PATHOLOGICA 2022;114:455-464;
DOI: 10.32074/1591-951X-826

Review

Expanding the spectrum of "mesenchymal" tumors of the central nervous system

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Summary
In this review, we summarize the clinical, histopathological, and molecular features of central nervous system (CNS) tumors with *BCOR* internal tandem duplication, intracranial mesenchymal tumor with *FET*/*CREB* fusion, CNS *CIC*-rearranged sarcomas and primary intracranial sarcoma *DICER1*-mutant, now included in the 2021 WHO classification of CNS tumors. Possible relationships between tumors occurring in the CNS and their systemic counterparts are discussed.

Key words: CNS tumor with BCOR internal tandem duplication, intracranial mesenchymal tumor with *FET*/*CREB* fusion, CNS *CIC*-rearranged sarcomas, primary intracranial sarcoma *DICER1*-mutant, central nervous system

Received and accepted: November 4, 2022

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How to cite this article: Pizzimenti C, Gianno F, Gessi M. Expanding the spectrum of "mesenchymal" tumors of the central nervous system. Pathologica 2022;114:455-464. https://doi.org/10.32074/1591-951X-826

Introduction

In recent years, large molecular studies have permitted a better classification of undifferentiated, poorly differentiated round cell tumors, mainly under the definition of CNS-PNETs, or spindle cell neoplasms occurring in the CNS [1]. One important result of these studies was the widening of the spectrum of "mesenchymal" neoplasms potentially occurring in the CNS; this group includes now mesenchymal tumor with *FET*/*CREB* fusion, *CIC*-rearranged sarcomas and *DICER1*-mutant intracranial sarcoma. Furthermore, these analyses led to the identification of neuroepithelial tumors which share a common genetic background with pediatric sarcomas, like CNS tumors with *BCOR* internal tandem duplication (*BCOR* ITD).
Even though many aspects of biology of these rare tumors have been better defined, some intriguing issues are still to be definitively addressed, and especially their exact relationships with their systemic counterparts.

Incidence, distribution and localisation

Although a large number of cases have been progressively documented in recent years, these neoplasms are rare and precise information regarding their incidence and prevalence in general population is still not available. Based on available literature, the two most frequently reported entities seem to be mesenchymal tumor with *FET*/*CREB* fusion and the CNS tumor *BCOR* ITD [2].
Intracranial mesenchymal tumor with *FET*/*CREB* fusion occurs more

frequently in adult population: in a large series, the median patient age at presentation was 17 years with a predominance in the female population [3]. They are mainly extra-axial or intraventricular tumors, localized, in particular, in hemispheric meninges, the falx and the tentorium [3-5].

In the CNS, tumor in the *BCOR* ITD and *CIC*-rearranged sarcoma affect mainly the pediatric population: infants for CNS tumor *BCOR* ITD (mean age 3.5 years) [6], while adolescents and young adult (usually ≤ 21 years) for *CIC*-rearranged sarcoma. CNS tumors *BCOR* ITD showed predominantly a cerebellar localization, especially in younger patients (< 5 years old), although they can also occur in cerebral hemispheres [2,6,7]; CNS *CIC*-rearranged sarcomas may show variable localization including cases at spinal level [1,8-10].

The mean age of patients with primary *DICER1*-mutant intracranial sarcoma is 6 years with a wide range of age and predominant intracranial localization [11-14].

Integrated diagnosis

A combined histopathological- and molecular-based approach is often necessary to reach the final diagnosis. A variable histopathological spectrum and an unspecific immunohistochemical profile are common, hindering an easy recognition in routine diagnostic neuropathology.

Intracranial mesenchymal tumor with *FET*/*CREB* fusion is a mesenchymal neoplasm characterized by the presence of fusion of a FET RNA-binding protein family gene (usually *EWSR1*, rarely *FUS*) with a member of the CREB transcription factors family (*CREB1, ATF1, or CREM*). Such cases have been reported in the past as angiomatoid fibrous histiocytoma of the meninges (AFH) or intracranial myxoid mesenchymal tumors (IMMT) [3,15-22]. They may display extremely variable histopathological features, including presence of myxoid stroma, desmoplastic areas, epithelioid and spindle cell cytology [3,15-22] (Fig. 1). Angiomatous areas and intralesional inflammatory infiltrates are common, as seen in AFH of soft tissues [3,4,16]. Meningioma-like areas and amianthoid fibers can be detected. The immunophenotype of tumor cells is variable. The cells may often express vimentin, EMA and CD99 and could be CD68 and CD163 positive [3,19-22]. A common and unique feature is a focal immunoreactivity for desmin [3-5,18-22]. Cytokeratins, glial markers, melanocytic markers are usually negative[3]. These tumors show often a low proliferative activity [20], but cases with increased proliferative and mitotic activity have been reported [4,19,21]. The final diagnosis relies on the identification of translocation involving FET family genes with CREB transcription factors genes. Notably, epithelioid features seem to be associated to *EWSR1-ATF1* fusions [3,21]. Because molecular alterations involving *EWSR1* are not specific and can be identified in other CNS tumors, extreme caution must be used in the interpretation of results obtained with FISH-based methods: a further confirmation of the presence of a specific *FET-CREB* fusion with other methods should be recommended. Intracranial mesenchymal tumor with *FET*/*CREB* fusion may present additional mutations in several genes, including *BRAF* [22].

CNS tumor *BCOR* ITD is as a malignant neoplasm characterized by a predominantly solid or microcystic growth pattern, glial-like cytology, a dense capillary network, formation of pseudo-rosettes, and by the presence of an ITD in exon 15 of the *BCOR* gene. Differently from other entities described herein, this tumor is considered to derive from a neuroepithelial cell of origin (see below) and therefore included in the CNS embryonal tumors along to medulloblastoma, ETMR and ATRT [2].

This neoplasm can present variable neuropathological features and immunohistochemical profile. CNS tumor *BCOR* ITD often resembles a glial neoplasm and can show solid, microcystic or perivascular architecture, often with a prominent, dense vascular stroma (Fig. 2). The cells, usually round or oval, often appear embedded in a glioma-like fibrillary stroma; Homer-Wright rosettes can be found; the tumor may show in part an infiltrative growth pattern; usually these neoplasms display high proliferative and mitotic activity [6,23-25].

The differential diagnosis, given the common occurrence in the posterior fossa in children, should include medulloblastoma, ependymomas and ETMR. From an immunohistochemical point of view, the neoplasm, usually CD56 and vimentin positive, may present a variable expression of glial markers such as GFAP, OLIG2 and S100 but may also show positivity for NeuN; the expression of other neuronal markers is uncommon [6,23-25]. SATB2, BCL2 and TLE1 as well as pan-NTRK are usually positive [26]. The widespread positivity for *BCOR*, EGFR and Cyclin D1 is helpful but *BCOR* over-expression is unspecific and can be encountered in numerous other CNS neoplasms, including high-grade gliomas [27]. The definitive diagnosis relies on the identification of the presence of duplication in the 15 exon of *BCOR* gene (Fig. 3). Notably, several *BCOR* alterations have been also described in other CNS neoplasms, including mutations and fusions [27]. Mutations have been identified in retinoblastomas, in various glial tumors, particularly those with high-grade histol-

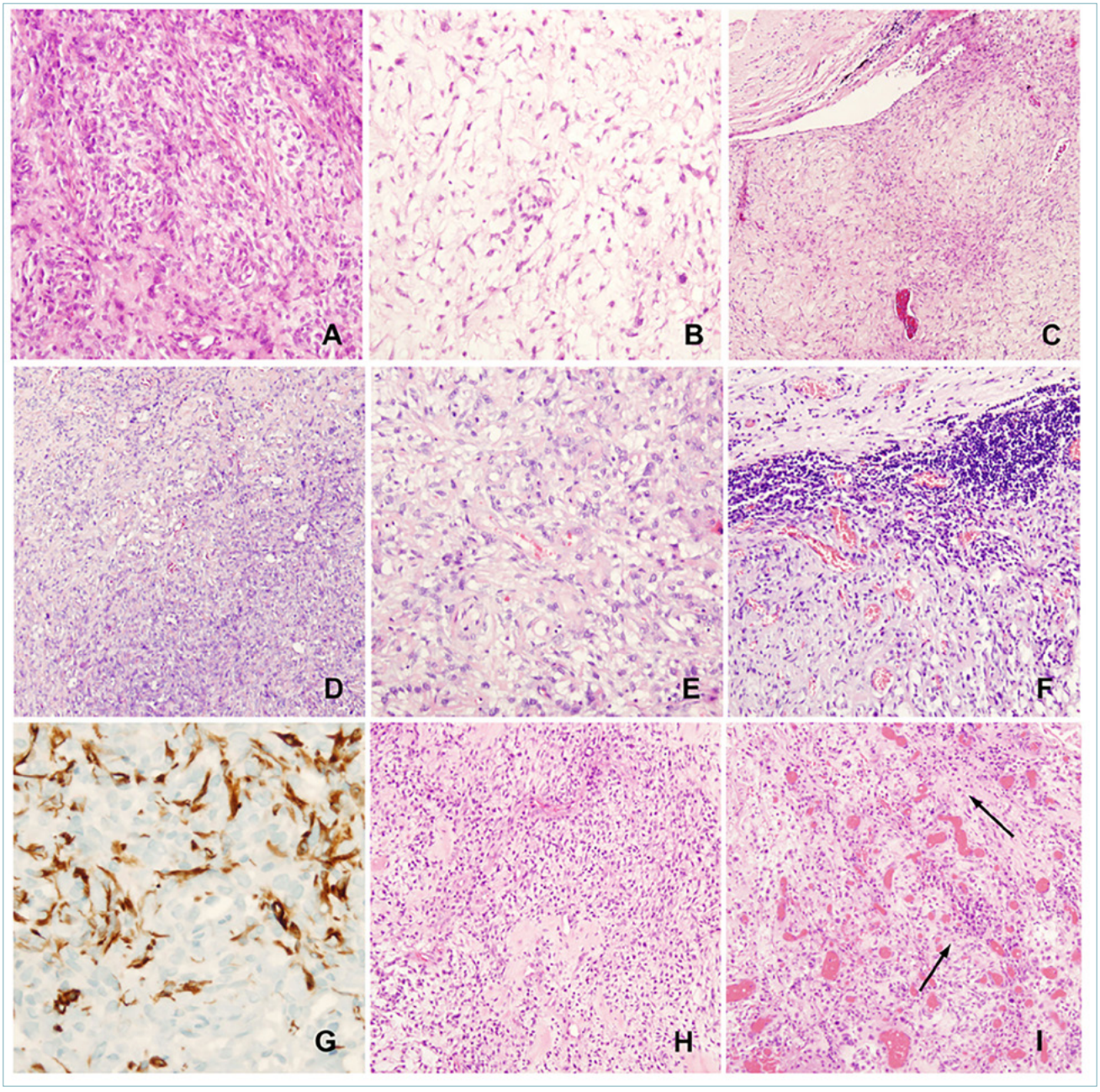

Figure 1. Histopathological features of intracranial mesenchymal tumors with FET/CREB fusion. A case of intracranial mesenchymal tumors with *FET/CREB* fusion, in the posterior fossa of a 60 years old patient, showed dense cellularity and spindle cell cytology, alternating with myxoid areas (A-B). Angiomatous vessels were present at the periphery (C). Another case, showed a more solid, fibro-histiocytic histology (D) with abundant inflammatory infiltrates at its periphery (E). The tumor was partially positive for desmin (F). Another tumor, occurred in a 55 years old patient and localized in the frontal meninges, showed delicate myxoid features (H). Prominent vascularity and inflammatory infiltrates were present (arrow)(I). All tumors presented *EWSR1* rearrangement in FISH analysis.

ogy, including high-grade astroblastomas. Moreover, *BCOR* genetic alterations were also found in about 5% of medulloblastomas being apparently more common in infantile SHH-medulloblastoma subgroup [27].

CIC-rearranged sarcoma of the CNS is a high-grade,

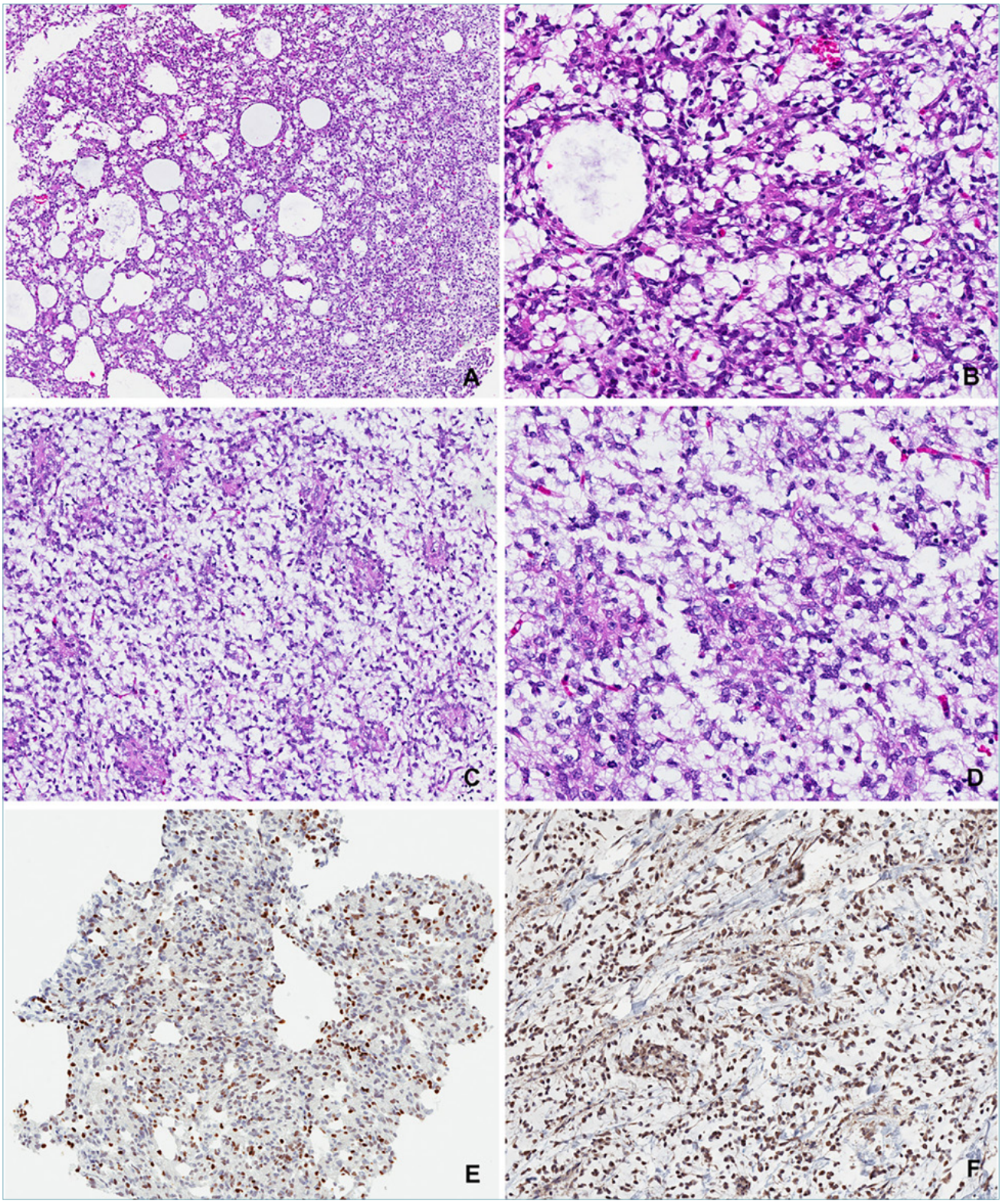

Figure 2. Histopathological features of CNS tumor *BCOR* ITD. A CNS Tumor *BCOR* ITD affecting the cerebellum in a two-year-old boy. The tumor presented with solid or microcystic growth pattern (A, C). The cells were embedded in a fibrillary stroma and appeared arranged around vascular structures (B, D). The tumor was partially OLIG2 positive (E) and diffusely BCOR positive (F).

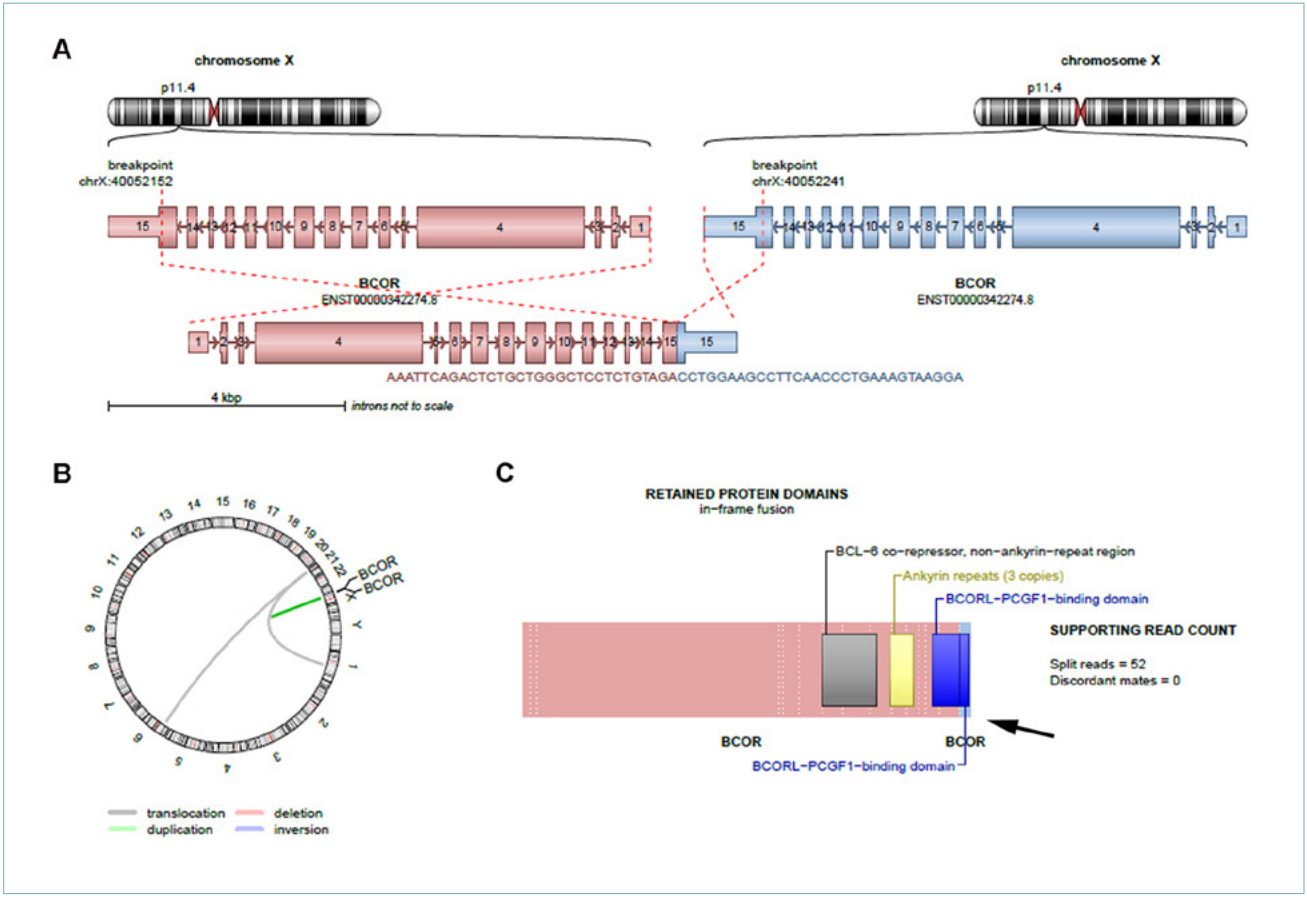

Figure 3. *BCOR* Internal Tandem Duplication (*BCOR* ITD).Schematic plot of internal tandem duplication in *BCOR* exon 15 (*BCOR* ITD) at chromosome X (in A). In OGM Circle Plot (Access Software, Bionano Technologies) chromosomal rearrangement are shown as green line (fusion) involving parts of *BCOR* gene (in B.). The in-frame fusion (depicted in light blue, arrow) affects the *BCOR* PUFD domain leading to an altered PCGF1-binding affinity, dysregulating transcription (in C.).

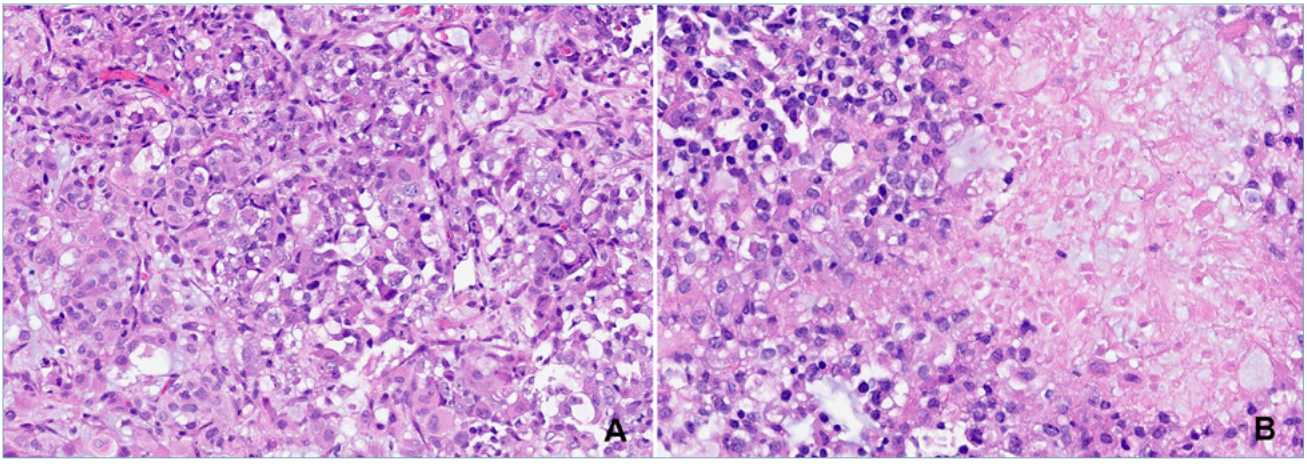

Figure 4. Histopathological features of CIC-rearranged sarcoma. A *CIC*-rearranged sarcoma (harboring a *CIC-LEUTX* fusion) occurred in the spinal cord of a 4 years old boy. The tumor was extramedullary. The tumor was composed of large epithelioid cells with abundant cytoplasm (A). Necrotic changes were present (B).

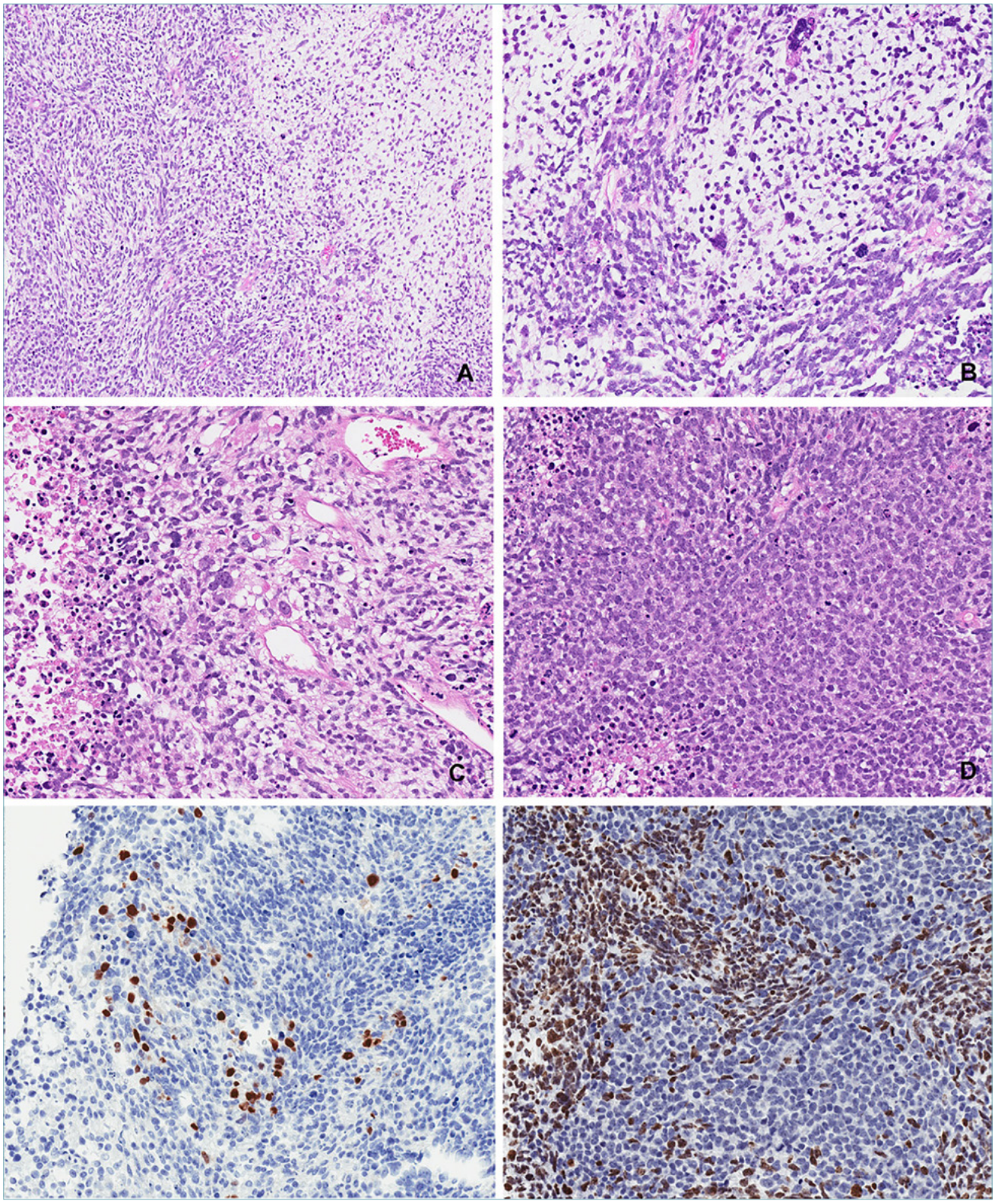

Figure 5. Histopathological features of DICER1-mutant sarcoma. A *DICER1*-mutant intracranial sarcoma in a 18 years old female patient localized in the temporal lobe. The tumor showed high cellularity, partial spindle cell cytology and myxoid stroma (A, B). Pleomorphic cells and hyaline globules were seen (C) along as highly cellular round cell undifferentiated areas (D): here focal myogenin positive staining was present (E). Partial loss of H3K27me3 was found (F). The tumor harbored a *DICER1* p.E1813A mutation.

poorly differentiated neoplasm defined by the presence of a fusion of *CIC* with different partner genes (such as *NUTM1* and *DUX4*) [2]. They show histopathological features similar to their systemic soft tissue counterpart [10]: *CIC*-rearranged sarcomas are formed by undifferentiated round cells arranged in nests or showing a more solid growth pattern; necrosis is common; epithelioid or spindle cell cytology as long as desmoplastic or myxoid stroma have been also described [28] (Fig. 4). In most cases, the differential diagnosis includes other round cell neoplasms, like rhabdomyosarcoma and Ewing's sarcoma. WT1 and ETV4 positivity, a weak CD99 expression and negativity for NKX2-2 and FLI1 stainings can be very helpful to orientate the diagnosis [28,29]. Heterogeneous ERG/CD31 co-expression in a subset of *CIC*-rearranged sarcoma may be a potential pitfall in differential diagnosis with vascular tumors [30]. Expression of pan-cytokeratin, smooth muscle actin, and neurofilament protein has been reported [8,28]. The final diagnosis relies on demonstrating *CIC*-rearrangement using FISH, NGS- or RT-based methods.

Primary intracranial sarcoma *DICER1*-mutant composed of spindle or pleomorphic tumor cells, with evidence of myogenic and occasionally of chondroid differentiation. The tumors show often spindle cell cytology with anaplastic features, focal rhabdomyoblastic differentiation, foci of primitive embryonal-type tissue and in some cases chondroid differentiation [11,31-34] (Fig. 5). The presence of eosinophilic globules is also a typical feature [11] : they are PAS+ and are stained with alpha-1-antitrypsin. The tumor shows patchy expression of muscular markers (like desmin and myogenin) highlighting the rhabdomyosarcomatous component. Nuclear positivity for TLE1 expression [35] and loss of H3K27me3 were observed in primary intracranial sarcoma *DICER1*-mutant [12,35]: therefore, these tumors may be included in the differential diagnosis of high-grade cellular malignant spindle cell neoplasms with loss of H3K27me3 (in particular MPNST) [12]. The histology of primary intracranial sarcoma *DICER1*-mutant overlaps considerably with other *DICER1*-associated tumors, notably to type II/III pleuropulmonary blastoma (PPB): therefore, distinguishing primary intracranial sarcoma, *DICER1*-mutant from metastatic PPB is pivotal [31].

Information, if any, on a possible presence of a *DICER1* syndrome or presence of other *DICER1*-related neoplasms in clinical history of the patient significantly may further facilitate the neuropathological approach to diagnosis. Confirmation of presence of *DICER1* mutation in sporadic cases is mandatory for the final diagnosis.

Taxonomy and oncogenesis

The most intriguing issue for these CNS neoplasms in particular for CNS *BCOR* ITD, *CIC*-rearranged sarcoma and for intracranial mesenchymal tumor with *FET*/*CREB* fusion is the relationship with their systemic counterparts.

Tumors harboring *BCOR*-internal tandem duplication represent a histologically heterogeneous group of neoplasms, comprising CNS tumors and sarcomas; the latter group includes clear cell sarcomas of the kidney (CCSK), high-grade endometrial stromal sarcomas (HG-ESS), myxoid mesenchymal tumor of infancy (PMMTI) and undifferentiated round cell sarcoma (URCS) in bone and soft tissues [36,37].

BCL-6 transcriptional corepressor (*BCOR*) (located at Xp11.4) encodes a protein which functions as a co-repressor bounding to BCL-6 and forming part of the Polycomb Repressive Complex 1 which through ubiquitination leads epigenetic silencing [27]. Besides ITD, various alterations affecting *BCOR* gene have been described: they include fusions (i.e., *BCOR-CCNB3, BCOR-MAML3 and ZC3H7B-BCOR*), mutations and internal tandem duplications (ITD) [27].

The main similarities between CNS and non-CNS tumors *BCOR* ITD neoplasms are clinical and include the median age of the patients at the time of diagnosis, the local presentation and the poor prognosis. The histopathology, however, varies greatly and depends on the tissue and site of occurrence [26,38].

Moreover, CNS tumors *BCOR* ITD and *BCOR* ITD sarcomas present close but distinct transcriptomic signature and DNA methylation profile, suggesting the possibility of a common, acquired oncogenic pattern in distinct cell types within specific tissues. Notably, expression analysis revealed that the CNS *BCOR* ITD group seems to be enriched in genes expressed in neuro-glial cells whereas *BCOR* ITD sarcomas predominantly expressed embryonal/developmental genes: this correlate well at histopathological level, with the evidence that CNS tumors *BCOR* ITD, but not *BCOR* ITD sarcomas express neuro-glial markers (like GFAP, Olig2, Neu-N). The difference in molecular signatures is probably dependent on their different cell of origin. As previously mentioned, the putative origin of CNS *BCOR* ITD from neuroepithelial cells led to the inclusion of this tumor among CNS embryonal tumors, rather than mesenchymal neoplasms in WHO classification of CNS tumors.

The relationships between intracranial mesenchymal tumors with *FET*/*CREB* fusion and their systemic counterpart is more difficult be addressed.

Soft tissue AFH, pulmonary *CREB* sarcoma and intracranial mesenchymal tumors with *FET*/*CREB* fusion

share many features but also present some differences at histopathological level (i.e. desmin expression) [4]. Methylation profiling analysis added interesting information on taxonomy of those tumors occurring in the CNS. CNS tumors seem to be different from their soft tissue counterparts, suggesting the existence of two epigenetic subgroups [4,39]. The first subgroup includes tumors that have epigenomic similarities with the systemic AFH and SFT and have mostly *EWSR1-ATF1* and *ESWR1-CREB1* fusions; these tumors occur mostly in adolescents and young adults, show a spindle cell cytology and a hemangioma-like vascularity. The second subgroup includes tumors with epigenomic similarities with the clear cell sarcoma of soft tissue (CCS) enriched in cases mostly with *ESWR1-CREM* and *FUS-CREM* fusions; they occur in early childhood and show a round or epithelioid/rhabdoid morphology and lack of hemangioma-like features [39].
There is no sufficient evidence to distinguish *CIC*-rearranged sarcoma in the CNS from histologically and genetically similar tumors in other extra CNS tissues.
Despite a similar histopathology, the majority of intracranial sarcomas with *CIC*-rearrangement studied to date showed *NUTM1* and *LEUTX* as the fusion partner, whereas those in extracranial bone and soft tissue had *DUX4, FOXO4* and *NUTM2A* as the fusion partner [10,40,41]. *CIC* gene product encodes a member of the high mobility group (HMG)-box superfamily of transcriptional repressors. Gene truncation (besides fusions) may be also sufficient to enable an oncogenic de-repression of transcription.
Primary intracranial sarcoma, *DICER1*-mutant, as previously indicated, overlaps considerably in terms of histopathology with other *DICER1*-associated tumors particular with PPB. These tumors occur in a specific genetic setting defined by mutations in the *DICER1* gene (either somatic or germline as part of the *DICER1* syndrome). *DICER1* syndrome is a rare autosomal dominant familial tumor predisposition disorder with a heterozygous germline mutation of *DICER1* gene (chromosome 14, region q32.13) that increases the risk of development of different types of malignant and benign tumors [42]. Patients with *DICER1* syndrome commonly develop pleuropulmonary blastoma (PPB), multinodular goiter, ovarian Sertoli-Leydig cell tumors, and rarely CNS tumors including ETMR, pituitary blastoma and pineoblastoma [42]. The *DICER1* gene encodes an RNase III endoribonuclease that facilitates the activation of the RNA-induced silencing complex essential for double stranded-RNA and mi-RNA processing. Disruption of this pathway results in alterations in protein expression and in cell proliferation as well as derangement of cell differentiation and DNA repair [31]. *DICER1* behaves as either a tumor suppressor gene due to loss-of-function mutations or an oncogene, due to gain-of-function mutations. It retained function as a haploinsufficient tumor-suppressor gene with the loss of one allele leading to tumor progression, but loss of both alleles having an inhibitory effect for tumor development; therefore, one intact allele is needed for cell survival [31].
Recent investigations revealed that some genetic alterations seem to be more common in intracranial *DICER1*-mutant sarcoma compared with other *DICER1*-associated tumors; they include *TP53* inactivation and activating alterations of genes in the RAS pathway (*KRAS* and *NF1)* [11]. Moreover, it seems that primary intracranial sarcoma, *DICER1*-mutant, may have a significantly higher tumor mutational burden in comparison to other *DICER1*-related tumors [12].

Prognosis and outcome

Given their rarity, it is difficult to draw any assumptions in term of outcome and prognosis.
CIC-rearranged sarcoma and CNS tumor *BCOR* ITD show generally aggressive clinical behavior [8]; the initial therapeutic strategy is mainly multimodal including most often the first-line surgery, radiotherapy and adjuvant chemotherapy [6]. However, cases with prolonged survival have been described [6,43]. For *CIC*-rearranged sarcoma, it remains uncertain whether the specific fusion partner may influence the biology and therefore the prognosis of the patients with these tumors.
The clinical course of intracranial mesenchymal tumor with *FET/CREB* fusion is unpredictable, ranging from cases with a relatively indolent behavior, to tumors prone to rapid recurrence [3].
The prognosis for patients with *DICER1*-mutant primary intracranial sarcoma remains unknown, because only limited data clinical for patient with long-term follow-up are available. Moreover, the possible prognostic relevance of tumors arising in the settings of germline *DICER1* mutations has not been defined There is no evidence that the presence of a germline or somatic mutation may influence the prognosis of a patient with *DICER1*-mutant intracranial sarcoma.

Conclusions

In conclusion, the WHO classification of CNS tumors 2021 now includes new entities among the groups of mesenchymal non-meningothelial tumors and embryonal tumors. These tumors share specific molecular and histopathological features. Given their rarity in the CNS, particular awareness is needed for practicing

neuropathologists to suspect the presence of such tumors in routine neuropathology: a combined histopathological and molecular-based approach is therefore necessary to pinpoint the final diagnosis.

Aknowledgments

Special thanks to Prof. Caterina Giannini for providing histopathological images of the *CIC*-rearranged sarcoma case and to Dr. Isabella Giovagnoni e Dr. Sabina Barresi for the *BCOR* ITD exon 15 graphics.

Conflict of interest

The authors declare no conflict of interest.

Funding

None.

Ethical consideration

None.

Authors' Contributions

MG conceived the manuscript; CP and MG drafted the manuscript; FG provided iconographic material; all authors revised and approved the final version of the manuscript.

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