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Central nervous system tumors of uncertain differentiation

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A B S T R A C T

Background: The 2021 World Health Organization classification for brain tumors introduced several new entities and categories.
Tumors of uncertain differentiation are a new subcategory that includes the intracranial mesenchymal tumor, FET-CREB fusion-positive; the CIC-rearranged sarcoma; and the Primary intracranial sarcoma, DICER1-mutant.
Methods: A search was made in Pubmed and Google Scholar to include all articles with the term "uncertain differentiation", "Mesenchymal, non-meningothelial", "FET-CREB fusion positive", "DICER1-mutant sarcoma" and "CIC-Rearranged sarcoma" in their title. These articles were reviewed to draft a concise review on this subject.
Results: This review on CNS non-meningothelial mesenchymal tumors is meant to provide an update with diagnostic, prognostic, and therapeutic implications.
Conclusion: Tumors of uncertain differentiation include a variety of mesenchymal, non-meningothelial tumors that have distinct molecular characteristics and consequently behave in a very particular matter.
Given that these tumors have been described only recently, there is still an important lack of information regarding the most appropriate treatment and prognosis.

1. Introduction

In 2021 the World Health Organization (WHO) published the fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS),[1] this latest version introduces relevant changes by including molecular characteristics in the diagnosis of CNS tumors while also keeping other approaches to tumor characterization, like histology and immunohistochemistry.[2] Mesenchymal, non-meningothelial tumors now hold a category of their own in this update. Tumors of uncertain differentiation are a new subcategory and include the new types that have been added such as the intracranial mesenchymal tumor, FET-CREB fusion-positive; the CIC-rearranged sarcoma; and the Primary intracranial sarcoma, DICER1-mutant.[2]

This review attempts to gather the available information regarding these new categories.

2. Methods

A search was made in Pubmed and Google Scholar to include all articles with the term "uncertain differentiation", "Mesenchymal, non-meningothelial", "FET-CREB fusion positive", "DICER1-mutant sarcoma" and "CIC-Rearranged sarcoma" in their title. These articles were reviewed and later organized in order to obtain the necessary information to develop a concise review of this tumor entity.

3. Discussion

3.1. Mesenchymal, non-meningothelial tumors

The group of mesenchymal, non-meningothelial tumors of the CNS comprises various entities thought to arise mainly from the meninges and surrounding bone structures. As a whole, these neoplasms are histologically similar to their extracranial bone and soft tissue counterparts.[3]

CNS mesenchymal, non-meningothelial tumors constitute less than 1% of all CNS neoplasms. Their histology and immunophenotype are often non-specific, which makes them sometimes difficult to diagnose.[4] The development of molecular techniques and their implementation in clinical practice has led to a better classification of these tumors and the consequence introduction of different molecularly defined entities to the WHO classification of CNS tumors.

In the 2021 WHO classification, tumors termed as mesenchymal, non-meningothelial tumors include soft tissue tumors; in this category the term "hemangiopericytoma" has been retired, and now this tumor is called "solitary fibrous tumor", rather than the previous hybrid term: "solitary fibrous tumor/hemangiopericytoma".[2] The other subtypes of mesenchymal, non-meningothelial tumors are vascular tumors represented by hemangioblastomas, skeletal muscle tumors represented by rabdomyosarcomas, chondro-osseous tumors, notochordal tumors and finally tumors of uncertain differentiation,[2] which we will now review in further detail. Table 1 summarizes the clinical characteristics of each

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tumor category.

3.2. Intracranial mesenchymal Tumor, FET- CREB fusion-positive

Intracranial mesenchymal tumor, FET-CREB fusion-positive was introduced in the 5th Edition of the WHO classification of CNS tumors as a provisional entity,[1,2] it was previously described as either intracranial angiomatoid fibrous histiocytoma or intracranial myxoid mesenchymal tumor.[5] It is a mesenchymal neoplasm characterized by the fusion of a FET family member, usually EWSR1, with a member of the CREB family of transcription factors.[4]

Diagnostic criteria for Intracranial Mesenchymal Tumor, FET::CREB fusion-positive are: 1) primary intracranial location; 2) variable morphological features including spindle cells, mucin-rich stroma, haemangioma-like vasculature, or epithelioid cells in a mucin-poor collagenous stroma; 3) demonstration of a FET::CREB family fusion.[1]

Sloan and their team described histological and molecular characteristics of this tumor subtype[5]; in their series, intracranial mesenchymal tumors with FET-CREB fusion demonstrated a wide variety of morphological and histologic features.

Morphological features that resemble meningiomas have been described, histologically these tumors are multinodular and well-circumscribed and are frequently surrounded by a fbrous pseudocapsule.[6]

Immunohistochemically these tumors are positive for desmin expression, and most cases are also positive for EMA and CD99 in a membranous pattern.[4,5]

Sloan's team analyzed 20 patients, and next-generation sequencing revealed that eight tumors harbored EWSR1-ATF1 fusion, seven had EWSR1-CREB1 fusion, four had EWSR1-CREM fusion, and one had FUS-CREM fusion.

These tumors are usually supratentorial, well delineated, of extra-axial location and occur in children and young adults with a median age at diagnosis of 14 years.[5,7] Female patients are affected in up to 62% of cases.[8] Some cases of infratentorial location have been reported in the literature.[6]

Presenting symptoms are dependent of size and location; they include most frequently headaches or nausea, and also may present occasionally with seizures, tinnitus, or diplopia.

These tumors have been described radiologically as well circumscribed and lobulated, often with both solid and cystic components, they show strong enhancement after contrast administration, usually intratumoral blood products, and substantial peritumoral edema are found.[5] They are exclusively extra-axial and in close relationship to meningeal structures, even showing a "meningeal tail" in some cases, characteristic that may give this tumor the appearance of a meningioma.

Patients harboring these tumors usually receive surgery as the first line of treatment. The available data suggest improved outcomes for patients that are able to undergo gross total resection.[5]

Optimal adjuvant treatment has not been defined yet, however radiation therapy to the surgical bed has been suggested given the risk for local recurrence, especially after incompletely resection.[5]

With the available information the prognosis for this pathology is uncertain, as the number of cases reported is low; some of the reported cases had an indolent course, while others recurred in the short term, and up to 8% of the reported cases have died from the disease.[4,5,8–10]

3.3. Primary intracranial sarcoma, DICER1-mutant

Primary intracranial sarcoma, DICER1-mutant, is a new entity in the 5th edition of CNS tumor classification of the WHO.[2]

Patients with DICER1 predisposition syndrome have an increased risk of developing pleuropulmonary blastoma, cystic nephroma, embryonal rhabdomyosarcoma, and several other tumor entities.

In 2018 Koelsche et al published a study describing a group of 22 primary intracranial sarcomas, including 18 in pediatric patients, which all displayed similar methylation patterns and possessed DICER1 inactivating mutations.[8] It is interesting to note that he tumors in this study were previously classified as gliosarcoma, glioblastoma, malignant tumor, extra-skeletal mesenchymal chondrosarcoma and primitive neuroectodermal tumor.

Given the rarity of intracranial sarcomas, it is likely that histological characteristics alone would not be enough to adequately classify these tumors. The mutation of DICER1 clearly defines a molecular group that unifies these tumors under a common basis. Because the histology of these tumors is highly variable and the differential diagnosis vast, confirmation of the DICER1 mutations is a very valuable tool in order to achieve a definitive diagnosis.

Histologically, these tumors were composed of spindle and pleomorphic cells arranged in fascicles mixed with areas of reduced cellularity.[4]

Although its name would suggest an exclusive intracranial location, some cases of infratentorial and spinal locations have been described.[11] Almost all cases have been described in children and young adults, still a

Table 1
Summary of clinical and radiological characteristics of the different tumor entities

Tumor Subtype	Epidemiology	Pathology	Radiological Characteristics	Treatment	Prognosis
Intracranial Mesenchymal Tumor, FET- CREB fusion-positive	Female Median age of 14 years	Diagnostic criteria: 1) primary intracranial location 2) Variable morphological features including spindle cells, mucin-rich stroma, haemangioma-like vasculature, or epithelioid cells in a mucin-poor collagenous stroma 3) Demonstration of a FET::CREB family fusion	Exclusively extra-axial Close relationship to meningeal structures Well circumscribed and lobulated Strong contrast enhancement	Improved outcomes after gross total resection Adjuvant radiation therapy has been suggested Optimal adjuvant treatment has not been defined yet	Prognosis is uncertain Variable Outcomes
Primary intracranial sarcoma, DICER1-mutant	Equal sex distribution Mostly in children Have been described in adults	Composed of spindle and pleomorphic cells arranged in fascicles mixed with areas of reduced cellularity	Mostly Supratentorial Solid and cystic mass Frequent Hemorrhage Leptomeningeal attachment Heterogeneous contrast enhancement	Gross total resection as initial treatment Adjuvant ICE Chemotherapy Radiation Therapy to surgical bed	Varies according to case series PFS close to 50% at 2 years OS close to 70% at 2 years
CIC-rearranged Sarcoma	Equal sex distribution Median age of 10 years	All CIC-rearranged sarcomas have a fusion of CIC transcriptional repressor with various partners, most often DUX4,	Extra-axial solid and cystic mass Variable contrast enhancement Frequent Hemorrhage	Published cases show surgical resection as primary treatment Variable Chemotherapy regimens Adjuvant craniospinal radiotherapy	Not enough information

wide variety of ages have been described ranging children to elder adults with the sex distribution being almost equal across the reported cases [11, 12. 13].

Radiological descriptions are scarce but usually present as a solid and cystic mass, with hemorrhage and leptomeningeal attachment, and a heterogeneous contrast enhancement pattern.[8,12]

Information regarding clinical characteristics of this tumor entity relies on several reported series.

In 2019 Maki Sakaguchi et al published a report of 2 cases of rhabdomyosarcoma under the designation that Koelsche proposed: "spindle cell sarcoma with rhabdomyosarcoma-like features, DICER1 mutant".[13] The cases described involved a 10-year old and a 29-year old patient, they developed supratentorial masses that underwent surgical resection. Adjuvant treatment was initiated with multimodal chemotherapy and fractionated radiotherapy. The pediatric patient developed several recurrences and underwent different lines of treatment. Last follow-up was at 68 months.

Diaz Coronado published a series of 28 tumors classified as primary CNS sarcoma, DICER1 mutant.[12] The median age of the patients was 6 years ranging from 2 to 17.5 years, and 66 of 70 patients had supratentorial tumors. Patients with nonmetastatic disease that were treated with a combination of chemotherapy and radiation therapy had a 2-year progression-free survival rate of 58% and a 2-year overall survival rate of 71%.

Kamihara et al published a series of 6 pediatric patients with DICER1-associated central nervous system sarcoma.[14] The six patients presented at ages 3–15 years with CNS tumors located in the temporal, parietal, fronto-parietal, and frontal lobes. Postoperative care included radiation and chemotherapy; at the last follow-up, three patients were alive without tumor progression at 46, 30, and 21 months, and three had died from the disease.

More recently a large series of different tumors with DICER1 mutations that included low and high-grade gliomas, as well as sarcomas was published by Liu et al.[15] Out of the 98 included patients, 6% had a CNS sarcoma as their tumor diagnosis. The median progression free survival for this cohort was 16 months. This series shows that DICER1-mutated CNS sarcoma in particular represents a poor prognosis, similar to high-grade gliomas.

Finally, Cardona et al published a case series in 2023 of adult patients with primary DICER1 mutated intracranial sarcomas. The median age at presentation was 20 years of age. Patients were treated with surgical resection followed by Ifosfamide, Cisplatin, and Etoposide (ICE) chemotherapy and radiotherapy. Progression-free survival was 14.5 months and Overall survival was 30.8 months.[16]

3.4. CIC-rearranged sarcoma

In addition to the tumor entities mentioned above, another bone and soft tissue sarcoma that is usually described outside of the CNS, the CIC-rearranged sarcoma, was relatively recently described in the brain.[2]

CIC-rearranged sarcoma is a high-grade mesenchymal tumor that usually occurs in the viscera, but as mentioned above, may occur within the CNS as well. To date, there have been scarce reports of primary CIC-rearranged sarcomas in the brain.[17–19]

All CIC-rearranged sarcomas have a fusion of CIC transcriptional repressor with various partners, most often DUX4, but also NUTM1 or NUTM2 have been observed.[4,20] While in most peripheral CIC-rearranged sarcomas the fusion partner is DUX4, in the brain the most common fusion partner is NUTM1.[4,21]

The majority of cases are described children and young adults with a median age of nearly 10 years, with no preference for male or female patients.[17,18,21–23]

In nearly half of the cases these tumors seem to manifest as an intracerebral hematoma or as a solid and cystic mass.[8,21]

Due to the rarity of this tumor entity treatment and outcomes of CNS CIC-rearranged sarcoma are not well published; the tumors in the soft tissues have an aggressive course and poor response to therapy.[17] Conolly et al described the case of a 27-year old male with a frontal lobe lesion that was confirmed to be a CIC-rearranged sarcoma after surgical resection. The patient received adjuvant therapy with fractionated radiotherapy to the surgical bed at a dose of 36Gy followed by craniospinal radiation up to 23.4Gy. The prognosis for this particular patient was not specified, although as a group, patients with confirmed CIC-rearranged sarcomas had a median overall survival from diagnosis of 16.3 months.[17] For patients with visceral CIC-rearranged sarcoma chemotherapy treatment with vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide has been described, although no information regarding its effectiveness for primary brain lesions exists.

The intracranial variant of these tumors seem to behave like their soft tissue counterparts, most tumors follow an aggressive course with frequent recurrences resulting in death in most of the reported cases.[17,18,21,24]

4. Conclusion

Tumors of uncertain differentiation include a variety of mesenchymal, non-meningothelial tumors that have distinct molecular characteristics and consequently behave in a very particular matter.

CRediT authorship contribution statement

Javier A. Jacobo: Conceptualization, Investigation, Methodology, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CNS: Central Nervous System
WHO: World Health Organization
OS: Overall Survival
PFS: Progression Free Survival