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Review

Ependymomas

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Summary

Ependymal neoplasms are a heterogenous group of neoplasms arising from the progenitors of the cells lining the ventricular system and the spinal central canal. During the last few years, significant novel data concerning oncogenesis, molecular characteristics and clinical correlations of these tumours have been collected, with a strong relevance for their pathological classification. The recently published 5th edition of WHO Classification of Central Nervous System Tumours integrates this novel knowledge and represents a substantial update compared to the previous edition. Concerning supratentorial ependymomas, the previous *RELA* fusion-positive ependymoma has been renamed into *ZFTA* fusion-positive and the novel *YAP1* fusion-positive ependymoma subtype has been added. Posterior fossa ependymomas should now be allocated either to the Type A or Type B subtypes based on molecular profiling or using the H3 K27me3 immunohistochemical surrogate. Regarding spinal ependymomas, a novel subtype has been added based on a distinctive molecular trait, presence of *MYCN* amplification, and on the unfavourable outcome. Finally, myxopapillary ependymoma is now classified as a grade 2 tumour in accordance with its overall prognosis which mirrors that of conventional spinal ependymomas. The aim of this review is to present these changes and summarize the current diagnostic framework of ependymal tumours, according to the most recent updates.

Key words: ependymoma, myxopapillary ependymoma, subependymoma, WHO classification, molecular pathology

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Introduction

Ependymal tumours are neuroepithelial neoplasms of the central nervous system arising from progenitors of the cells lining the ventricular system and the spinal central canal. Overall, these rare tumours account for 2-3% of all primary CNS neoplasms and can develop along the whole neuroaxis [1].

The latest CBTRUS report (which analysed data from 2014 to 2018) [1] described an overall incidence of 0.42 cases per 100 000 person-years with higher rates among males and older adults (40+), but incidences of the specific subtypes vary greatly according to age. Most of the paediatric ependymomas occur intracranially (about 90%), while spinal tumours are more common among adults (about 60%) [2].

Safest maximal surgical resection is the mainstay treatment for both children and adults, possibly followed by conformal radiotherapy according to patient's age, extent of resection and the specific diagnosis. So far, chemotherapy displayed limited efficacy in ependymoma and is under evaluation in ongoing clinical trials [3].

Histological diagnosis is mainly based on evaluation of morphological features on haematoxylin/eosin-stained slides and immunohistochemistry. Considered together, ependymal neoplasms are usually diffusely

positive for glial fibrillary acidic protein (GFAP) and S100. Also, epithelial membrane antigen (EMA) staining is detected in most cases with a dot-like or ring-like cytoplasmic pattern [4]. Conversely, OLIG2 is usually negative, but intermixed positive reactive glial cells can be observed. Cerebrospinal fluid (CSF) cytological examination is also warranted for initial disease staging and when tumour dissemination is suspected, based on clinical and/or radiological findings.

Except for recurrent chromosomal aneuploidies, no specific biological features were identified in ependymoma for decades. During the last years, specific, primary genetic alterations, associated with distinct tumour subtypes, have been described. These ependymoma subtypes were originally identified by DNA methylation profiling techniques and subsequently by identification of the associated specific genetic alterations. DNA methylation profiling nowadays represents an important ancillary method, although not yet IVDR-ready, supporting pathological diagnosis of many brain tumour entities including ependymomas [5]. Based on these developments, the classification of ependymal tumours has been substantially revised in the 5th edition of the WHO Classification of Tumours of the CNS which was published in 2021. Ependymomas are now classified according to a combination of histopathological and molecular features across three anatomic compartments (supratentorial, posterior fossa (PF), and spinal) as it will be described in the following sections [6]. Along with this molecular stratification, morphological subtyping (e.g. papillary, clear cell, and tanycytic patterns) and grading should still be performed, although the prognostic significance of these features has been debated. Two further specific entities have been confirmed based on specific morphology and molecular profile: myxopapillary ependymoma and subependymoma.

Finally, genetic tumour predisposition syndromes can also play a role in ependymoma development. Spinal ependymomas, but not intracranial ones, have been associated with constitutional genetic syndromes, mainly Neurofibromatosis type 2 (OMIN n° 101000).

The aim of this review is to report the recent innovations in the diagnostic classification and molecular profiling of ependymal tumours, including their subtypes, the potential differential diagnoses, and diagnostic pitfalls.

Ependymoma

The main macroscopic and microscopic features of ependymomas are similar across the different anatomic sites. Macroscopically, ependymomas usually appear as soft or spongy grey-whitish lesions, possibly with gritty consistency due to calcifications. Microscopically, the interface between the tumour and the adjacent non-neoplastic tissue is usually sharp, but a more infiltrative attitude can be observed, especially in recurrent cases. Perivascular pseudorosettes are a cornerstone morphological marker (Fig. 1), while true ependymal rosettes (i.e. neoplastic cells around a lumen representing an ependymal channel) are rarer [7]. Immunohistochemical profile overlaps within ependymal tumours in general, as previously described.

Supratentorial ependymomas as well as posterior and spinal ependymomas are classified as grade 2 or 3 neoplasms, according to histological features (mitotic figures, microvascular proliferations and necrosis), although the association between histological grading and outcome is inconsistent. Moreover, similarly to other tumour entities, grade-specific terms (e.g. “anaplastic ependymoma”) have been removed in the 2021 WHO Classification.

Supratentorial Ependymoma

Supratentorial ependymomas most commonly arise from radial glia within frontal or parietal lobes [8]. They represent one-third of all intracranial ependymomas [9] and are more frequent in children showing a decreasing frequency according to age (from about to 40% in children to about 10% in adults > 45 years) [10].

Along with histological classification, molecular evaluation should be performed to assess the presence of *ZFTA* or *YAP1* gene fusions (Fig. 2). This can be done with multiple diagnostic tests aimed at detecting genetic rearrangements like interphase FISH, RT-PCR, and RNA NGS [11,12]. The choice of the specific assay depends on laboratory facilities, available expertise and specific setting (e.g. routine diagnostics, referral evaluation or research). However, it should be noted that *ZFTA* or *YAP1* gene fusions are not detected in 17-30% of supratentorial ependymomas: in these cases, it is suggested to use the suffix “NEC” (Not Elsewhere Classified) if alternative genetic alterations are detected, while the suffix “NOS” (Not Otherwise Specified) is used when genetic analysis was uninformative or unfeasible [13]. DNA methylation profiling enables to ascertain the specific supratentorial ependymoma subtype, but the the clinical and prognostic significance of these multiple subgroups remains to be clarified. In agreement with this consideration, the WHO 2021 Classification does not provide specific grading criteria according to molecular features. Among potential differential diagnoses, tumours with *BCOR* internal tandem duplication (ITD) and *MN1*-altered astroblastomas should be considered and excluded through appropriate immunohistochemistry and molecular analyses [11,14].

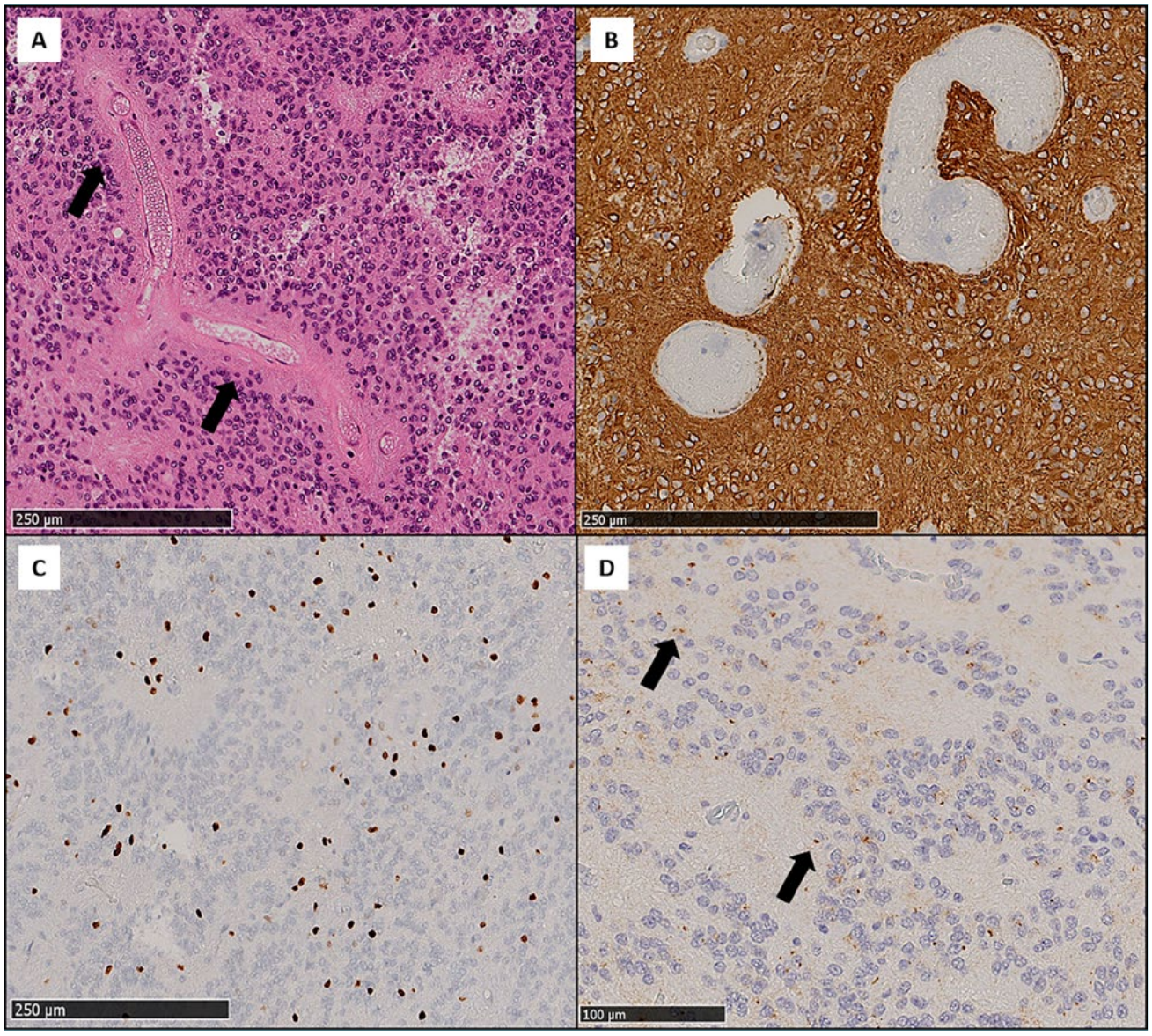

Figure 1. Example image of ependymoma morphological and immunohistochemical features. Figure 1A shows the characteristic hallmark of perivascular pseudorosettes (arrows, HE, original magnification: 100X), while the following images show positive staining for GFAP (1B, original magnification: 100X), negative OLIG2 (1C, original magnification: 100X) and dot-like EMA positivity (arrows, 1D, original magnification: 200X).

Supratentorial Ependymoma ZFTA fusion-positive

ZFTA gene rearrangements, usually with the *RELA* gene, are the most common molecular alteration within supratentorial ependymomas, occurring in 20-58% of these tumours among adults and 66-84% in children [11,15]. Multiple copy number variations can occur in *ZFTA* fusion-positive ependymomas (Fig. 3) and *ZFTA* rearrangements are usually due to chromothriptic events involving chromosome 11, i.e. events of massive chromosome fragmentation and abnormal reassembly that went unnoticed until recently, due to the limited resolution of conventional cytogenetics. The most frequent fusion partner gene is *RELA*, encoding the p65 subunit of NF-κB transcription factor complex: the aberrant fusion protein leads to a pathological activation of NF-κB signalling promoting oncogenic pathways [12,15].

Immunohistochemistry can help the identification of *ZFTA* fusion positive ependymomas since they

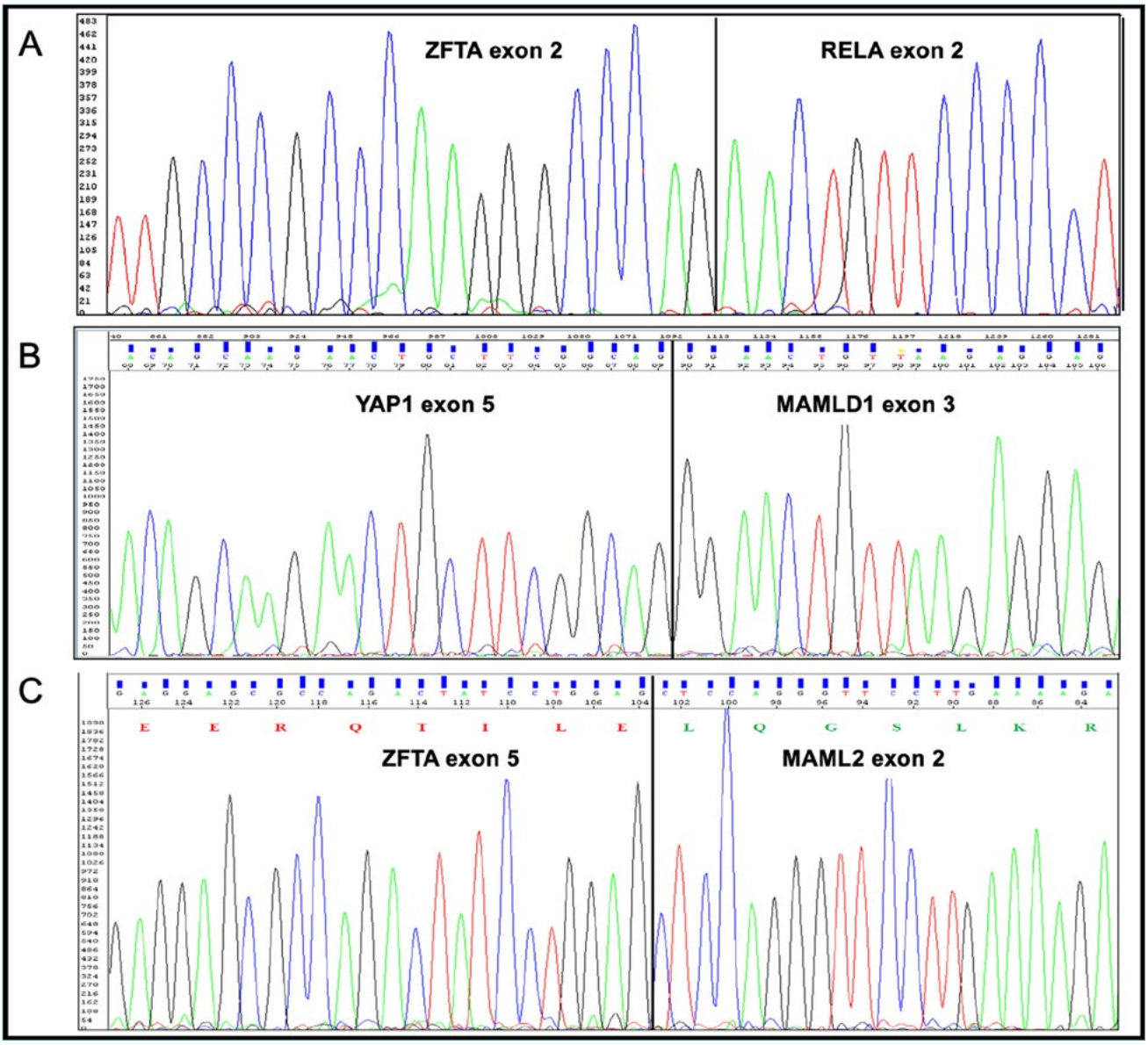

Figure 2. Sanger sequencing electropherograms of representative fusion transcripts detected in supratentorial ependymomas. Figure 2A: ZFTA-RELA, type 1; 2B: YAP1-MAMLD1; 2C: ZFTA-MAML2.

are usually positive for L1CAM (cytoplasm staining) (Fig. 4). Moreover, in cases harbouring the *ZFTA-RELA* rearrangement nuclear positivity for the p65 protein is also present [16]. Grading of *ZFTA*-fused supratentorial ependymomas is performed according to the previously mentioned histological features, but they are overall associated with a poorer outcome. Homozygous deletion of *CDKN2A/B* can also be present in a subgroup of these tumours, compromising cell cycle regulation and possibly negatively impacting prognosis [17,18].

Of note, tumours carrying *ZFTA* fusions with partners different from *RELA* appear to show a highly variable morphological spectrum, which includes features of pleomorphic xanthoastrocytoma, astroblastoma or sarcoma-like patterns. These tumours clustered into multiple subgroups according to their epigenetic profile and alternative *ZFTA* gene partners included *NCOA1/2*, *MAML2* and *MN1* [19].

Supratentorial Ependymoma YAP1 fusion-positive

A second, but rarer subgroup of supratentorial epend-

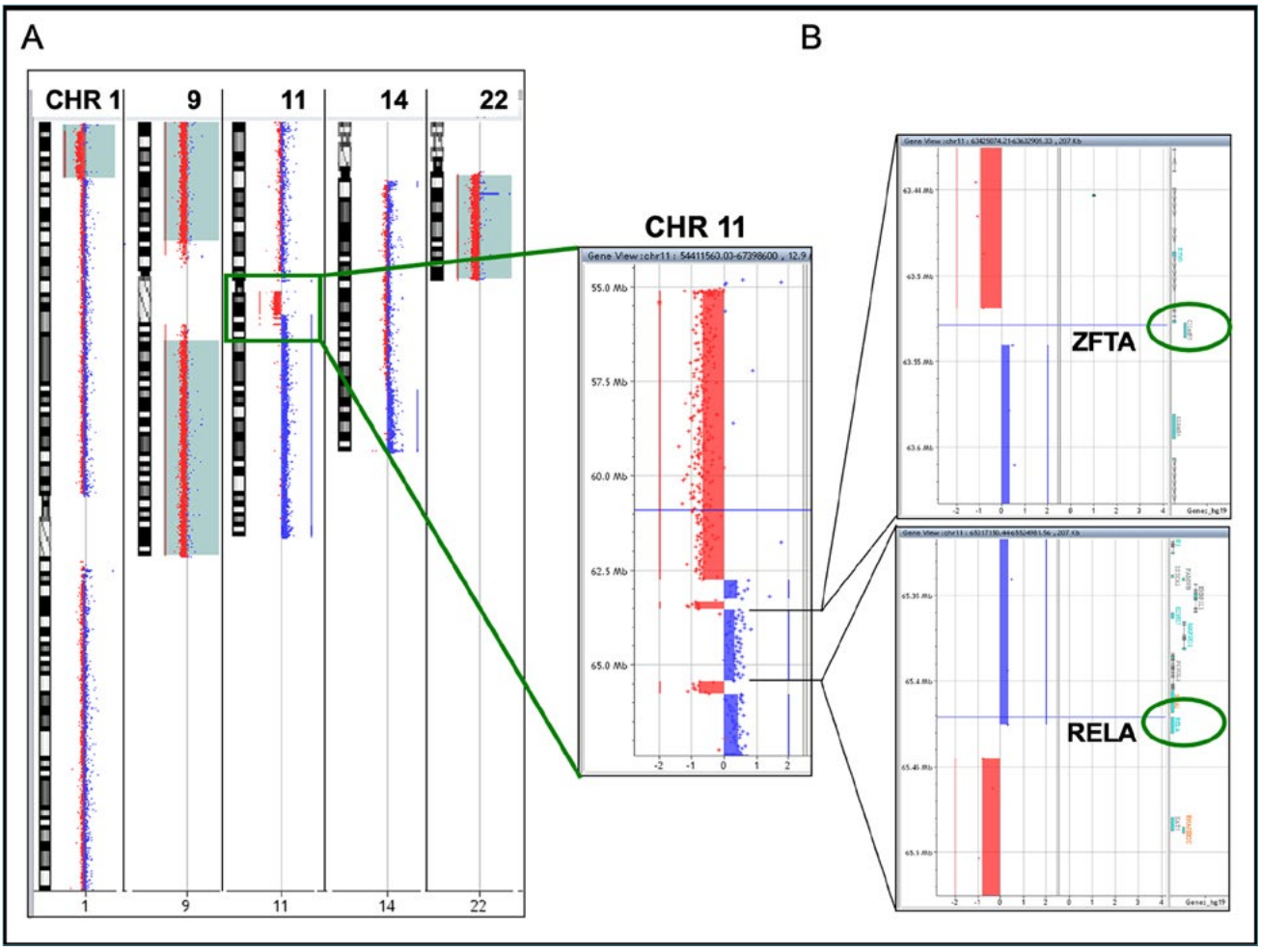

Figure 3. Copy number profiling of a supratentorial ependymoma with ZFTA-RELA fusion. Figure 3A shows multiple unbalanced chromosomes including 1p34p36 deletion, whole chromosomes 9 and 22 deletion, gain of 14q24q32 and multiple copy-number changes on chromosome 11. A zoom-in of chromosome 11 (3B) highlights multiple gains/losses with breakpoints spanning both ZFTA and RELA loci.

ymomas is characterised by the presence of the *YAP1* gene fusions. The most frequent rearrangement is with the *MAMLD1* gene, but different partners are possible. These tumours usually occur in young children, representing 6-7.4% of supratentorial ependymomas in the paediatric population with a prevalence in females (1:0.3) [20,21].

These ependymomas derive from radial glia cells and *YAP1-MAMLD1* fusion leverages its oncogenic activity through the recruitment of NFI and TEAD family members [22]. Immunohistochemical profile is similar to other ependymomas, but, differently from *ZFTA* fusion positive tumours, there is no expression of L1CAM or p65 and *YAP1*-fused supratentorial ependymomas are associated with a relatively favourable prognosis [11]. As reported for *ZFTA* gene fusions, identification of *YAP1* rearrangements can be achieved through multiple techniques including interphase FISH analysis and RNA NGS.

Posterior Fossa Ependymoma

Posterior fossa (PF) ependymomas develop within the fourth ventricle or in the cerebellopontine angle [23]. Pathogenesis of these tumours is complex and involves copy-number and epigenetic alterations, as demonstrated by alterations in DNA methylation pattern, loss of H3 p.K27me3 and EZHIP overexpression [24-26].

Analysis of DNA methylation profiling and DNA/RNA NGS data identified several subgroups of posterior

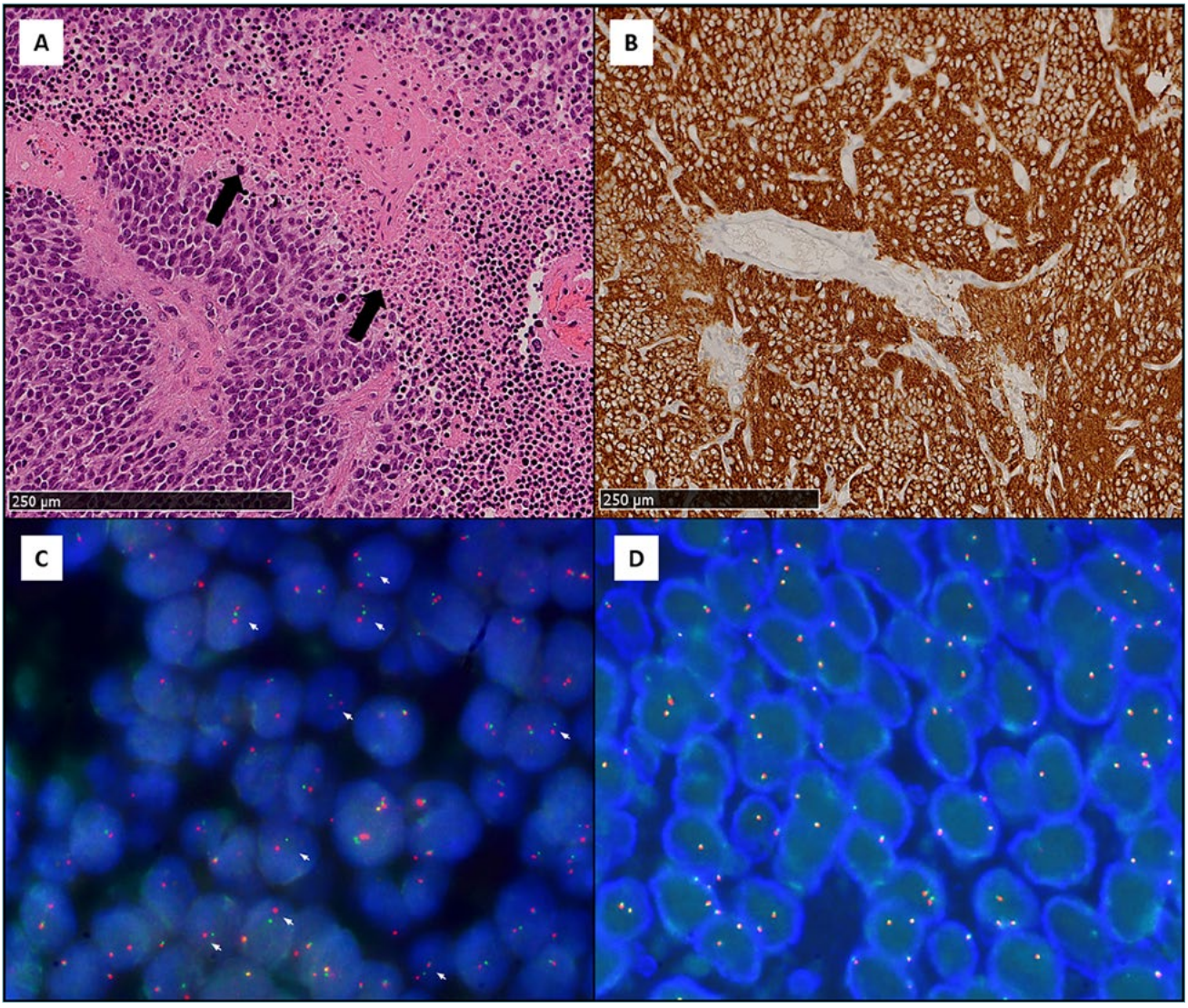

Figure 4. ZFTA fusion-positive ependymoma. Images showing the classical features of ependymoma as well as high grade traits like necrosis (arrows, 4A, HE, original magnification: 100X) and positive L1CAM immunohistochemistry (tumour harboured the ZFTA-RELA translocation) (4B, original magnification: 100X). Molecular status was investigated by FISH using break apart probes showing ZFTA rearrangement (arrows, 4C) and negative YAP1 (arrows, 4D).

fossa ependymomas; the two main subgroups, PFA and PFB, were consistently replicated in independent studies and are now incorporated in the 2021 WHO classification. Notably, evidence that PFB ependymomas display a more favourable course is accumulating. Immune staining for Histone H3 p.K27 trimethylation is an additional important marker for the diagnostic stratification of PF ependymomas into the two main subgroups PFA and PFB (Fig. 5), and represents in most instances a robust surrogate of DNA methylation profiling [20,27].

Posterior Fossa group A (PFA) Ependymoma

Posterior fossa group A (PFA) ependymomas usually occur in younger children (median age: 3 years) [20,23]: in this age group, the vast majority of PF ependymomas (95%) are PFA. This group seems to harbour a poorer prognosis than PFB and chromosome 1q gain is an adverse prognostic indicator, while the prognostic significance of mutations of genes coding for the Histone H3 protein and EZHIP is unknown [25,28].

These tumours probably arise from undifferentiated glial precursor cells in the developing hindbrain. Epigenetic alterations seem to be the main oncogenic driv-

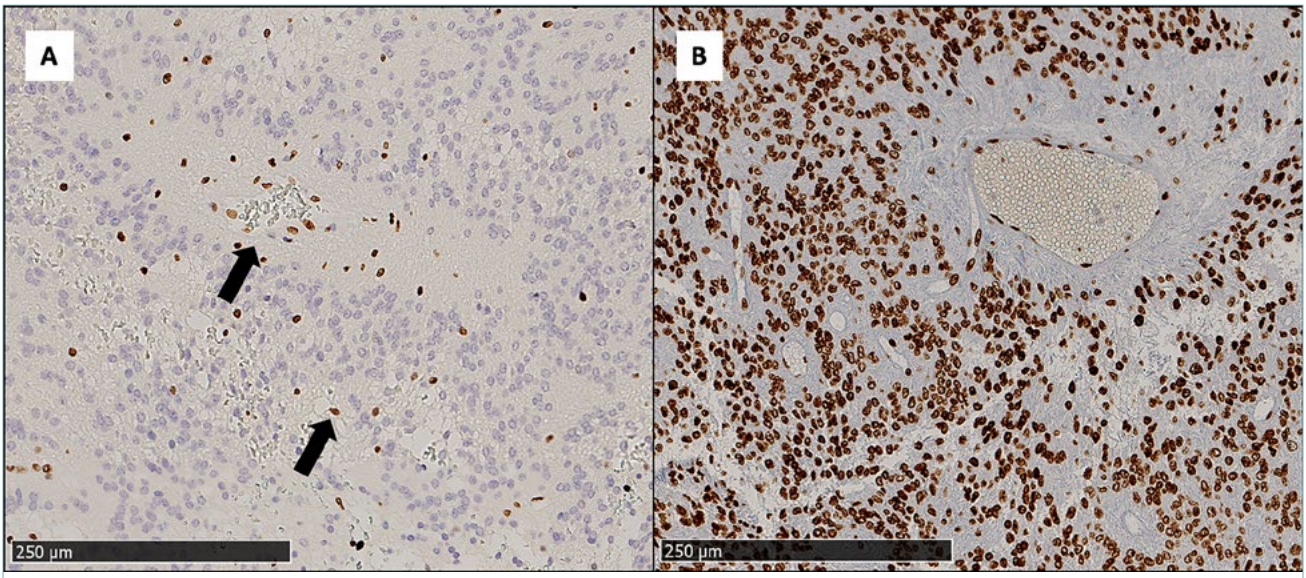

Figure 5. Immunohistochemical staining for H3 K27me3. Figure 5A shows a loss of H3 K28 trimethylation consistent with a PFA ependymoma Of note, expression by endothelial cells is present as expected (arrows, original magnification: 100X). Figure 5B shows a PFB ependymoma with retained expression of H3 K28me3 (original magnification: 100X).

ers of these tumours, since PFA ependymomas show a characteristic hypermethylation of CpG islands and global DNA hypomethylation [29] that converge to the inhibition of Polycomb Repressive Complex 2 (PRC2) lysine methyltransferase activity. The reduction of H3 p.K27 trimethylation is associated with overexpression of EZHIP [30] which mimics the oncohistone by binding the methyltransferase EZH2 and inhibiting the function of PRC2 [30,31]. Among PFA ependymomas, 9% exhibit EZHIP mutations and about 4% harbour the H3 p.K27M mutation, which are mutually exclusive and undetected in other ependymoma subgroups [25].

These molecular characteristics are diagnostically relevant, since the reduction of Histone H3 p.K27me3 can be evaluated by immunohistochemistry and posterior fossa ependymomas with less than 80% positive cells (nuclear positivity) should be classified in the PFA group (Fig. 5A) [14,27]. Endothelial cells can be used as positive internal control and show a nuclear positive staining. Therefore, H3 p.K27me3 analysis by immunohistochemistry allows diagnostic stratification of PF ependymomas into the two main subgroups PFA and PFB, representing a first-tier test, complemented with methylation profiling in inconclusive cases.

PFA ependymomas are highly heterogenous. Pajtler et al. identified two major subtypes, called PFA-1 and PFA-2 further comprising nine minor subtypes with differences according to age at diagnosis, gender ratio, outcome, and frequencies of genetic alterations [25]. Indeed, robustness as well as elucidation of biological and clinical significance of further PFA subtyping still require additional investigation.

Posterior Fossa group B (PFB) Ependymoma

Differently from PFA ependymomas, expression of nuclear Histone H3 p.K27me3 is retained in posterior fossa group B (PFB) ependymomas (Fig. 5B), but this finding is not specific of this group of tumours. PFB are significantly more common (90%) than PFA ependymomas in adults, but extremely rare in children aged less than 5 years (< 5%) [20]. Preliminary data subdivide PFB ependymomas into five molecular subtypes with apparently different features: PFB-1, PFB-2, and PFB-3 are common in patients aged 25-30 years, PFB-4 seems to occur in younger people (< 15 years) and PFB-5 in older ones (> 40 years). Also, PFB-3 and PFB-5 would be more common in females while PFB-2 and PFB-4 predominate in males [32].

In addition to H3 p.K27me3 retention, several cytogenetic alterations have been detected in PFB ependymomas, such as loss of chromosome 22q, monosomy of chr. 6, and trisomy of chr. 18 [20,32]. Although PFB group shows a more favourable outcome than PFA, incomplete surgical resection is associated with poor prognosis. Biomarkers of worse prognosis are still to be elucidated: loss of chromosome 13q has been suggested, but in a single study only [32].

Spinal Ependymoma

Spinal ependymomas are intramedullary tumours,

most frequently involving the cervical or cervicothoracic segments [33]. These neoplasms represent about 20% of primary spinal tumours with a median age at diagnosis ranging from 25 to 45 [1].
MRI findings are similar to supratentorial/infratentorial ependymomas, but rostral or caudal syringomyelia can also be present in about 60% of cases [33].
Concerning histopathological findings, the rare tanycytic pattern is more represented in this compartment and is characterized by spindle-shaped cells and bipolar processes, representing a potential diagnostic pitfall since it can mimic pilocytic astrocytoma or schwannoma. Immunohistochemistry can help distinguishing these entities since SOX10 is negative in ependymomas and positive in the latters [4].
WHO grade 2 or 3 is assigned according to the morphological features as previously reported, but WHO grade 3 is rare in this anatomic compartment.
Since spinal ependymomas frequently occur in patients with neurofibromatosis type 2 syndrome, it has been suggested that *NF2* gene could be involved in their development. In agreement with this hypothesis, sporadic somatic *NF2* mutations and chromosome 22 losses are recurring alterations in these tumours [20].
Outcome is favourable both in children and adults, with overall 5-10 year survival rates of 90-100% [27]. However, subsequent recurrences are possible, especially in WHO grade 3 tumours. Extent of resection is an important prognostic factor as well as absence of *MYCN* amplification, since its presence defines a rare subgroup of spinal ependymomas with poor prognosis.

MYCN-amplified Spinal Ependymoma

MYCN-amplified spinal ependymomas represent a rare, recently defined subgroup with a higher incidence in females (1.7:1) and a median age at diagnosis of 31 years [34,35]. *MYCN*, a member of the MYC group of oncogenes, codes for a transcription factor involved in the regulation of neuronal embryogenesis. It is involved in the oncogenesis of multiple tumour types, including neuroblastoma, paediatric glioblastoma and medulloblastoma. The specific mechanisms by which *MYCN* promotes oncogenesis in spinal ependymomas have not yet been elucidated. Interestingly, multiple schwannomas have been reported in one patient with a *MYCN*-amplified spinal ependymoma, suggesting a possible relationship with neurofibromatosis type 2 [35].
From a diagnostic point of view, histological and immunohistochemical characteristics are similar to ependymomas in general, but most of these cases show aggressive histological features warranting a grade 3 classification [34]. MYCN protein expression can be detected by immunohistochemistry and usually consists in strong and diffuse nuclear staining. Variable loss of H3 p.K27me3 nuclear retention is also observed. Immunohistochemical staining for MYCN might thus serve as a suitable screening method and the amplification can be confirmed by interphase FISH analysis. *MYCN*-amplified spinal ependymomas also own a specific DNA methylation profile.
Spinal ependymomas with *MYCN* amplification are associated with a poorer outcome compared with other spinal ependymomas: median progression-free survival and overall survival of 17 and 87 months have been reported as well as frequent disseminations [34].

Myxopapillary Ependymoma

Myxopapillary ependymomas commonly arise in the cauda equina, filum terminale, or conus medullaris, but multifocal disease is possible with involvement of other CNS compartments. Rarely, myxopapillary ependymomas can also develop outside of the CNS, usually within the sacrococcygeal or presacral tissues. They are rare tumours with an incidence of 0.6-1.0 cases per 1 million person-years and a higher frequency in males [36]. Myxopapillary ependymomas are more common in adults with a bimodal peak around 25-29 years and 45-59 years. Overall prognosis is favourable (10-year survival rates > 90%) and complete resection is important for prognosis, but it can prove challenging [36]. CSF cytology is warranted before determining adjuvant treatments to exclude leptomeningeal dissemination [3] since dissemination is possible as well as distant metastases, although this is a rare event [37].
Macroscopically, myxopapillary ependymomas are often encapsulated and show a gelatinous appearance with soft consistency and pink to tan-grey colour. Cystic changes and haemorrhage are frequent. Usually, cuboidal or elongated neoplastic cells are arranged in papillary structures around hyalinized fibrovascular cores (Fig. 6A). A PAS-positive, basophilic, myxoid material is also present in microcysts within the tumour or around blood vessels (Fig. 6B). Haemorrhage with secondary haemosiderin deposition and fibrosis are frequent. Proliferation activity is usually low (absent/rare mitotic figures, Ki67 up to 2-3%), but features suggesting a more aggressive behaviour can be observed [38].
Because of their morphological features, the range of entities which can be included in the differential diagnosis is wide and includes metastatic carcinomas, paragangliomas, schwannomas, chordomas and myxoid chondrosarcomas. Immunohistochemistry is especially helpful: myxopapillary ependymomas are characterized by reactivity for GFAP, S100, CD99,

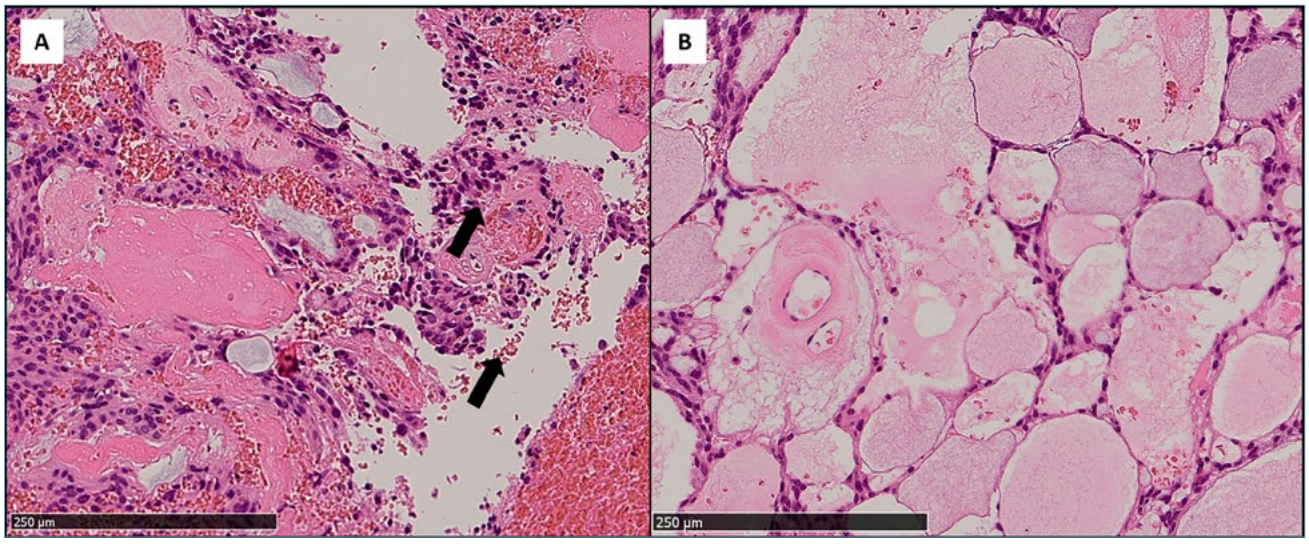

Figure 6. Example image of myxopapillary ependymoma showing the perivascular papillary arrangement of neoplastic cells (arrows, 6A, HE, original magnification: 100X) and the microcystic areas with myxoid material (6B, HE, original magnification: 100X).

CD56 and often for AE1/AE3 pancytokeratin cocktail, but they do not show immunoreactivity for OLIG2, CAM5.2, CK 5/6, CK 7, and CK 20 [4]. Differently from the previously described ependymomas, EMA is usually negative.

WHO 2021 changed the grading of these tumours from 1 to 2 based on their outcome and recurrence rates, which are similar to conventional spinal ependymomas [6].

In most cases, myxopapillary ependymomas can be conclusively diagnosed based on histological and immunohistochemical features: however, they also harbour a specific methylation profile which can be exploited for diagnostic purposes [20].

Subependymoma

Subependymoma is a further, rare ependymal tumour typically arising in the fourth (in 50-60% of cases) or lateral ventricles (in 30-35% of cases), although it can arise along the whole neuroaxis [39].

Collection of epidemiological data is hampered by asymptomatic cases, but an overall incidence of 0.055 cases per 100,000 person-years has been reported, usually occurring in middle or older males [39]. Subependymoma has also been reported in association with multiple genetic syndromes [40,41].

Due to their slow and limited growth, they can be incidentally discovered on neuroimaging or at autopsy. Prognosis is excellent: recurrences after surgical resection are rare and anaplastic transformation is exceptional [39,42,43].

Macroscopically, they appear as grey masses protruding into the ventricles with a firm texture. Subependymomas histology shows small, round to oval neoplastic cells within a fibrillary matrix (Fig. 7). Microcystic changes and calcifications are frequents, while nuclear pleomorphism and other features suggestive of potential aggressiveness, like microvascular proliferations, mitotic figures or necrotic foci are rare [39]. Perivascular pseudorosettes can be focally observed as well as the pre-sence of nodules of classic ependymoma (so-called “mixed ependymoma-subependymoma”): these patterns are considered predictive of a more aggressive behaviour. Haemorrhagic changes and haemosiderin deposits can also be present. Immunohistochemical findings overlap the general ependymoma profile.

No changes have been introduced regarding subependymomas classification in the 2021 WHO classification of CNS tumours. Nevertheless, in recent years it has been shown that these tumours harbour a specific epigenetic profile that is distinct according to the anatomic compartment. There are also recurrent copy-number alterations including chromosome 19 loss. DNA methylation profiling can thus be used to further investigate lesions with mixed or ambiguous morphology, or with unexpected clinical behaviour [23].

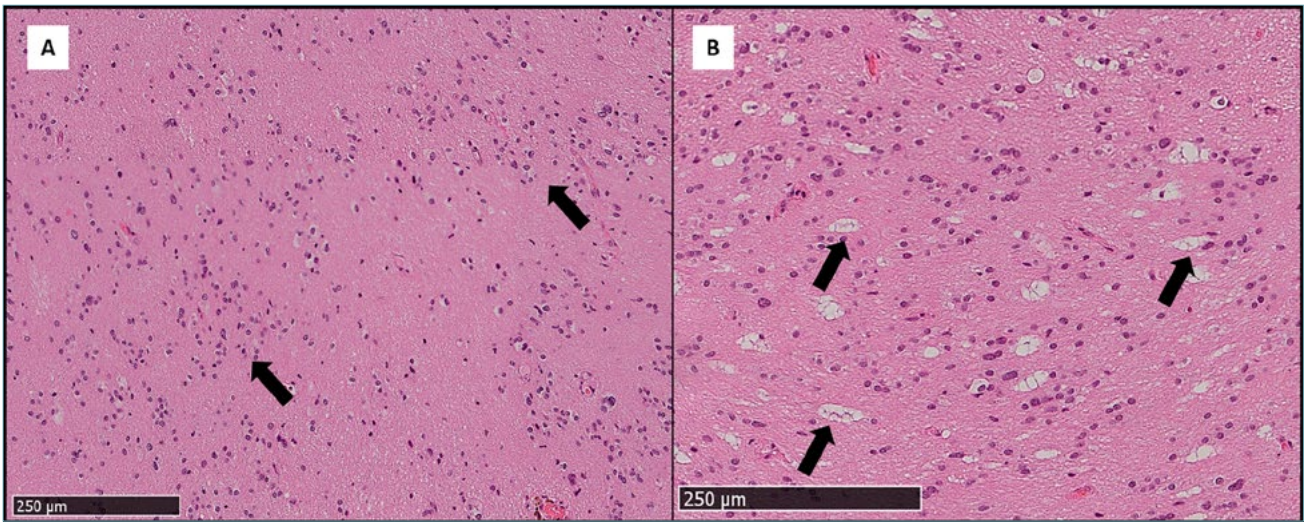

Figure 7. Example of subependymoma showing the characteristic clustering of neoplastic cells (arrows, 7A, HE, original magnification: 70X) and microcystic lacune (arrows, 7B, HE, original magnification: 100X).

Conclusions

Ependymal tumours are a heterogenous group of neoplasms with peculiar molecular characteristics which are being identified. Based on this data, several, significant innovations in ependymoma classification have been introduced in the latest WHO classification of CNS tumours, further integrating morphological features with molecular hallmarks. This effort will hopefully help improve the prognostic relevance of the different diagnostic entities and ultimately enable patient-tailored management and treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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Ethical consideration

None.

Authors' contributions

All authors contributed to manuscript drafting and editing.

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