrophic calcifications, perivascular lymphoid infiltrates, and a prominent capillary network. Less common histologic findings include prominent

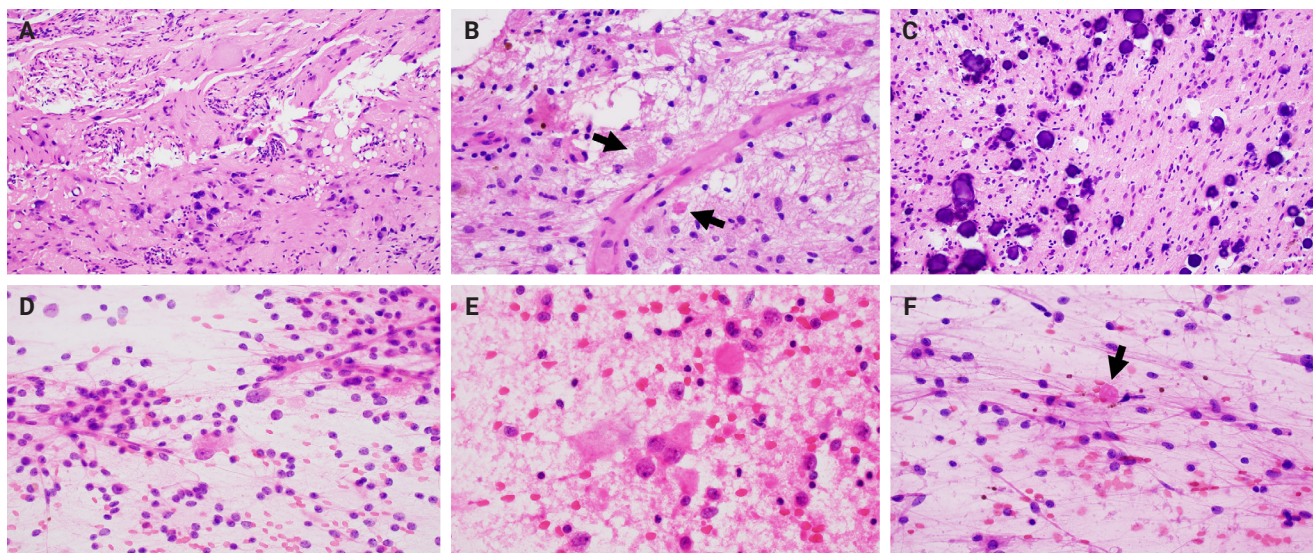


Fig. 1. Ganglioglioma/gangliocytoma features at intraoperative consultation. (A–C) Frozen sections reveal moderately hypercellular tissue composed of an admixture of atypical and abnormally aggregated glial and ganglioid elements. The background may have piloid elements, eosinophilic granular bodies (EGBs, arrows), and/or microcalcifications. (D–F) Smear preparation reveals a monomorphic population of enlarged glial cells with round to elongated nuclei and variably hyperchromatic chromatin and thin, fibrillary cellular processes. Dysplastic ganglioid cells may be encountered, including cells with abnormally dispersed chromatin and/or binucleation. Careful examination can also reveal EGBs (arrow).

piloid histology, perinuclear halos (i.e., “oligo-like” morphology), and nuclear pleomorphism (Fig. 3). Mitotic activity is typically low to absent [5]. Microscopic infiltration along the tumor edge may be present despite its generally compact growth pattern (Fig. 2B) [1]. Rarely, gangliogliomas may exhibit anaplastic features such as increased mitotic figures, microvascular proliferation, and necrosis. However, the designation “anaplastic ganglioglioma” should be applied cautiously, particularly in the absence of comprehensive molecular characterization to exclude other high-grade gliomas with similar histomorphology, including pleomorphic xanthoastrocytoma [22–24]. In contrast to gangliogliomas, gangliocytomas are composed almost exclusively of large, dysmorphic ganglion cells and lack the neoplastic glial component that characterizes the former; a representative case is presented in Fig. 4.

Immunohistochemistry

Ganglion-like cells within gangliogliomas and gangliocytomas express neural markers such as MAP2, neurofilament, and synaptophysin (Figs. 2D, E, 4E). They often lack NeuN immunoreactivity, which is expressed in adjacent non-neoplastic neurons. The glial component of these tumors demonstrates positivity for glial fibrillary acidic protein and Olig2 (Fig. 2F, G) [25].

CD34 expression, either diffuse or patchy in an arborescent pattern, is frequently observed within the tumor or adjacent cortex (Fig. 2H) [26] and may serve as a supportive diagnostic feature in diagnostically challenging cases. Proliferative activity is generally low, with Ki67 indices typically less than 5% [27]. A *BRAF* V600E mutation-specific antibody is available and often positive in dysplastic ganglion-like cells [28]. These tumors are negative for *IDH1* (isocitrate dehydrogenase type 1) R132H and display retained nuclear ATRX expression, distinguishing them from other gliomas with IDH mutations.

MOLECULAR AND CYTOGENETICS

Gangliogliomas exhibit a diverse range of molecular alterations, with the *BRAF* V600E mutation being the most common, identified in approximately 10%–60% of cases. Its prevalence is highest in cortical tumors and lowest in spinal cord lesions [21,29,30]. Additional genetic abnormalities include other *BRAF* mutations, *BRAF* gene fusions (most frequently *KIAA1549::BRAF*), *KRAS* activating mutations, and *NF1* inactivating mutations or deletions [31]. The *BRAF* V600E mutation can be detected via immunohistochemistry or molecular techniques such as gene sequencing, including droplet digital polymerase chain reaction

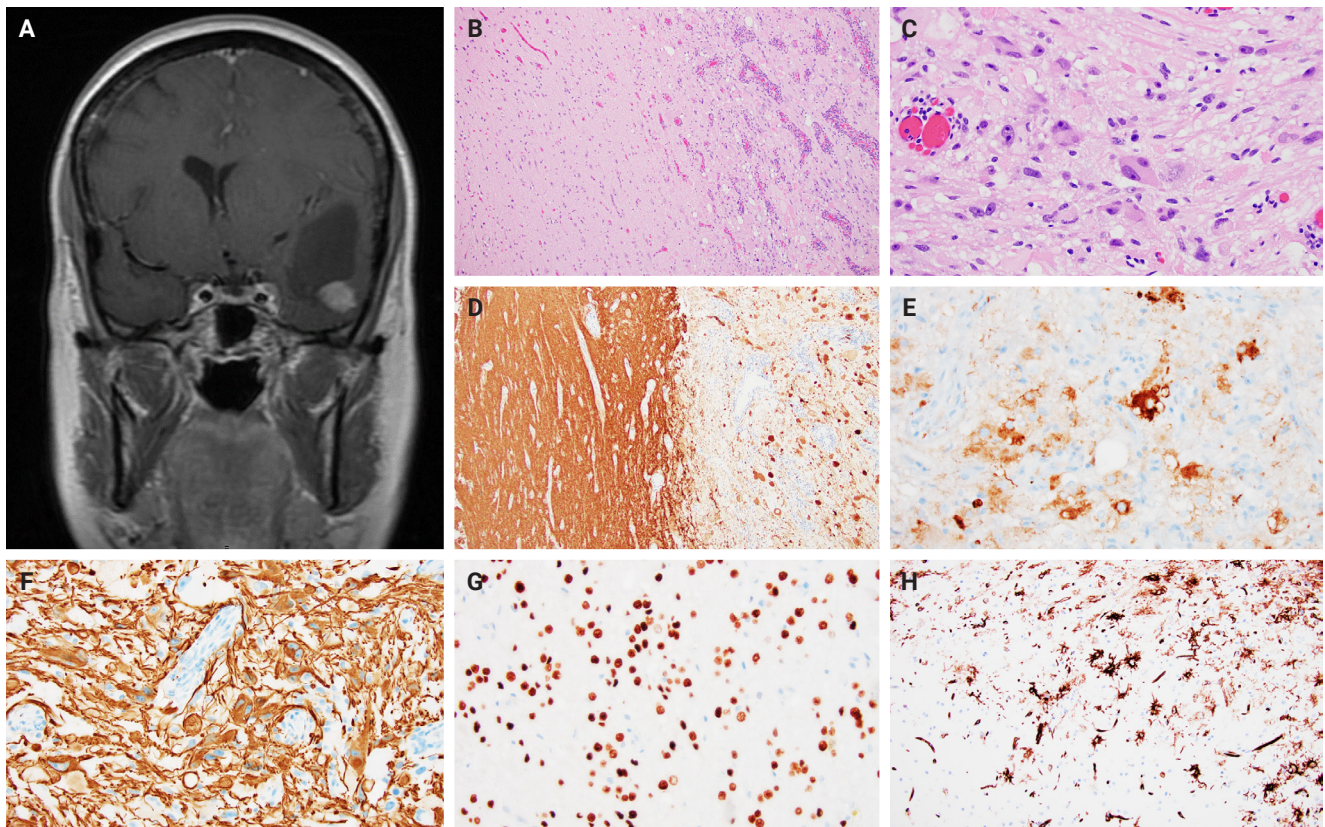


Fig. 2. Representative findings in ganglioglioma. (A) Coronal magnetic resonance imaging reveals a cystic lesion with an enhancing mural nodule located in the left temporal lobe. (B) Low magnification hematoxylin and eosin (H&E) reveals a mildly hypercellular tumor (image right), well-demarcated from the adjacent brain (image left). (C) High magnification H&E reveals a biphasic tumor composed of an admixture of mildly atypical and hyperchromatic glial cells and multinucleated ganglioid cells. Immunohistochemistry reveals synaptophysin-positive ganglioid cells (D, E) and glial cells that are positive for glial fibrillary acidic protein (F) and Olig2 (G). CD34 immunostain highlights ramified elements within and adjacent to the tumor (H).

[28]. In cases negative for *BRAF* V600E, broader molecular testing using next-generation sequencing or gene fusion panels is recommended to identify other MAPK pathway-activating alterations [31]. Furthermore, gangliogliomas demonstrate a distinct genome-wide DNA methylation profile, which can aid in diagnosis, particularly in histologically ambiguous cases [32]. However, despite the high accuracy of DNA methylation profiling, gangliogliomas may remain difficult to classify, comprising 8.7% of tumors lacking confident methylation-based classification [33]. Gangliocytomas currently lack a defined molecular signature, and no characteristic genetic profile has been published to date.

DIFFERENTIAL DIAGNOSIS

Distinguishing the various cortical-based neuroepithelial lesions

requires careful integration of clinical, radiologic, histopathologic, immunohistochemical, and molecular features. FCD typically lacks well-circumscribed tumor architecture and retains NeuN immunoreactivity in dysplastic neurons, with genetic alterations often involving the phosphoinositide 3-kinase/AKT/mammalian target of rapamycin pathway. The presence of MAPK activating alterations (such as *BRAF* V600E) can be helpful to exclude this entity [13,34]. In contrast, infiltrating low-grade gliomas demonstrate entrapped NeuN-positive neurons within a neoplastic glial population and frequently harbor *IDH1/IDH2* mutations. In adolescents and young adults, tumors with diffuse architecture may harbor MAPK pathway alterations (i.e., “Diffuse low-grade glioma, MAPK pathway-altered”), but dysplastic ganglion cells are absent. Polymorphous low-grade neuroepithelial tumor of youth (PLNTY) is characterized by *FGFR2* (fibroblast growth factor receptor 2)/*FGFR3* (fibroblast growth

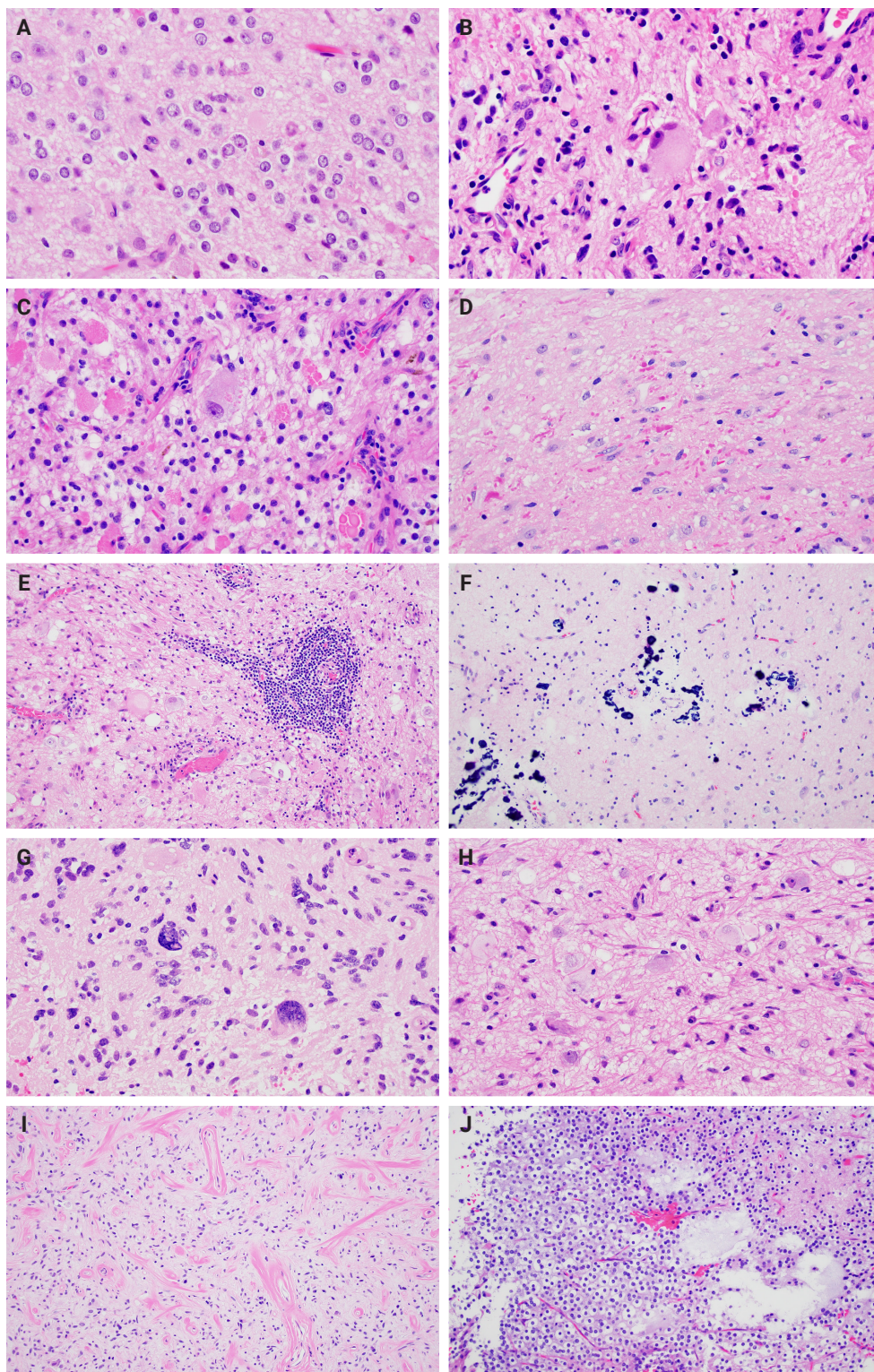


Fig. 3. Additional histopathologic findings in ganglioglioma. In some cases, the glial elements are much more prominent (A), and dysplastic ganglioid cells are only focally present (B). Eosinophilic granular bodies can be multiple and prominent (C), whereas Rosenthal fibers are not commonly encountered (D). Perivascular lymphocytic cuffing (E) and microcalcifications (F) are found in many cases. Some tumors may demonstrate nuclear pleomorphism (G), extensive piloid background (H), prominent hyalinized vasculature (I), and/or tumor cells with round nuclei and perinuclear halos ("oligo-like") (J).

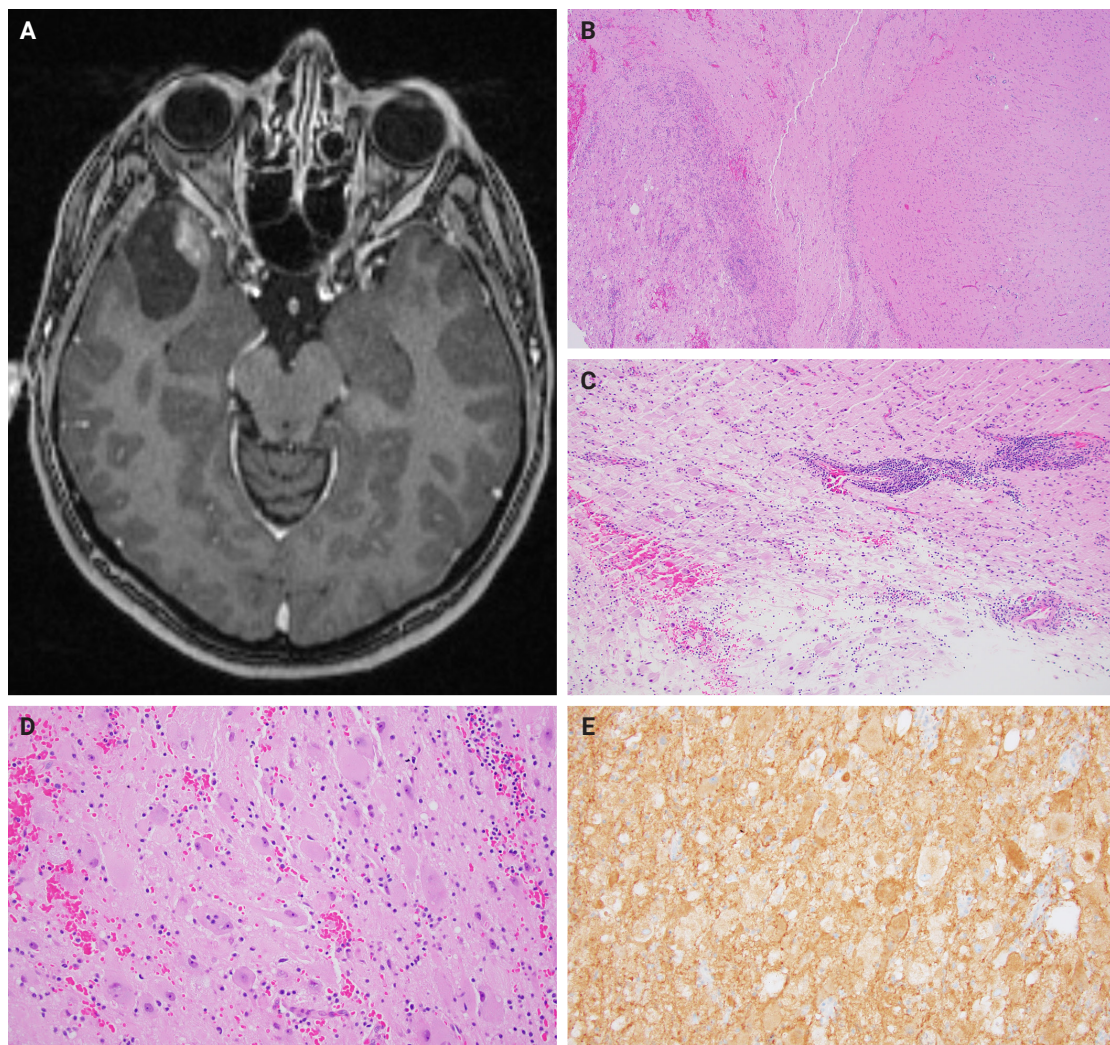


Fig. 4. Representative findings in gangliocytoma. (A) Sagittal magnetic resonance imaging reveals a solid and cystic mass within the anterior right temporal lobe with an enhancing mural nodule. (B) Low magnification hematoxylin and eosin (H&E) reveals a mildly hypercellular tumor (image left), well-demarcated from the adjacent brain (image right). (C) There are areas with prominent perivascular lymphocytic cuffs. (D) High magnification H&E reveals a tumor composed nearly entirely of dysplastic ganglioid cells with abundant eosinophilic cytoplasm and occasional bi/multinucleated forms. (E) Tumor cells are uniformly immune-positive for synaptophysin.

factor receptor 3) fusions or *BRAF* V600E mutations, diffuse CD34 positivity, and focally infiltrative oligodendroglial-like components [35], though significant overlap may exist between PLNTY and ganglioglioma. Dysembryoplastic neuroepithelial tumors show multinodular architecture with floating neurons in a mucinous matrix and frequent *FGFR1* alterations and typically lack CD34 expression [36]. Multinodular vacuolating neural tumors also exhibit multinodular growth, prominent vacuolization, and Olig2-positive neuronal cells, but lack dysmorphic neurons and CD34 staining [37]. Pleomorphic xanthoastrocytoma presents with xanthomatous cells, nuclear pleomorphism,

and a reticulin-rich stroma, often harboring both *BRAF* V600E mutation and *CDKN2A/CDKN2B* homozygous deletion [38]. Desmoplastic infantile ganglioglioma is distinguished by its large size in infantile patients and a markedly desmoplastic stroma [39]. Hypothalamic hamartomas, pathognomonic for Pallister-Hall syndrome, are congenital lesions presenting with gelastic seizures and *GLI3* mutations [40,41]. Lastly, dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) is associated with Cowden syndrome and *PTEN* loss and lacks *MAPK* alterations typical of gangliogliomas [42].

TREATMENT AND PROGNOSIS

The management of gangliogliomas and gangliocytomas centers on surgical intervention, with complete resection representing the cornerstone of treatment and the most significant prognostic factor, particularly for gangliogliomas [7]. Gangliogliomas are low-grade tumors associated with excellent long-term outcomes, with reported 15-year overall survival rates ranging from 83% to 94%. In cases that are progressive, recurrent, or refractory, targeted therapies such as RAF or MEK inhibitors have shown potential benefit, although their clinical utility remains under investigation [43-46]. Emerging molecular data suggest that certain genetic profiles, including co-occurrence of *BRAF* V600E with *CDKN2A/CDKN2B* homozygous deletions or midline tumors harboring both *BRAF* V600E and *H3* K27M mutations, may be associated with poorer outcomes [31,47-49]. Another report suggests tumors with *PTPN11/KRAS/NF1* and other MAPK pathway alterations may show atypical histologic features and adverse clinical outcomes [50]. Similarly, gangliocytomas are benign lesions with excellent long-term survival, and to date, specific prognostic markers have not been identified.

CONCLUSION

Gangliogliomas and gangliocytomas represent a distinct subset of neuroepithelial tumors with unique clinical, radiologic, and pathologic features. While generally associated with favorable outcomes, particularly when amenable to complete surgical resection, their biological behavior can vary depending on underlying molecular alterations and anatomical location. Advances in molecular profiling have enhanced our understanding of their pathogenesis, revealing key roles for MAPK/ERK signaling pathway abnormalities. These findings have prompted exploration of targeted therapies in select cases, though their effectiveness and long-term outcomes remain uncertain. Through this review, we have highlighted the current knowledge surrounding these tumors, aiming to support clinicians and researchers in the comprehensive evaluation and management of gangliogliomas and gangliocytomas.

Ethics Statement

Not applicable.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were

generated or analyzed during the study.

Code Availability

Not applicable.

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Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

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