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REVIEW ARTICLE

Mesenchymal Non-Meningothelial Tumors of the CNS: Evolving Molecular Landscape and Implications for Neuroradiologists

Neetu Soni[1], Manish Ora[2], Denes Szekeres[3], Girish Bathla[4], Amit Desai[1], Vivek Gupta[1], Aparna Singhal[5], Amit Agarwal[1]

ABSTRACT

The World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) significantly revised the terminology and diagnostic criteria of “mesenchymal non-meningothelial” tumors of CNS to better align with the classification of these soft tissue tumors outside the CNS. The CNS chapter only covers the entities with distinct histological or molecular characteristics that occur exclusively or primarily in the CNS. These tumors usually arise from the meninges and are rarely intraparenchymal in origin, mainly in the supratentorial compartment. These tumors are grouped into three main categories: soft tissue, chondro-osseous, and notochordal. Soft tissue tumors, the largest group, are further divided into fibroblastic, vascular, and skeletal muscle subtypes. Notably, a new subcategory for "tumors of uncertain differentiation" has been introduced, encompassing three new histomolecular entities: FET::CREB fusion-positive, CIC-rearranged sarcoma, and primary intracranial sarcoma, DICER1-mutant. Emerging entities like dural angioleiomyomas and spindle cell neoplasms with NTRK-rearrangements have been reviewed, although not introduced in WHO CNS5. Given the often non-specific histology and immunophenotype of mesenchymal non-meningothelial tumors of uncertain differentiation, molecular techniques have become indispensable for accurate diagnosis. This review provides a comprehensive overview of primary mesenchymal non-meningothelial CNS tumors, including their clinical, radiological, histopathological, and molecular characteristics and treatment strategies.

ABBREVIATIONS: ALK: Anaplastic lymphoma kinase; ATF1: activating transcriptase factor-1; CREB: cAMP response element-binding protein; CREM: cAMP response element modulator; CIC: Capicua transcriptional receptor; EWSR1: Ewing sarcoma RNA binding protein; FUS: fused in sarcoma; NAB2: nerve growth factor-inducible protein A binding protein 2; STAT6: signal transducer and activator of transcription 6; WHO: World Health Organization WHO CNS5: World Health Organization Classification of Tumors of the Central Nervous System, fifth edition.

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(1) Department of Radiology, Mayo Clinic, Jacksonville, 4500 San Pablo Road, Jacksonville, FL 55902, USA (N.S, A.D, V.G, A.A), (2) Department of Nuclear Medicine, Sanjay Gandhi post graduate institute of medical science, Lucknow 226014, India, (MO), (3) University of Rochester, School of Medicine and Dentistry, Rochester NY 14620 (D.S), (4) Department of Radiology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55902, USA (G.B), (5) Department of Radiology,619 19th St S, Birmingham, AL 35294 (AS)
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Please address correspondence to Neetu Soni, MD, FRCR, Department of Radiology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 55902, USA; soni.neetu@mayo.edu

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Introduction

CNS mesenchymal tumors are a broad group with different clinical, pathological, and biological features. These usually arise from mesodermal-derived precursor cells capable of developing into connective tissues. In the CNS, they commonly arise from the meninges and rarely in the parenchyma or choroid plexus. Meningioma represents the most frequent meningeal mesenchymal tumor. Primary mesenchymal non-meningothelial CNS tumors are rare. The nomenclature and histology of these tumors are often similar to the extra-CNS soft tissue tumors.[1, 2]

The World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) categorizes "mesenchymal non-meningothelial" tumors by cell of origin (fibroblastic, endothelial, muscular, cartilaginous, notochoral or undetermined) and genetic/epigenetic data. The WHO CNS5 has significantly revised the "mesenchymal, non-meningothelial" tumor section, covering only tumor types with unique histopathological or molecular features that occur specifically in the CNS or are relatively common in the CNS than other tissues. Many tumors common in soft tissues and rarely found in the CNS (such as lipoma, liposarcoma, osteoma, angiosarcoma, fibrosarcoma, and others) have been excluded from this classification. Conversely, three new histomolecular entities of uncertain differentiation have been introduced, such as intracranial mesenchymal tumor (*FET::CREB* fusion-positive), *CIC*-rearranged sarcoma, and primary intracranial sarcoma (*DICER1*-mutant). Terms like "hemangiopericytoma" is replaced with solitary fibrous tumor (SFT). Vascular lesions like arteriovenous malformation and cavernous hemangioma are categorized under hemangiomas.[3]

Mesenchymal non-meningothelial CNS tumors are subclassified based on their differentiation (Table 1).[3]

- Fibroblastic and myofibroblastic tumors: Solitary fibrous tumor
- Tumors of uncertain differentiation: Intracranial mesenchymal tumor (*FET::CREB* fusion-positive), *CIC*-rearranged sarcoma, primary intracranial sarcoma (*DICER1*-mutant), and Ewing Sarcoma
- Skeletal muscle tumors: Rhabdomyosarcoma
- Notochordal tumors: Chordoma
- Chondro-osseous tumors: Mesenchymal chondrosarcoma (**Fig. 1**), chondrosarcoma
- Vascular tumors: Hemangiomas and vascular malformations; hemangioblastoma

Though excluded from WHO CNS5, the intracranial inflammatory myofibroblastic tumor is briefly mentioned due to its rarity in the brain.[4] Rhabdomyosarcoma remained in the WHO CNS5 due to its distinctive CNS characteristics compared to soft tissue counterparts. Emerging entities like dural angioleiomyomas and spindle cell neoplasms with *NTRK*-rearrangements have also been reviewed, though not in WHO CNS5. Further studies are required for possible future inclusion.[5] Although these tumors have variable morphology, molecular techniques have enhanced their characterization and precise identification. Significant work is still ahead, with undiscovered molecular alterations and newly reported CNS tumors lacking proper classification.[6] Herein, we review the clinical, radiological, histopathological, and molecular characteristics and treatment strategies of the primary mesenchymal non-meningothelial CNS tumors.

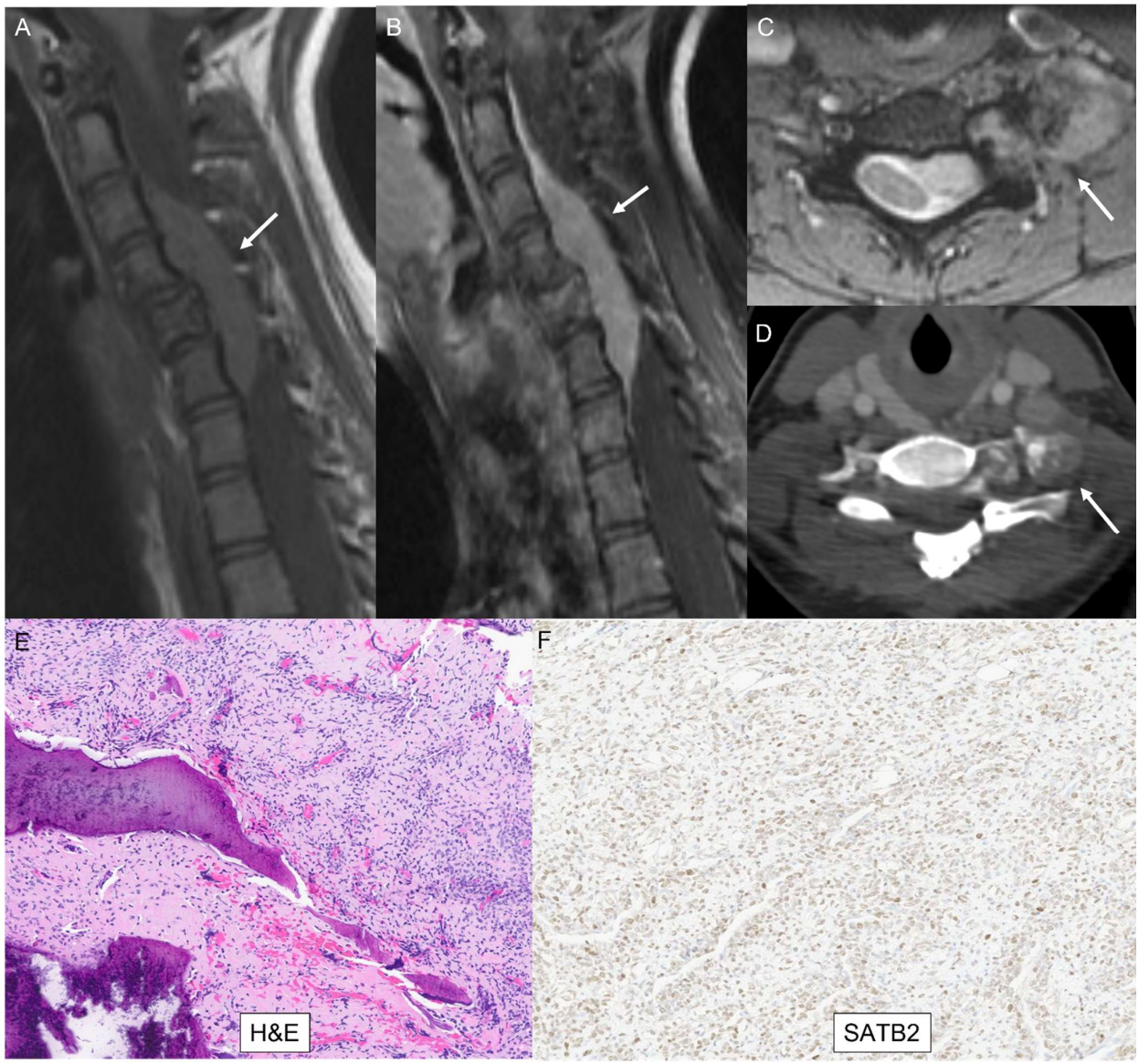

Fig. 1: Spinal mesenchymal chondrosarcoma with *HEY1-NCOA2* fusion gene in a 16-year-old girl. Sagittal and axial MR images (A-C) reveal a lobulated well-circumscribed mass in the extradural space of the cervical spine extending along the left neural foramen (arrow). Lesion shows an isointense signal on T1W image (A), with homogenous contrast enhancement (B) and areas of signal drop out on axial gradient image (C). Amorphous calcification noted within the tumor on axial CT (D, arrow). H&E revealed spindle cell morphology with abrupt areas of cartilage formation (E, arrows). Tumor showed positive staining for CD99 and SATB2 (F) on immunohistochemistry. Molecular testing confirmed the presence of a *HEY1-NCOA2* gene fusion event in the tumor, further confirming a diagnosis of mesenchymal chondrosarcoma. The *HEY1-NCOA2* fusion is most frequently observed in mesenchymal chondrosarcomas.

Table 1: New WHO 2021 Classification of CNS Mesenchymal Tumors and their Molecular Markers

Mesenchymal, non-meningothelial tumours involving the CNS			
	Fibroblastic and myofibroblastic tumours	Solitary fibrous tumour	Partially or completely lack *STAT6* nuclear expression on immunohistochemistry
		Haemangiomas and vascular malformations	

Soft tissue tumors	*Vascular tumours*		Diagnostic molecular pathology is not clinically relevant
		Haemangioblastoma	
	Skeletal muscle tumours	Rhabdomyosarcoma	*PAX3*::*FOXO1* or *PAX7*::*FOXO1* fusion in alveolar subtype, with a worse prognosis
	Tumours of uncertain differentiation	Intracranial mesenchymal tumour, *FET*::*CREB* fusion-positive	Diagnostic *FET*::*CREB* family gene fusions
		CIC-rearranged sarcoma	*CIC* gene fusion and upregulation of ETV complements
		Primary intracranial sarcoma, DICER1-mutant	*DICER1* mutations with DNA methylation profile distinct
		Ewing sarcoma	Definitive diagnosis requires confirmation of *FET*::*ETS*–type gene fusion
Chondro-osseous tumors	*Chondrogenic tumours*	Mesenchymal chondrosarcoma	*HEY1*::*NCOA2* gene fusion
		Chondrosarcoma	*IDH* mutation (approximately 60%)
Notochordal tumors		Chordoma	*SMARCB1* deletions in poorly differentiated chordomas
Emerging entities:		Spindle cell carcinoma, NTRK-rearranged	frequently having *GJA4 p.Gly41Cys* mutations
		Dural angioleiomyoma	*NTRK1/2/3* gene fusions with DNA methylation profile distinct

Discussion

Fibroblastic and Myofibroblastic Tumors:

Solitary Fibrous Tumor

Solitary fibrous tumors (SFTs) are dura-based fibroblastic CNS neoplasms (<1% of all CNS neoplasms). SFTs occur in individuals aged 51-60, without gender predisposition. These are primarily supratentorial and rarely infratentorial, pineal, and sellar in locations.[7, 8] Presenting symptoms depend on the location. Intracranial, subdural, and subarachnoid hemorrhages are rarely present from immature intratumoral vessels rupture.[9] SFT has a variable histological spectrum comprising spindled cells arranged in fascicles and sheets admixed with hyalinized, dilated, branching blood vessels with "staghorn" appearance. These tumors lack pseudoinclusions and calcification typical of meningioma.[3] The rare epithelioid variant is associated with aggressive behavior.[10] *NAB2-STAT6* (nerve growth factor-inducible protein A binding protein 2: signal transducer and activator of transcription 6) gene fusion is a sensitive and specific molecular marker. *STAT6* immunohistochemistry differentiates SFT from meningiomas, Ewing sarcoma, chondrosarcoma, malignant peripheral nerve sheath tumors (MPNST), and other sarcomas. CD34 is typically positive immunohistochemically, but its expression is reduced in higher grades.[7, 8, 11, 12]
SFTs are typically solitary iso- to hyperdense dural-based masses without calcifications and adjacent calvarial hyperostosis on CT-scan. They appear isointense on T1-weighted images (T1WI) with variable contrast enhancement, and a dural tail may be present. T2WI helps differentiate these tumors, showing a mixed “yin-yang” pattern of hyperintensity (high cellularity) and hypointensity (fibrotic areas) with variable flow voids. T2 signal intensity varies by tumor grade, with lower signals in grade-1 and higher in grade-2/3. Moderate heterogeneous enhancement is seen in highly cellular areas, while fibrotic regions show intense enhancement.[13, 14] Imaging features often

fail to distinguish SFT from meningioma. Meningiomas typically appear hypo-to-isointense on T1WI and iso-to-hyperintense on T2WI. SFT is favored by the absence of calcification, narrow-based attachment, lack of dural tail, and flow void. Grade-3 SFTs tend to be aggressive with irregular or multi-lobulated borders and adjacent parenchymal and calvarial erosions (**Fig. 2**).[14] 18F-Fluorocholine (18F-FCH), and Gallium-68 Dotatate PET/CT-scan help detect intracranial SFTs, local recurrence, and distant metastases.[15]

The differential diagnosis includes fibrous meningioma, anaplastic meningioma, Ewing sarcoma, synovial sarcoma, lymphoma, Mesenchymal chondrosarcoma, dural metastasis, and malignant peripheral nerve sheath tumor (MPNST). Fibrous meningioma expresses EMA and is negative for CD34 and nuclear *STAT6* expression. Ewing sarcomas are characterized by *EWSR1* (Ewing sarcoma breakpoint region 1) gene rearrangement and share the hypercellularity and CD99 positivity of SFT but lack *STAT6* staining.[16] Synovial sarcomas show positive staining with cytokeratin, EMA, and *TLE1* (Transducin-like enhancer of split 1) and lack *STAT6*. MPNST is usually negative for CD34 and *STAT6* and may show focal S100 protein and *SOX10* expression.[17] Two large cohorts of SFTs with *NAB2:STAT6* gene fusion and overexpression of *STAT6* have shown a higher propensity for recurrence and metastasis.[18-20] High tumor grade, subtotal resection, CD34-negative immunostaining, and a high Ki-67 index (>10%) are independent predictors of poor prognosis in SFT.[4, 21] Aggressive biology is associated with *TP53* mutations, and *p16* overexpression.[8, 22] Surgical resection is the preferred treatment, with a 60% recurrence rate.[23] The risk of metastasis is high (35–45%), specifically in high-grade or dedifferentiated SFTs, requiring active treatment. Metastases may occur decades after initial diagnosis and warrant long-term follow-up.[20]

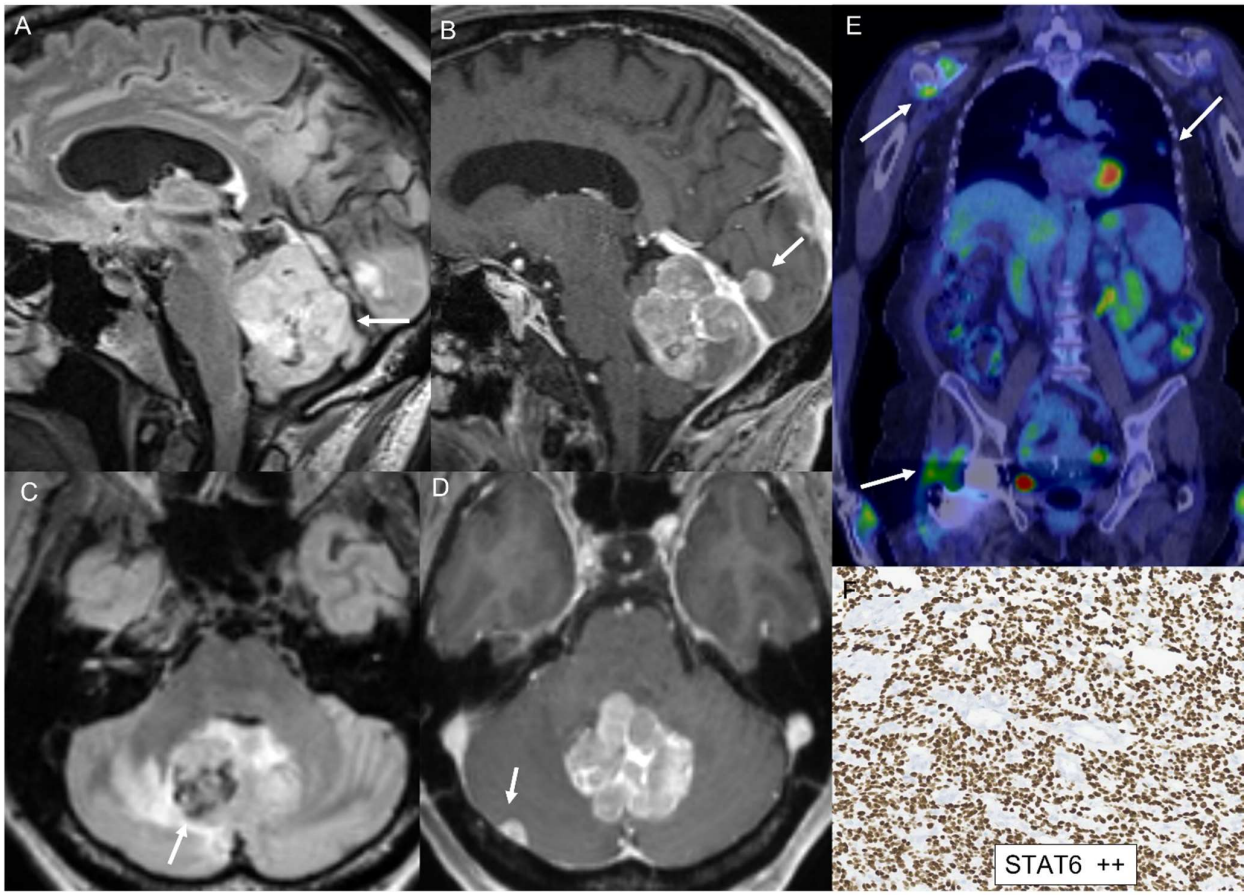

Fig. 2:Metastatic solitary fibrous tumor in a 69-year-old-woman. MR images (A-D) depict a large multi-lobulated mass along the inferior tentorial surface (arrow) with avid contrast enhancement and adjacent cerebellar edema. Smaller similar nodules are noted along the superior tentorial surface and along right cerebellar convexity (B,D, arrows). Osseous and pulmonary metastatic deposits with increased uptake seen on FDG-PET study (E, arrows). The tumor cells show nuclear expression of STAT6 (F), compatible with the presence of *NAB2- STAT6* fusion and diagnostic of solitary fibrous tumor. ***Intracranial Inflammatory Myofibroblastic tumor (IMT)***

IMT is a rare low-grade tumor composed of myofibroblast spindle cells with inflammatory cell infiltration. It usually occurs in the lungs and abdomen, with rare intracranial dura and leptomeninges involvement. Intracranial IMT diagnosis is challenging because it lacks specific clinical symptoms and characteristic radiographic features.[24, 25] Most IMTs are iso or low signal on TIWI and T2WI (**Fig. 3**). They show prominent enhancement with low signal intensity on DWI.[24, 26] Rearrangement and overexpression of the anaplastic lymphoma kinase (*ALK*)

gene are associated with IMT (**Suppl Fig 1**).[27] *NTRK* (neurotrophic-tropomyosin receptor tyrosine kinase) alterations have been described in pediatric fibroblastic/myofibroblastic tumors involving the cortex and leptomeninges with meningioangiomatosis growth patterns along the Virchow-Robin spaces.[4, 28] In a review of CNS-IMT in 51 children, complete resection (27 cases) was associated with a 100% response rate and 18.5% recurrence. Partial resection without adjuvant therapy led to disease progression in nearly half of the cases. ALK inhibitors demonstrated promising results in unresectable cases, with 57.1% of seven patients achieving a complete response and 42.9% a partial response.[25]

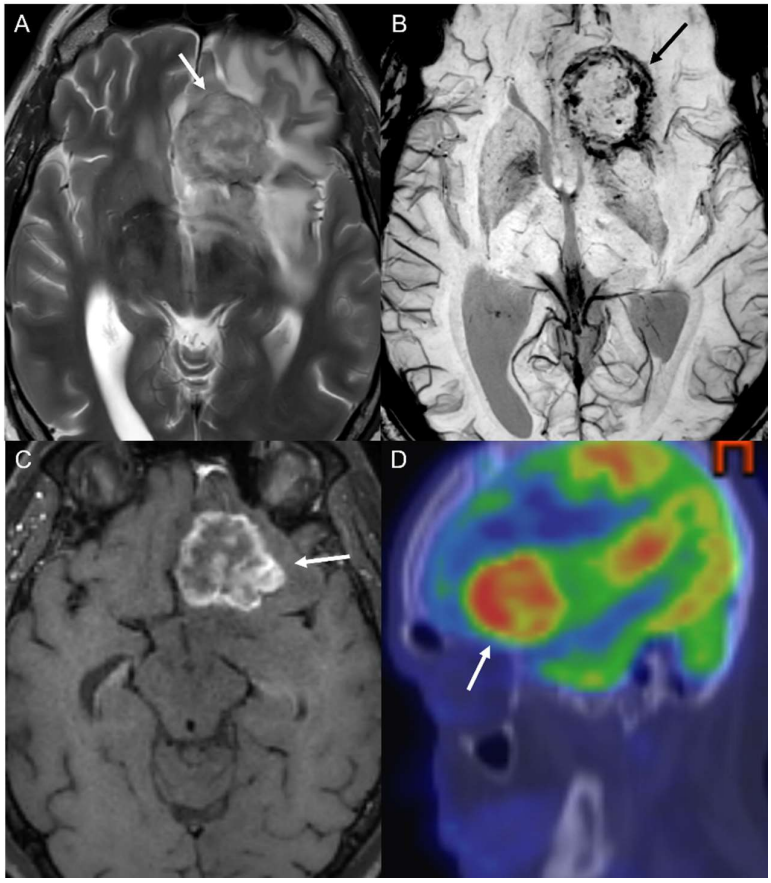

Fig. 3: Intracranial Inflammatory Myofibroblastic tumor in a 35-year-old man. Multiple axial MR images (A-C) reveal a lobulated mass (arrows) in the left basifrontal region with extensive vasogenic edema in the adjacent parenchyma, disproportionate to the size of the mass (A). Lesion shows foci of signal drop out (hemorrhage) on SWI (B) and heterogenous enhancement (C). Lesion shows increased uptake on FDG-PET exam (D). Rapid increase in the size of the mass was noted in the follow-up MRI after three months with clinical deterioration (Suppl. Fig 1). Surgical resection was performed with histopathology revealing epithelioid inflammatory myofibroblastic tumor (IMT). Immunohistochemistry depicted perinuclear ALK staining, correlating with the presence of *RANBP2-ALK* gene fusion (Suppl. Fig 1).

Tumors of uncertain differentiation:

Intracranial Mesenchymal Tumor, FET::CREB Fusion-Positive

It is a group of rare CNS tumors characterized by genetic fusion of a FET RNA-binding protein (usually *EWSR1*, rarely *FUS*) to CREB transcription factors (*CREB1)*[29, 30], *ATF1* [29, 31, 32], and *CREM* [29, 32-34]. [1, 3, 30] These are also termed angiomatoid fibrous histiocytoma. The median age is 17 years (4–70) with a female predominance (male to female ratio, 1:2.2). Rarely reported in the fifth and sixth decades.[34, 35]

These tumors are usually circumscribed extra-axially or intraventricularly and located at the cerebral convexities, falx, lateral ventricles, tentorium, cerebellopontine angle, and rarely spinal canal.[34, 36, 37] Symptoms depend on location and mass effect, including headache, tinnitus, seizures, and focal neurological deficits.[38] Histopathologically, the tumor shows diverse cell morphology (epithelioid/rhabdoid to stellate/spindle) with low mitotic activity. The stroma can be myxoid or collagenous, often with dilated thin-walled blood vessels, hemosiderin, and peripheral lymphoplasmacytic infiltration.[34] EWSR1:CREB1 fusion is associated with stellate/spindle cell morphology, mucin-rich stroma, and hemangioma-like vasculature, while EWSR1:ATF1 fusion is associated with epithelioid cells with mucin-poor collagenous stroma.[34] Immunohistochemistry is positive for EMA, CD99, and Desmin. MUC4, S-100, and synaptophysin show variable expression. Skeletal and smooth muscle markers, *GFAP*, and *OLIG2* are negative.[34] Tumors do not express synaptophysin, *SSTR2A*, and

myogenin.[34] Pathognomonic *FET::CREB* fusion is detected using FISH or DNA/RNA sequencing on next-generation sequencing (NGS) analysis. Differential diagnoses include sarcomas, chordoid, microcystic, and rhabdoid meningioma subtype.[30, 33, 35] These are well-circumscribed lobulated and can have solid or solid-cystic appearance. Tumors are T1-hypointense and T2-hyperintense with avid enhancement, internal hemorrhage, and perilesional edema (Fig.4, Suppl. Fig 2, 3). They can mimic meningiomas with a dural tail or adjacent bony involvement.[34, 36, 39-42]

Tumors have variable courses, from slow growth to rapid recurrence with rare CSF dissemination or systemic metastases. WHO does not provide a definite grading. Gross total resection results in better outcomes. Adjuvant radiotherapy is required for recurrent and incompletely resected tumors.[1] *FET::CREB* fusion tumors are aggressive with a high recurrence rate (~ 40%). Risk factors include younger age, infratentorial location, subtotal resection, and possibly *EWSR1-ATF1* fusion. Median progression-free and overall survival are 12 months and over 60 months. [35]

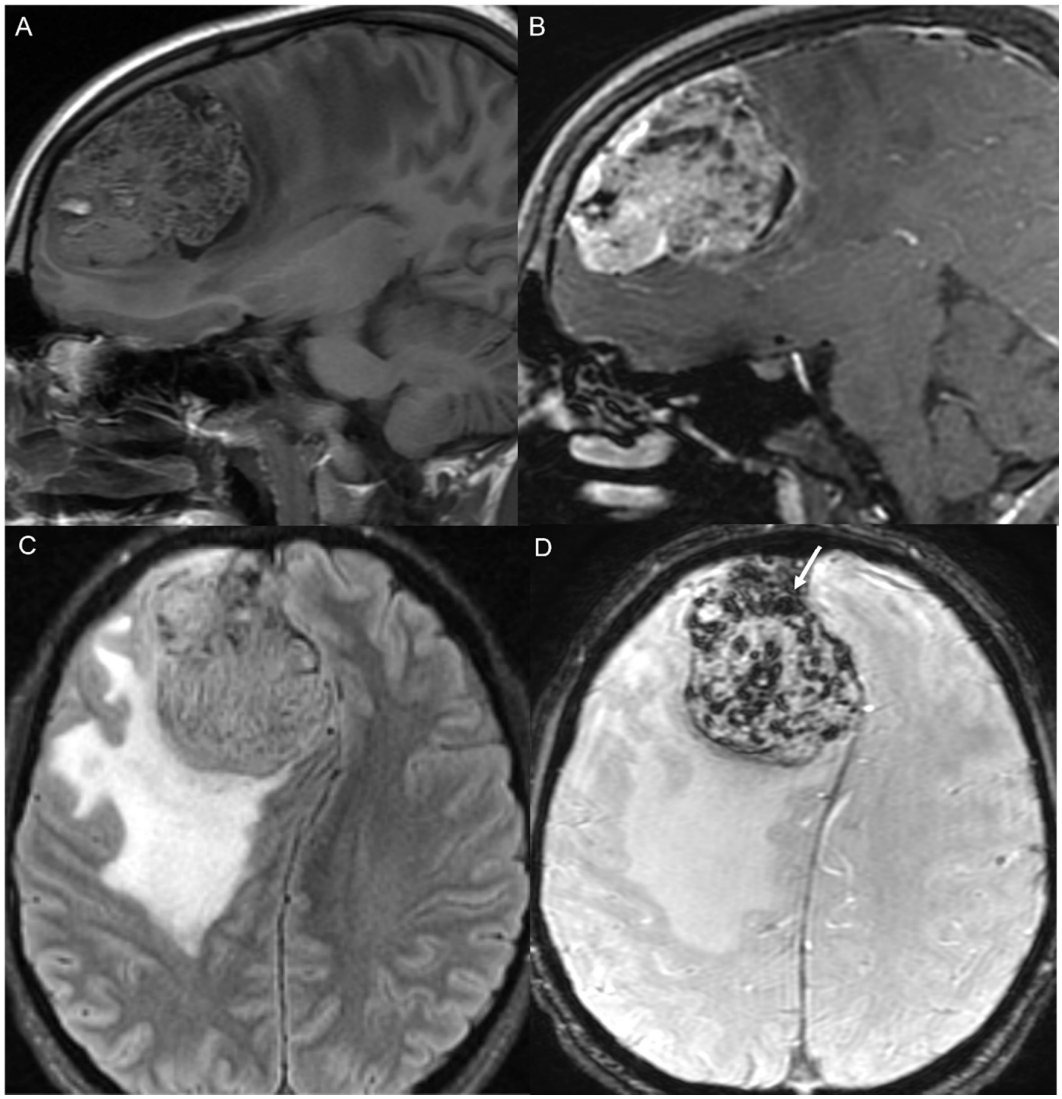

Fig. 4:Intracranial mesenchymal tumor, *FET::CREB* fusion-positive in a 19-year-old-man. Sagittal T1W (A) and contrast enhanced (B) images reveal a large extra-axial dural based mass along the frontal convexity with heterogenous enhancement. Lesion shows heterogenous hyperintense signal on FLAIR (C) with areas of signal-drop out(calcification) on SWI (arrow) (D). Histopathology demonstrated a low-grade mesenchymal neoplasm with clear cell features and fibrillary deposits. Further molecular characterization by targeted next generation sequencing (Sarcoma Targeted Gene Fusion/Rearrangement Panel) revealing *FET::CREB* fusion.

CIC-Rearranged Sarcoma

CIC-rearranged sarcoma is a rare, highly aggressive WHO grade-4 round cell mesenchymal neoplasm and one of the most common subgroups of “Ewing-like sarcomas”.[43] These are clinically and molecularly distinct subtypes of poorly differentiated sarcoma, defined by *CIC*-related gene fusions.[44] They can occur at any age (6 to 83), with a preference for adolescents and young adults without sex predilection. Tumors can be found anywhere in the neuroaxis; 85% are supratentorial, and 15% are spinal. Presenting symptoms are neurological deficits or raised intracranial pressure. [5, 45, 46]

The tumors are well-circumscribed with frequent hemorrhage and necrosis. Histologically akin to their extra-CNS counterparts comprising sheets of highly undifferentiated small round cells with necrosis, lobulated growth pattern, and desmoplastic stroma.[47, 48] Approximately 95% of *CIC*-rearranged sarcomas are characterized by *CIC-DUX4* gene fusions, including multiple fusion partner genes such as *FOXOE4, LEUTX, NUTM1, and NUTM2A.*[43, 49] *CIC-NUTM1* sarcomas affect the pediatric population and are mistaken for nuclear protein of the testis (NUT) carcinomas.[50] The WHO CNS5 diagnostic criteria include *CIC* gene fusion, predominant round cell phenotype, mild nuclear pleomorphism, variable epithelioid and spindle cell admixture, variably myxoid stroma, variable CD99, and frequent ETV4 and WT1 expression. The DNA-methylation profile is a desirable diagnostic criterion.[3, 5] Suspected cases require positive confirmation of *CIC* gene fusion. The unique methylome permits DNA methylation microarray profiling to improve diagnosis.[51]

Radiological data are scarce in the literature and are limited to case reports. Tumors manifest as a hematoma (50%) or solid-cystic mass (38%). They typically present as large solid T2 iso-to-hyperintense variably enhancing extra-axial masses with flow voids and perilesional edema (Fig. 5, Suppl. Fig 4). They show an aggressive course with frequent local recurrences (61%), resulting in death (38%).[5, 45, 46, 50, 52, 53] A retrospective review highlights the aggressive nature of *CIC*-rearranged sarcomas, including metastasis and chemo-resistant nature.[54]

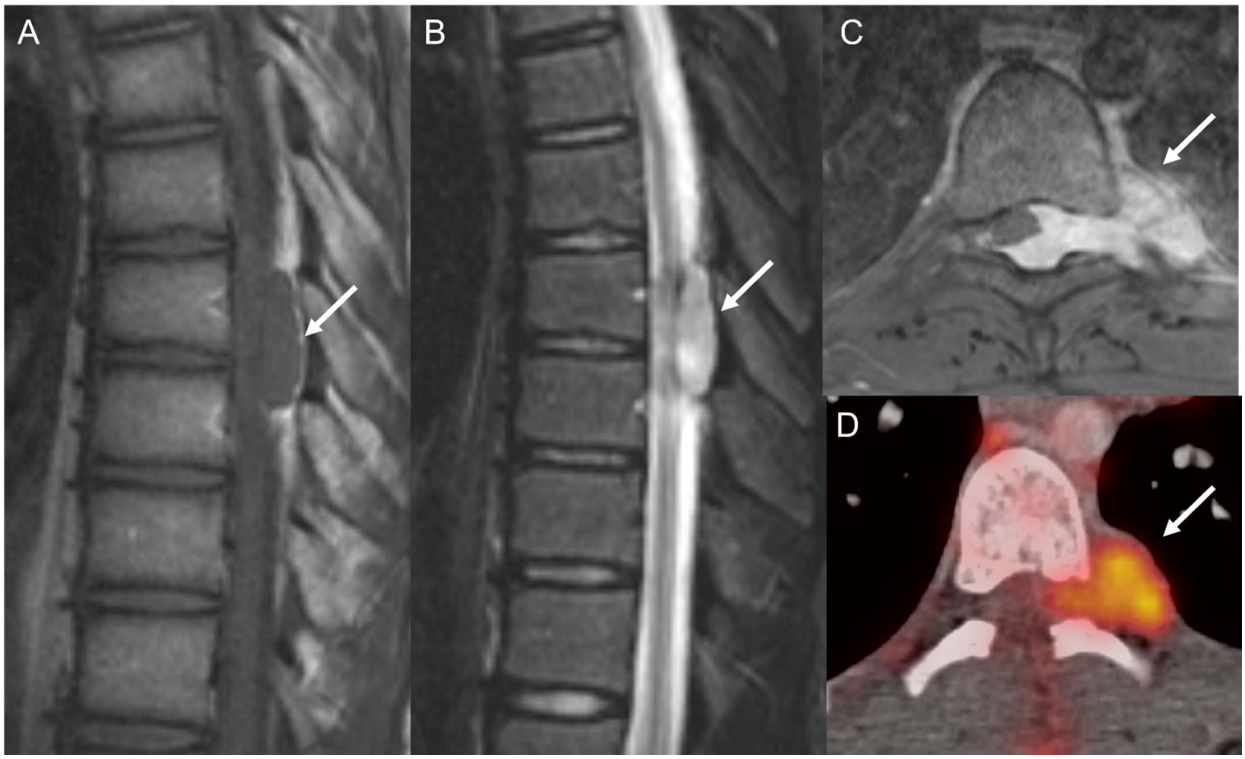

Fig. 5:Spinal CIC-rearranged sarcoma in a 14-year-old-boy. MR images depict a small well-circumscribed peridural mass in the midthoracic region (arrows) with isointense T1 signal (A), hyperintense T2 signal (B) and avid contrast enhancement (C).The tumor extends through the left neural foramen into the paraspinal space with mass effect on the cord. Tumor shows increased uptake on FDG-PET study (arrow) (D). Histopathology (Suppl. Fig 4). revealed sarcomatous cells with neoplastic cells positive for cyclin and calretinin immunohistochemical stains. Molecular cytogenetic studies (FISH) showed balanced rearrangement of the CIC locus in 91% of the nuclei (181/200).

Primary Intracranial Sarcoma, DICER1-Mutant

Primary *DICER1*-mutant sarcoma (DCS) is an aggressive intracranial tumor caused by *DICER-1* gene mutation, which encodes for a micro-RNA processing enzyme.[36] Most are supratentorial (92%), with occasional infratentorial and spinal location. The symptoms include headaches, seizures, or focal neurological signs. The median diagnosis age is six years (2–76 years) with equal sex distribution.[55-61] *DICER1* alterations are linked to pineoblastoma and pituitary blastoma.[62] The exact histogenesis and cell origin are unknown, as with extracranial sarcomas of the kidney, cervix, and other sites harboring *DICER1* mutation.[55, 63, 64] Tumors, originating in the meninges or perivascular spaces, can appear as intra-axial or extra-axial masses, with intra-axial masses typically peripheral within the cerebral hemispheres.[56, 61, 65]

Histologically, these tumors comprise pleomorphic spindle cells arranged in fascicles displaying eosinophilic intracytoplasmic globules, rhabdomyogenic differentiation with high mitosis, intratumoral hemorrhage, and necrosis (Suppl. Fig 5).[55, 56, 59] In contrast to rhabdomyosarcoma, they have limited myogenin expression. DCS presents several mutations associated with *DICER1* alterations, including mutations in the *MAP*-kinase pathway (mainly *KRAS*, *NF1,* and *PDGFRA* genes) *TP53* mutations, loss of *ATRX* expression, loss of *H3K27me3 and* transducin-like enhancer-1 expression.[55, 56, 59, 66, 67] *DICER1* gene (chromosome 14q32) alteration encountered in 98% of reported cases can be somatic or germline as part of *DICER1* syndrome.[55, 65] Seventy-five percent of DCS had multiple somatic *DICER1* alterations, with *TP53* as the most common co-mutation.[62] The. *DICER1* germline mutation is often associated with familial *DICER1* syndrome and sporadically neurofibromatosis type 1 (NF-1), warranting genetic counseling and germline testing.[36, 56, 59] Spinal imaging and CSF sampling is recommended even though specific grading and staging systems are not yet defined. The WHO CNS5 classification mandates the essential diagnostic criteria as primary intracranial sarcoma with pathogenic *DICER1* mutation and DNA-methylation profile (for unresolved lesions).[3]

Radiological data are scarce. DCS are usually well-circumscribed solid-cystic masses with hemorrhage, frequent leptomeningeal, and rarely dural involvement invading brain parenchyma. On MRI, usually T1-hypointense, T2 iso-to-hyperintense, diffusion-restricting, enhancing circumscribed mass with hemorrhage and peritumoral edema (Fig. 6).[56, 57, 59-61, 65, 67] Differentials include anaplastic and malignant meningioma, SFT, gliosarcoma, fibrosarcoma, synovial sarcoma.[68] DCS lack *NAB2:STAT6* fusion (SFT), *PAX3:FOXO1* fusions (alveolar rhabdomyosarcoma), and meningioma mutations (*NF2, TRAF7, KLF4, SMO, AKT1, SMARCB1*).[55, 63, 64] Treatments included surgery and chemoradiation, with a 75% response rate and median progression of 14.5 months.[62] The prognosis remains uncertain due to the limited number of cases and lack of long-term follow-up data, though an aggressive course is suspected[55, 56, 65] A child with a rapidly progressing pineal DCS developed multiple spinal cord metastases and local recurrence.[60]

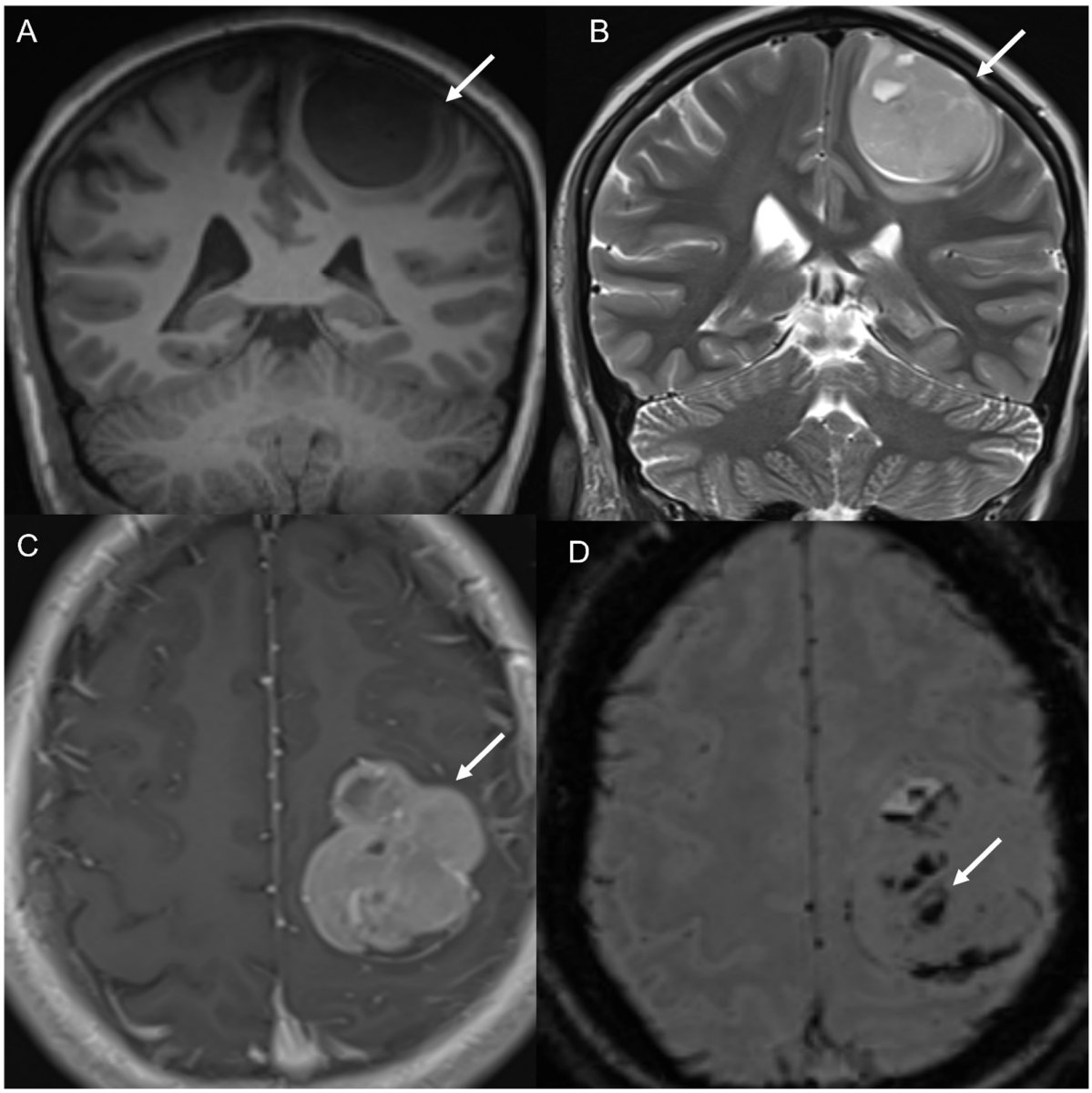

Fig. 6: Primary intracranial sarcoma, *DICER1*-mutant, in a 15-year-ol-girl. MR images depict a small well-circumscribed extra-axial dural based mass along the left frontal convexity with buckling of the underlying cortex (arrows). Tumor shows hypointense T1 signal (A), hyperintense T2 signal (B) and avid contrast enhancement (C). Multiple foci of signal-drop out noted on SWI suggesting hemorrhagic foci. Histopathology (Suppl. Fig 5). demonstrates cellular composed of spindled and pleomorphic tumor cells with high mitotic activity. The tumor cells are positive for MyoD1 (patchy, focal), and negative for Desmin on immunohistochemistry. "Somatic Disease/Germline Comparator Exome" sequencing panel showed pathogenic germline variant for *DICER1*. Overall, the histomorphologic, immunophenotypic and genetic findings are diagnostic of primary intracranial sarcoma, *DICER1* -mutant.

New insights for well-known tumors

Rhabdomyosarcomas

Rhabdomyosarcoma is histologically classified into embryonal, alveolar, pleomorphic, and spindle cell subtypes. Primary CNS alveolar rhabdomyosarcoma is a rare mesenchymal tumor that shares common histological, molecular, and demographic features with non-CNS rhabdomyosarcoma. These tumors are typically found in children and young adults with poor outcomes.[5, 69-72] Infratentorial/skull base (66%) dominates over supratentorial locations (34%). Headaches and mass effects are common symptoms. Supratentorial tumors may cause hemiparesis and cranial nerve palsies in infratentorial tumors.[73]

Histologically, tumors consist of highly cellular primitive round cells with scanty cytoplasm, hyperchromatic nuclei, and fibrovascular septae. Immunohistochemistry is positive for Desmin and myogenin and negative for *GFAP*. Myogenin immunostaining distinguishes the alveolar subtype from the more common embryonal subtype. In the pediatric population, pineal region tumors simulate atypical rhabdoid and teratoid tumors, medullomyoblastoma, teratomas with a rhabdomyosarcomatous component, pineal anlage tumors, and pineoblastomas with rhabdomyoblastic differentiation.[5, 70, 74-76] Rhabdomyosarcomas are characterized by consistent chromosomal translocations and chimeric genes, with *PAX3-FOXO1* and *PAX7-FOXO1* expressed as novel fusion transcripts.[77]

WHO CNS5 essential diagnostic criteria are "A malignant primitive tumor with at least focal immunohistochemical demonstration of skeletal muscle lineage and absence of non-rhabdomyosarcomatous components. Confirming a *FOXO1* gene fusion is crucial in challenging cases (other than alveolar rhabdomyosarcoma)".[3] Limited radiological data available from two case reports[71, 76] showed a mixed solid-cystic cerebellar vermis mass with heterogeneous enhancement [71] and multiple enhancing lesions in the brainstem, cerebellum, and spinal cord in another case[76]. Treatment for intracranial rhabdomyosarcoma includes surgery, adjuvant radiotherapy, and chemotherapy. Early radiation may lead to improvement in survival.[71, 72, 76]

Vascular tumors

Hemangiomas and vascular malformations

Cerebral hemangiomas are benign vascular neoplasms with tightly packed capillary and cavernous vessels. They can occur in isolation, multiple, or as part of a *PIK3CA*-related overgrowth syndrome (Klippel–Trénaunay syndrome).[4] A report describes a parafalcine mass in a child with macrocephaly and facial dysmorphism, mosaic for *PIK3CA R108H.* Hemangiomas usually do not recur after complete resection.[78] Cavernous Malformations (CMs) comprise multiple tightly packed sinusoidal vessels lacking arterial or venous features without intervening CNS tissue. Most CMs are single, asymptomatic, nonhereditary lesions with or without associated developmental venous anomalies (DVA). About 20% of CCMs are familial with an autosomal dominant inheritance. They result from the functional loss in one of the three genes, *KRIT1* (*CCM1*), *CCM2*, or *PDCD10* (*CCM3*). Larger CCMs have the heterogeneous internal signal on T1- and T2WI (popcorn appearance), with a characteristic T2 hypointense ring (hemosiderin). Susceptibility-sensitive sequences are more sensitive for small CCMs.[79-81] Quantitative Susceptibility Mapping MRI allows accurate assessment of iron content, and a threshold increase of 6% reflects new symptomatic hemorrhage.[82] Neuroinflammation quantification is promising for assessing the risk of rupture and screening patients for brain surgery. Flutriciclamide ([18F]GE-180) translocator protein (TSPO) targeting PET tracer uptake correlates with neuroinflammation and can be used for disease monitoring.[83] Solitary lesions with refractory seizures, focal neurological deficits, or mass effect can be resected. CCM treatments include surgical resection, stereotactic radiosurgery, and symptom management.[84] Cerebral arteriovenous malformations (AVMs) consist of variably sized abnormal arteries and veins with direct fistulous connections without intervening capillary beds.[85] The risk of rupture is 2%–5% per year, with significant mortality (25%).[86] AVMs have an association with hereditary hemorrhagic telangiectasia syndrome (Osler–Weber–Rendu disease).[87] Peterson et al. proposed the *RAS-MAPK* pathway for developing sporadic and syndrome-associated AVMs.[85] On CT, vessels in AVMs are iso-hyperdense with significant enhancement and areas of calcifications. Honeycomb flow voids are noted on T2WI due to high flow. Conglomerates of tortuous vessels with early venous drainage are noted on angiography.[88] Hemangioblastoma is a benign vascular tumor composed of neoplastic stromal cells with clear cytoplasm, characteristic Inhibin positivity, and *VHL* gene alterations. VHL-associated tumors are multiple and occur at a younger age. [4, 89] These are well-demarcated solid-cystic enhancing masses, frequently present as a cyst with a peripheral enhancing T1 hypo-isointense and T2-hyperintense mural nodule with serpentine flow voids. Angiography is useful for identifying small lesions mimicking AVM. Lightbulb-like intense and homogenous hyperperfusion within the solid component on arterial spin labelling (ASL) is helpful.[90]

Emerging entities

Dural Angioleiomyomas

Angioleiomyomas are benign smooth muscle vascular tumors noted in lower extremities subcutaneous tissue. Dural angioleiomyomas are rare, with <80 cases reported. It affects adults between the fourth and the sixth decades. These are intradural perivascular tumors with histopathological similarities with soft tissue angioleiomyomas, frequently having *GJA4* mutations.[91] In a large series (202 cases) of CNS vascular and perivascular lesions, only 3 cases (1.5%) were dural angioleiomyomas.[91] Histology shows abnormally enlarged vascular cavities separated by thick fibrous septa lined by endothelial cells stained with CD34. Immunohistochemistry is positive for smooth muscle actin and Calponin and negative for HMB45, *GFAP*, *PS100*, *STAT6*, *EMA*, and *SSTR2a*. [91, 92] DNA methylation profiles formed a distinct epigenetic group, separating them from soft tissue angioleiomyomas, other vascular tumors, inflammatory myofibroblastic tumors, and meningiomas.[5, 91] *GJA4 p.Gly41Cys* mutation is a frequent event. [91] There was no evidence of rearrangement of the CCM1/2/3 genes or MAP3K3, PIK3CA, or KRAS as implicated in CCM and AVMs. [91] "Dural angioleiomyoma" is being suggested due to dural location and distinct methylation profile, which require further studies to confirm its inclusion in the WHO CNS tumors classification.[5, 91]

CT scan shows a round, well-circumscribed, hyperdense extra-axial lesion. MRI shows T1-hypointense and T2-hyperintense lesions with strong FLAIR signals and heterogeneous enhancement. There is no dural tail sign, hemorrhage, or hemosiderin deposits.[91 92] MR Perfusion showed progressive, centrifugal enhancement with slow contrast filling, rapid near the center but slower toward the outer edges.[93] Partial and flame-like enhancement arising from the tumor base and extending to its periphery is reported as characteristic.[94] The tumor can be excised without complications. No recurrences were found over a median follow-up of 14 months.[92]

Spindle Cell Neoplasms, NTRK-Rearranged (SCN-NTRK)

Neurotrophic receptor kinase *(NTRK)* gene fusions are involved in various CNS and soft tissue tumors. SCN-NTRK has been recently added to the 2020 WHO Classification of Soft Tissue Tumors.[5, 95] It is a rare neoplasm.[95-97] Debates persist about the lineage and terminology due to histopathological and molecular overlaps with other soft tissue entities. The available literature on these tumors is limited. It presents as large, solid-cystic, heterogeneously enhancing supratentorial masses. Tumors exhibit peritumoral edema and tend to both local recurrence and distant metastasis.[95-97] A recent study of 11 cases (2 CNS) revealed similar histopathological, immunophenotypical, and molecular (spindle cell tumors with coexpression of CD34 and S100 and variable *CDKN2A* homozygous deletion) features of soft tissue and CNS cases with unique and new methylation cluster.[95] These tumors predominately affect children and young adults. SCN-NTRK shares similar features in all locations. CNS SCN-NTRK is probably underdiagnosed, and further cases of CNSSCN-NTRK are needed to confirm their place in the following WHO Classification of CNS tumors.[95] *NTRK* gene fusions could become promising therapeutic targets in cancer therapy in CNS tumors.[97]

Conclusion

the WHO CNS5 classification has significantly refined the categorization of mesenchymal non-meningothelial tumors, emphasizing histomolecular characteristics and introducing new subcategories for tumors of uncertain differentiation. While the classification covers well-defined entities, emerging tumors like dural angioleiomyomas and spindle cell neoplasms with NTRK-rearrangements, although not included, highlight the need for ongoing research. As molecular techniques continue to evolve, they will play a critical role in improving diagnostic accuracy and potentially expanding future classifications.

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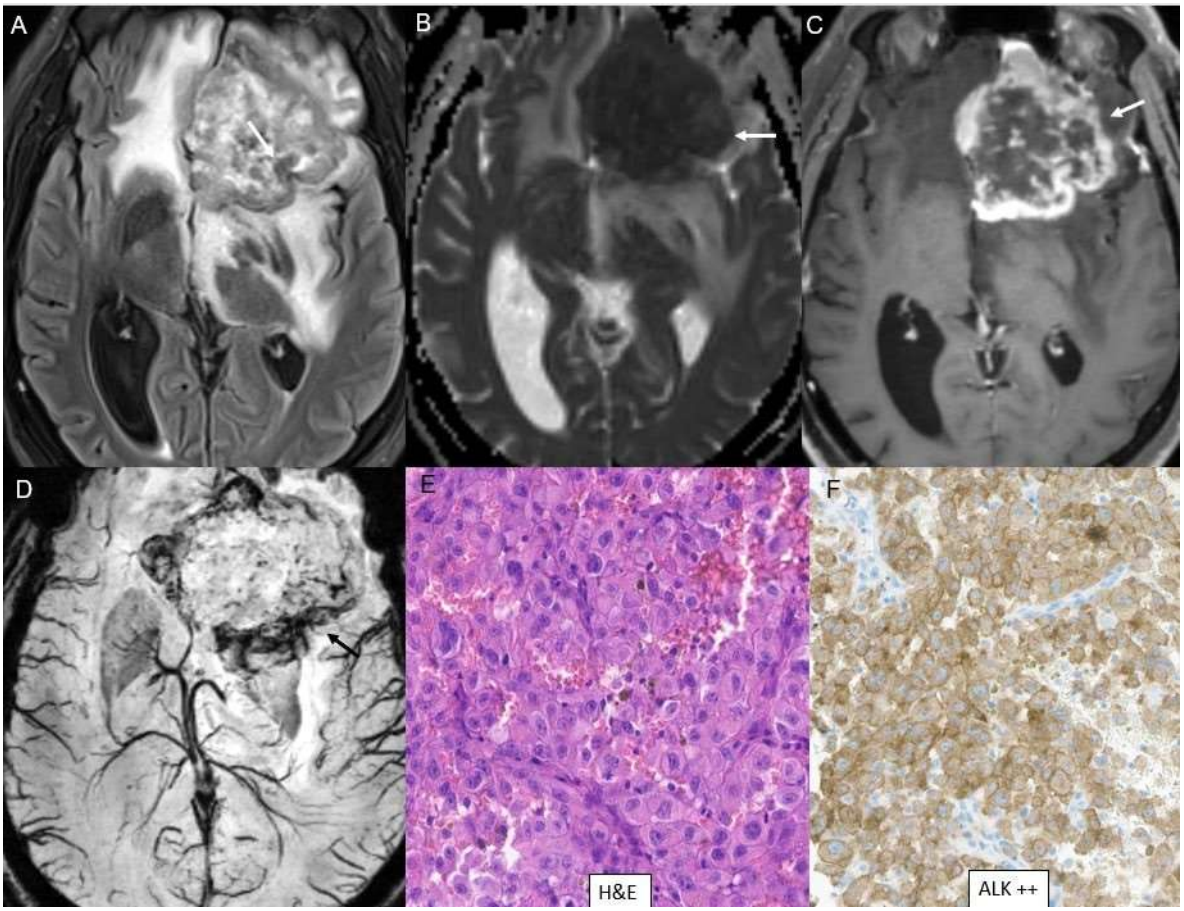
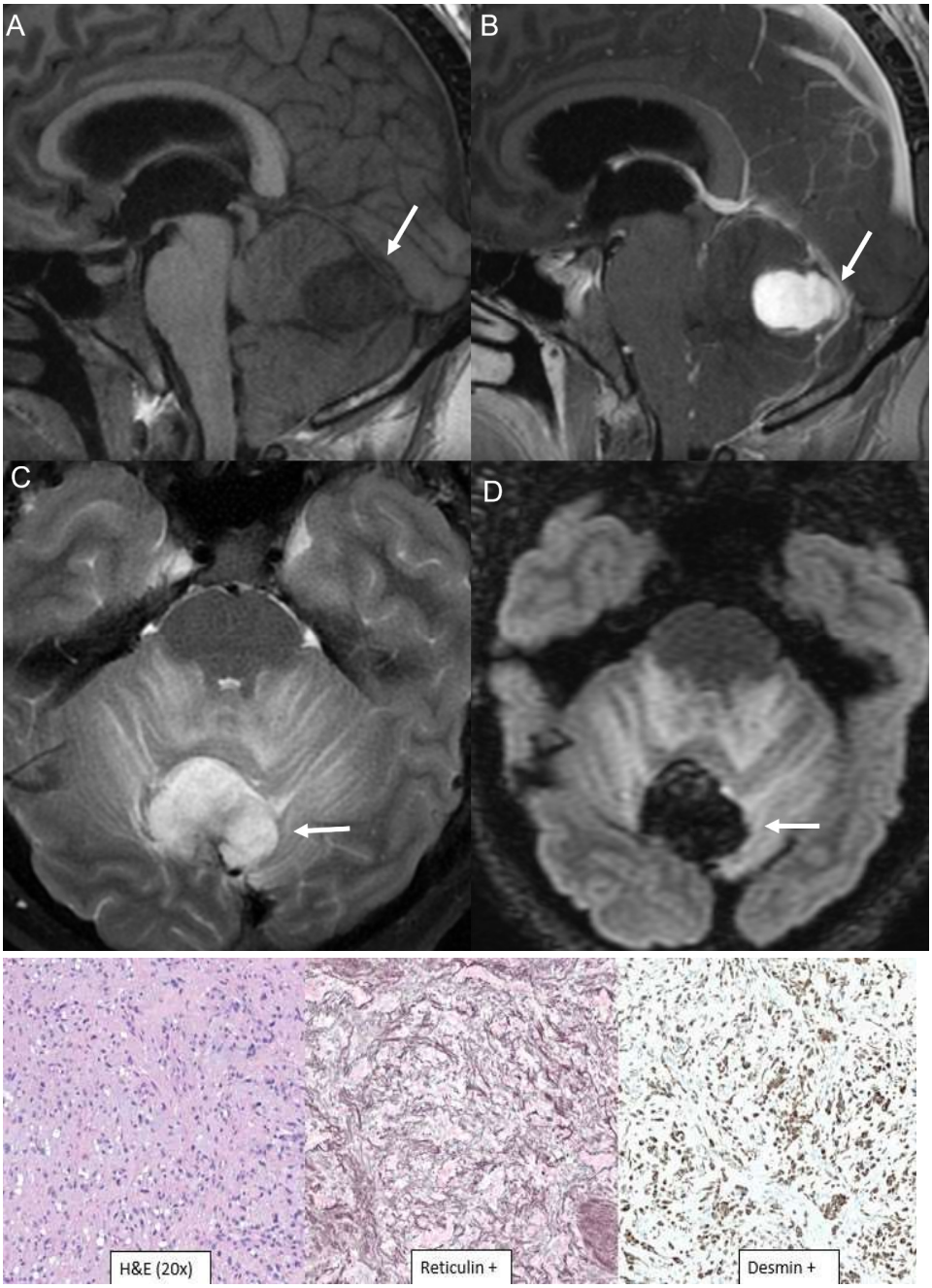
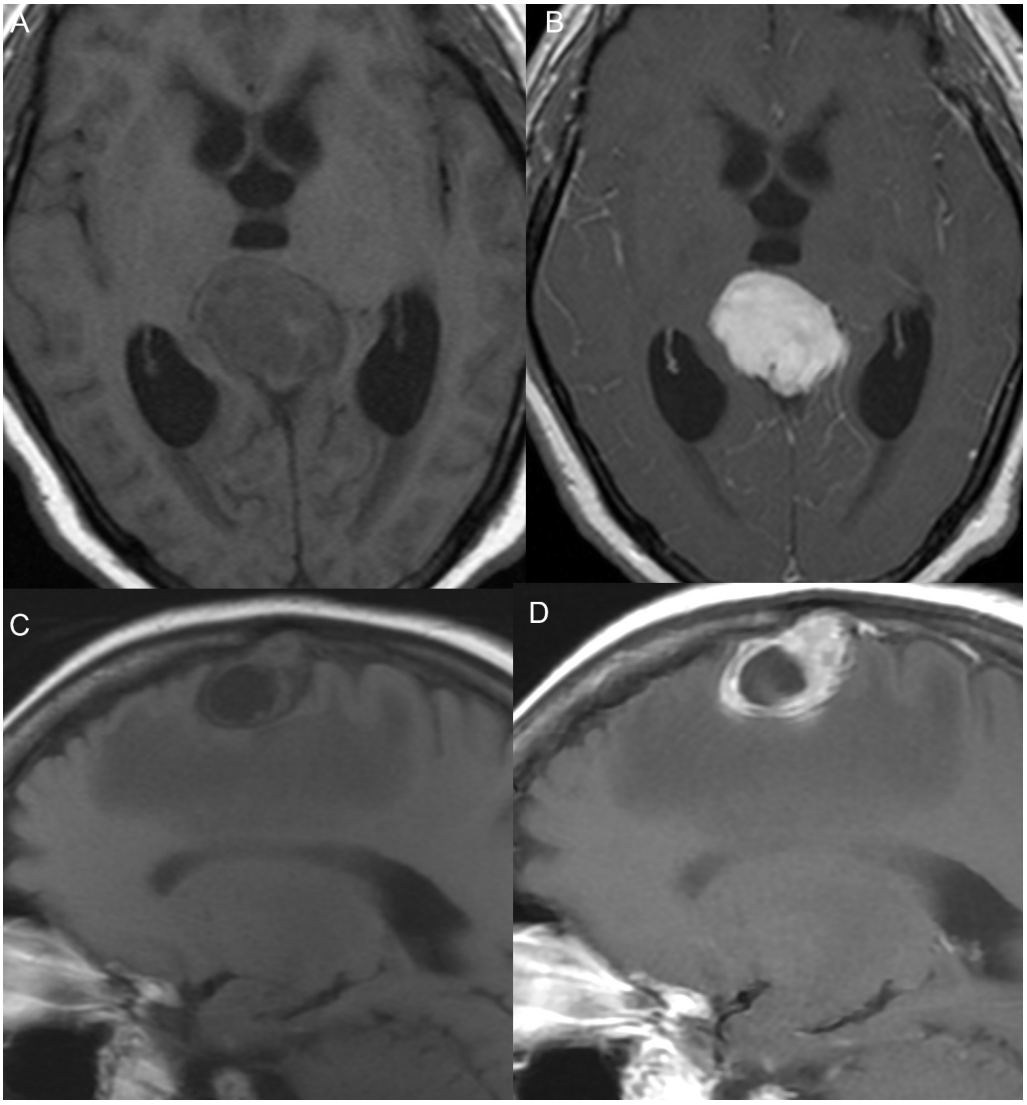
SUPPLEMENTAL FILES



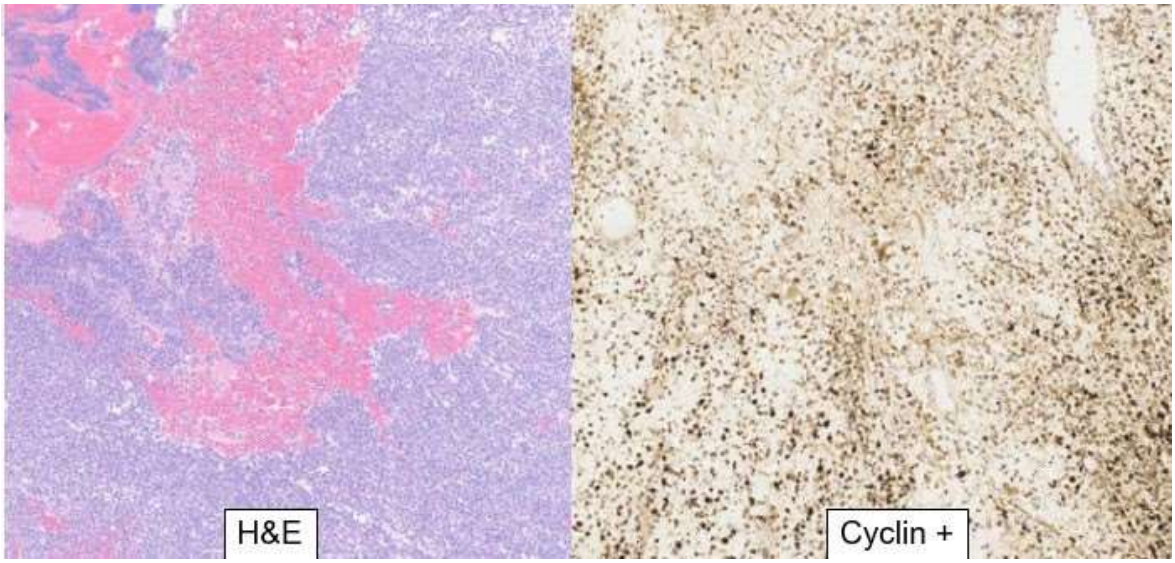
Supplemental Fig. 1: Intracranial Inflammatory Myofibroblastic tumor in a 35-year-old man. Rapid increase in the size of the mass was noted in the follow-up MRI after three months (arrow) with clinical deterioration. Surgical resection was performed with histopathology, revealing epithelioid inflammatory myofibroblastic tumor (IMT). HCE stain reveals multiple densely packed epithelioid cells with abundant myxoid stroma. Immunohistochemistry depicted perinuclear ALK staining, correlating with the presence of *RANBP2::ALK* gene fusion.



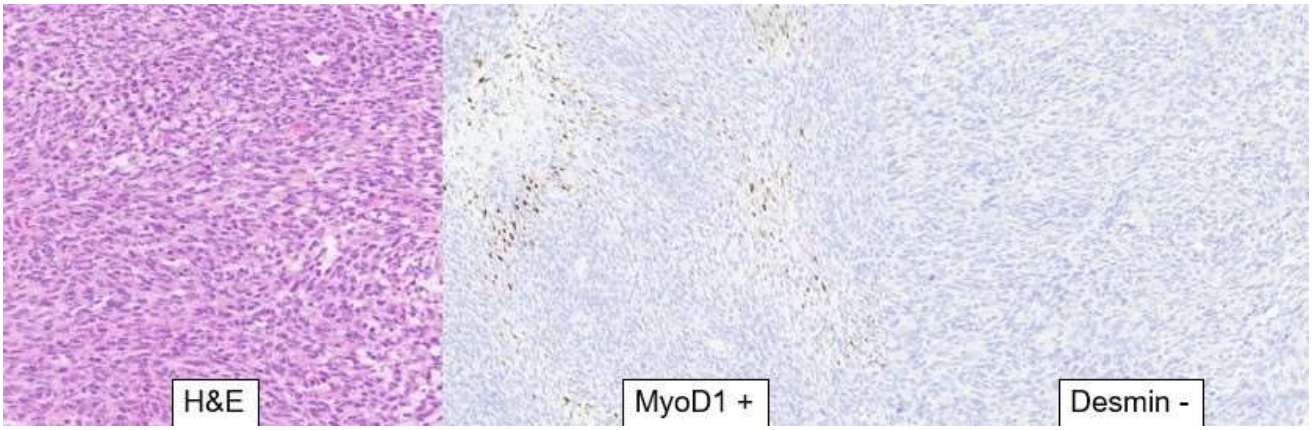
Suppl. Fig 2:Intracranial mesenchymal tumor, *FET::CREB* fusion-positive in a 21-year-old- man.Sagittal and axial MR images reveal a lobulated well-circumscribed mass (arrow) in the posterior fossa alongthe tentorium. Lesionshows hypointense signal on T1W image (A) with avid homogenous enhancement (B). Lesion appears hyperintense on T2W (C) with loss of signal on FLAIR and moderate edema in the adjacent cerebellum. Histopathology demonstrated a low-grade mesenchymal neoplasm involving the meninges. Tumor showed positive staining for connective tissue (reticulin) and muscle protein (desmin). Further molecular characterization by targeted next generation sequencing (Sarcoma Targeted Gene Fusion/Rearrangement Panel) revealing *FET::CREB* fusion.



Suppl Fig. 3 :Intracranial mesenchymal tumor, *FET::CREB* fusion-positive in two different patients. Pineal region extra-axial mass in a 43-year-old-man with iso-to-hypointense signal on T1W image (A) and avid homogenous contrast enhancement (B), with mass effect and obstructive hydrocephalus. Frontal convexity dural based massin 58-year-old woman (C,D) with solid-cystic appearance and peripheral enhancement and moderate adjacent parenchymal edema. Histopathology revealed spindle cells in a densely collagenous stroma. Further molecular characterization by targeted next-generation sequencing (SarcomaTargetedGeneFusion/RearrangementPanel) fusion of a FET RNA-bindingprotein familygene *(EWSR1)* and a memberof the *CREB* family of transcription factor, supporting the diagnosis.



Suppl. Fig. 4: Spinal CIC-rearranged sarcoma in a 14-year-old-boy. Histopathology reveals sarcomatous cells with neoplastic cells positive for cyclin (shown here) and calretinin immunohistochemical stains. Molecular cytogenetic studies (FISH) showed balanced rearrangement of the *CIC* locus in 91% of the nuclei (181/200).



Suppl. Fig. 5: Primary intracranial sarcoma, *DICER1*-mutant, in a 15-year-ol-girl. Histopathology demonstrates cellular composed of spindled and pleomorphic tumor cells with high mitotic activity. The tumor cells are positive for MyoD1 (patchy, focal), and negative for Desmin onb immunohistochemistry. "Somatic Disease/Germline Comparator Exome" sequencing panel showed pathogenic germline variant for DICER1. Overall, the histomorphologic, and genetic findings are diagnostic of primary intracranial sarcoma, DICER1-mutant.