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RESEARCH ARTICLE

A CASE OF DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMORIN AN ADOLESCENT MALE

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Abstract

Dysembryoplastic neuroepithelial tumors (DNETs) are low grade glioneuronal tumors frequently occurring in the pediatric population and in young adults. The correct diagnosis is based on Magnetic resonance Imaging, Immunohistochemistry, and identification of fibroblast growth factor receptor 1 and BRAF V600E mutations. These tumors are considered non-recurring lesions and gross total surgical resection are curative with disappearance of seizuresin up to 100% of cases. We report a 13-year-old male patient who was admitted to the emergency department for a generalized seizure, with a 5-year-history of iterative complex partial seizures for which he has been receiving valproic acid, with no improvement. A Magnetic Resonance Imaging was performedrevealing a 14x12mm, oval-shaped, circumscribed solido-cystic lesion, of the left fronto-parietal lobes cortex. A ring enhancing appearance could be also identified.Pathological assessment has revealedthe presence of a low-cellularity neoplastic proliferation made of round, uniform, mildly atypical cells, in an abundant myxoid stroma that contained numerous bundles of axons. Floating neurons were also observed. Follow-up of the patient showed a favorable evolution with complete disappearance of any seizures anti-convulsive therapy has been stopped.Follow-up MRI surveillance is planned in our patient.

Introduction:-

Dysembryoplastic neuroepithelial tumors (DNETs) are grade 1glioneuronal neoplasms[1,2]. They occur in children and young adultswith a peak incidence in the age group between 10-14 years [1]. DNETs were first described by Damas-Duport in 1998[3]. On the clinical level, the most characteristic symptoms remain to be early onset chronic drug-resistant partial complex seizures that are sometimes associated with headache and papilledema [3,4]. On the morphological level, the presence of low-cellularity oligodendrocyte-like cells proliferation is characteristic [5]. Some cases of misdiagnoses havebeen reported[6,7], emphasizing the key role of Imaging, morphology, immunohistochemistry, and molecular pathology to establish a correct diagnosis [8]. We report a 13-year-old female

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patient who was admitted to the emergency department for a generalized seizure. She has a 5-year history of iterative complex partial seizures for which she has been receiving valproic acid, with no improvement. Imaging revealed a 14x12mm, oval-shaped, circumscribed solido-cystic lesion, of the left fronto-parietal lobes cortex. A transcortical resection of the lesion has been performed.Pathological assessment has revealed a DNET. After resection, follow-up of the patient showed a complete disappearance of any seizures. Follow-up MRI surveillance is planned for our patients.

Case Presentation

We report a 13-year-old male patient who was admitted to the emergency department for a generalized tonic-clonicseizure, with a 5-year-history of iterative, drug-resistant partial complex seizures for which she has been receiving valproic acid, with no improvement. Clinical examination at admission found a confused patient. He regained consciousness 10 minutes after admission. The mother reported a fall during her seizure, explainingthe presence of abruise on the right side of his forehead. After the patient regained consciousness, he was well oriented to time and place.Arterial blood pressure was normal at 120/56 mmHg, and the respiratory rate was slightly elevated at 23 breaths per minute. The oxygen saturation was normal at 98% with no oxygen therapy. Neurological examination found a positive right Babinski sign and a quick right patellar reflex. No motor or sensitive deficits were found during the rest of the examination. A magnetic resonance Imaging (MRI) was performed revealing a 14x12mm, oval-shaped, circumscribed solido-cystic lesion, of the left fronto-parietal lobes cortex. A ring enhancing appearance could be also identified (Figure 1).

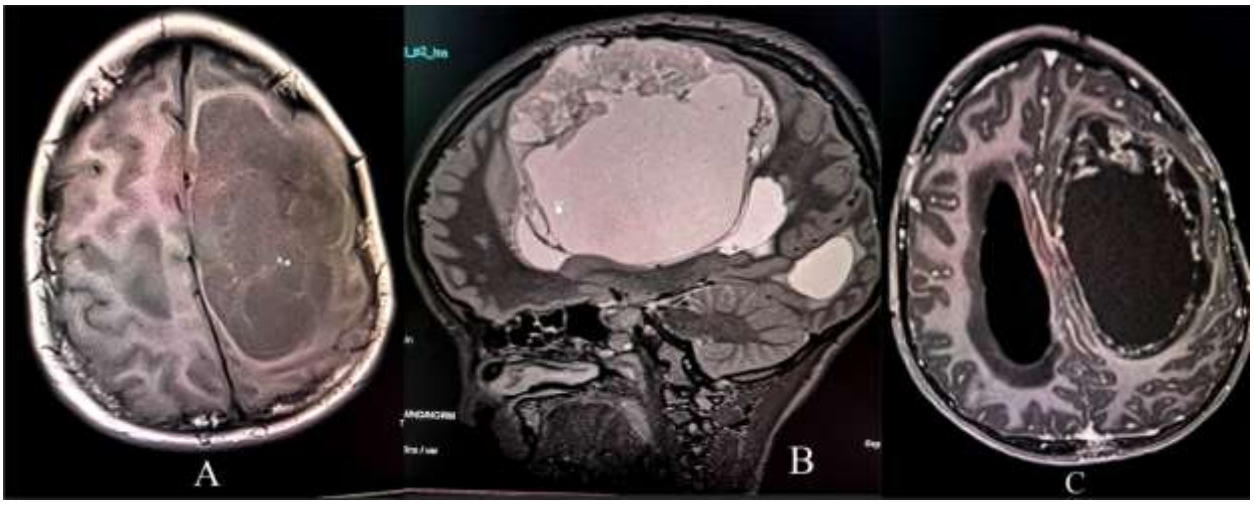

Figure 1:- T1 (A), T2 (B), and T1 with gadolinium injection (C) magnetic resonance Imaging (MRI) revealed a 14x12mm, oval-shaped, circumscribed solido-cystic lesion (Red arrow), of the left fronto-parietal lobes cortex. A ring enhancing appearance (Blue arows) could be also identified (C).

A complete blood count was performed, revealing no abnormalities. The patient's kidney and liver function were normal.A transcortical resection of the lesion has been performed. Pathological assessment has revealed the presence of a low cellularity neoplastic proliferation made of round, uniform, mildly atypical cells, in an abundant myxoid stroma that contained numerous bundles of axons that were organized in a perpendicular fashion to the cortical surface. We also observed floating neurons in form of cytologically normal neurons "floating" in the previously mentioned abundant myxoid matrix.No dysplastic ganglion-like cells have been observed. We have also not observed necrosis, significant mitotic activity, perivascular lymphoid infiltrates, or eosinophilic granular bodies(Figures 2 and 3).

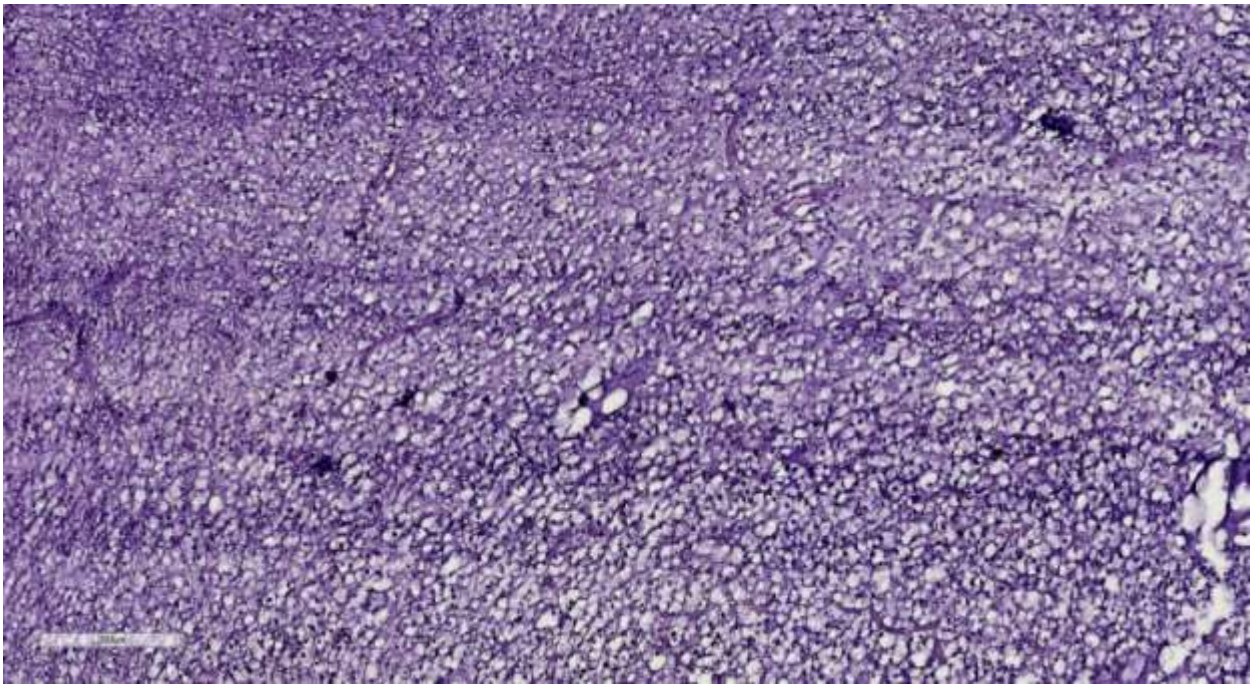

Figure 2:- Microphotography showing the low cellular nature of the proliferation, in presence of an abundant myxoid matrix. (HE; 20X).

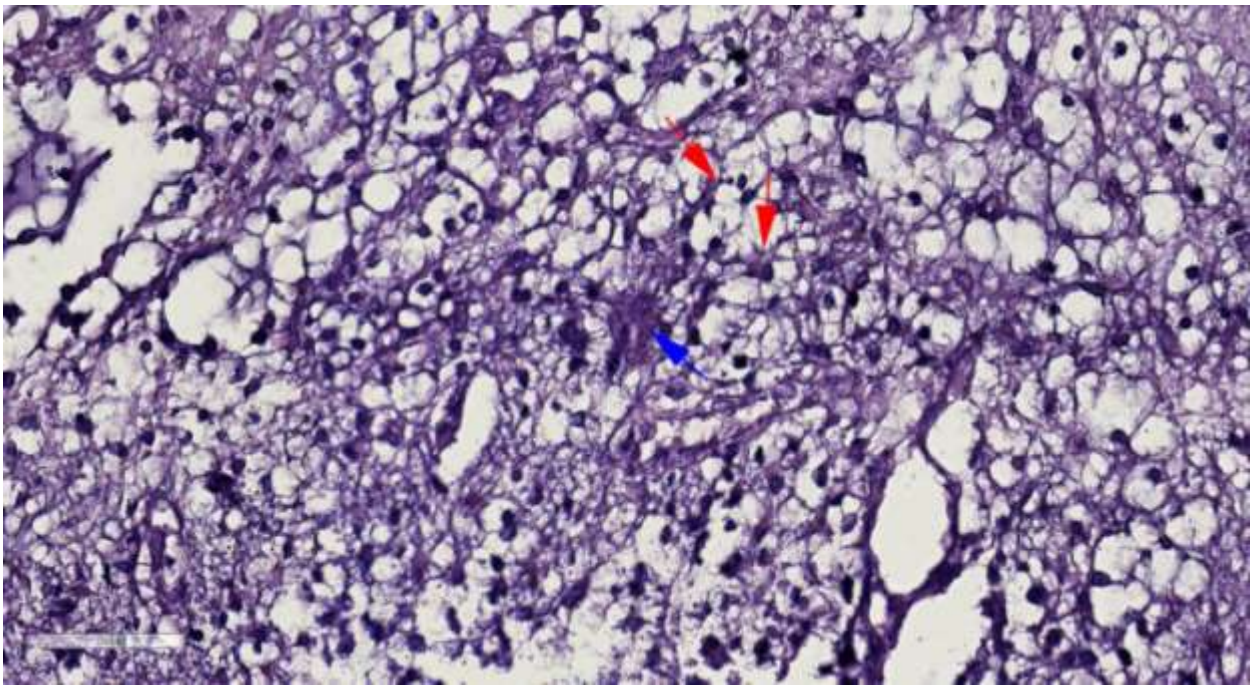

Figure 3:- Microphotography at higher magnification revealing the oligodendroglial-like morphology of the proliferating cells. Many bundles of axons are seen (Red arrow). Floating neurons are also visible in this field (Blue arrow). (HE; 400X).

An immunohistochemical study has been performed revealing an axon-rich stroma, highlighted by the anti-Glial Fibrillary Acidic Protein (GFAP) (Figure 4). However, observedoligodendroglial-like cells didn'tshow expression of GFAP. Floating neurons showed expression of synaptophysin and Neuron Specific Enolase (NSE), with no expression of chromogranin. The Ki67 helped confirm the weak mitotic (less then 1%).

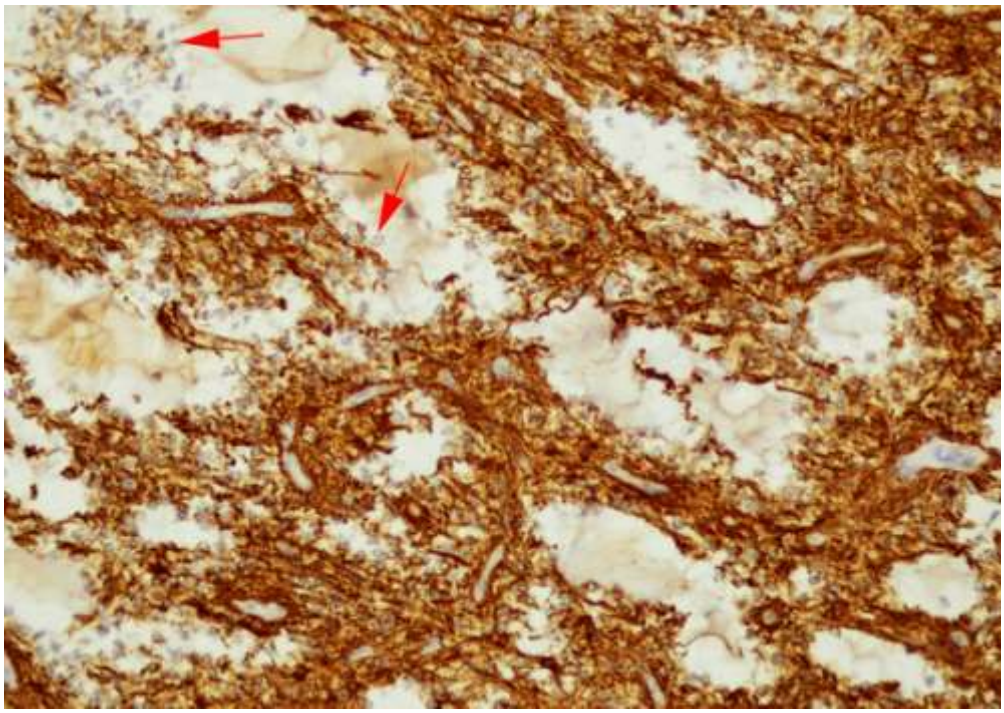

Figure 4:- The axon-rich stroma was highlighted by the anti-Glial Fibrillary Acidic Protein (GFAP). Oligodendroglial-like cells don't show GFAP expression (Arrow).

Follow-up of the patient showed a favorable evolution with complete disappearance of any seizures anti-convulsive therapy has been stopped.

Discussion:-

Dysembryoplasticneuroepithelial tumors (DNETs) are grade 1, mixed neuronal-glial neoplasms that occur classically in children and young adults [1].These tumors have been described for the first time by Damas-Duport in 1998 as benign lesions occurring in the supratentorial cortex.

On the epidemiological level, a slight male predominance is noted [3].The incidence isestimated at 0.03 person-year per 100,000. The peak incidence ranges from 10 to 14 years [9]. DNETs are responsible for approximately 17.8% of all epilepsy-associated tumors in adults, and for 23.4% in the pediatric population and is therefore considered to be the second most common type of epileptogenic tumors inchildren, ganglioglioma being the first one [10,11].

The pathogenesis of this entity seems to be linked to mitogen-activated protein kinase and mTOR signaling pathways. The activation of both pathways depends on the action of the Fibroblasts Growth Factor Receptor 1 (FGFR1). In approximately 80% of cases of DNETs, mutations of the FGFR1 can be detected in form of single nucleotide variations or duplications of the tyrosine kinase domain[12]. The consequence of these mutations would be anautophosphorylation of FGFR1 which leads to an upregulation of themTOR and the mitogen-activated protein kinase signaling pathways [8]. BRAF oncogene alterations have been also reported in form of copy number gain and V600E mutations [13]. Some familiar cases of DNETs, occurring secondary to germline fibroblast growth factor receptor 1 (FGFR1) p.R661P mutations have been reported [1]

Clinically, affected patients classically early onset,chronic,drug-resistant partial complex epilepsy before the age of 20 years[1]. In some studies, The mean age for the onset of epilepsy ranges between 11 and 25 years[14]. Other types of seizure have been also reported in reports of affected patients: generalized tonic-clonic, and simple partial seizures [4]. Our case had a 5-year history of partial complex seizures and rare episodes of generalized tonico-clonicseizures. The epileptogenic nature of DNETS could be explained by the production of inflammatory cytokine interleukin 1β and its receptorby activated microglia/macrophage cells that have been observed within the tumor and in the peritumoral region [15]. Some affected patients also presentpapilledema, headaches, and focal deficits [16].

Imaging is a key element of diagnosisand is presented by computerized tomography (CT scan) or magneticimaging (MRI). The DNET classically appears as a well-circumscribed or ill-defined lesion measuring between 10 to 25 mm in size[1, 4]. The lesion is cortical and takes the form of a solitary cyst or a multicysticlesion, with frequent calcifications[17]. The mesial temporal lobe, the frontal and parieto-occipital lobes are the most frequent locations for this entity [4]. Other locations, including caudate nucleus, the ventricles, the septum pellucidum, the corpus callosum, basal ganglia, brainstem, the tectum, the midbrain, and the cerebellum are exceptional [18]. In some rare instances, such as in cases of Jacobs' syndrome andtype 1 neurofibromatosis, multifocal DNETs have been reported [19]. When Computed tomography scan is performed, the lesion appears as a hypodense cystic or multicystic lesions. The deepest part of the lesion often shows calcifications. Deformities of the satellite skull can be observed on bone windows [8]. In conventional magnetic resonance imaging (MRI), DNETs take the form of a T1 hypointense and T2 hyperintense well-circumscribedcystic or multicystic lesion. DNETS appears as a hyperintense lesion on fluid-attenuated inversion-recovery (FLAIR) MRI. On this same sequence, a hyperintense rim surrounding the lesion can be observed, hence the name of "Ring sign" [20]. MRI can also identify intracystic septa, especially in larger lesions, and associated satellite cortical dysplasia [21].

On the pathological level, a low-cellularity multinodular proliferation of small round oligodendroglial-like cellsis observed. These cells are present on an abundant, alcianophilmucin-rich matrix where the neoplastic cells and the normally appearing neurons seem to be floating, hence the name of "floating neurons" [1]. Bundles of axons are arranged perpendicularly to the cortical surface and are lined by the neoplasticcells [22]. Dysplastic ganglion-like cells, necrosis and a high mitotic activity should not be observedinDNET.Focal cortical dysplasia can be present [23]. Several differential diagnoses should be kept in mind when typical features of DNET are absent. These include other glial and glioneuronal neoplasms such as pilocytic astrocytoma, oligodendrogliomas, and pleomorphic xanthoastrocytomas [4].In such cases, the use of immunohistochemistry is crucial and would show an expression of S-100 protein and Olig-2 by the small round cells and expression of neuronal markers such as synaptophysin and neuron specific enolase by the "floating neurons" [4]. As in our case, the mitotic activity is classically low with a low Ki67 index [24].There are three histologic subtypes of DNET, based on the cellular neoplastic subpopulation: simple, complex, and nonspecific subtypes. In the simple form, only glioneural cells can be observed. In the complex form, glioneural cells are observed with glial cells such as astrocytic or oligodendroglial differentiation which confers a more heterogeneous appearance to this subtype. The third subtype, the non-specificDNET is a diffuse form that often requires immunohistochemistry and molecular studies to establish a correct diagnosis [8].

On the molecular level, gains at chromosomes 5, 6, and 7, 6 are the most frequent reported copy number aberrations in DNETs [51]. 120 microRNAs have been found to be expressed differentially, mostly downregulated, in cases of DNETs[25]. In this same study the downregulation of miR-3138 and the upregulation of miR-1909 are considered to bevery supportive for the diagnosis of DNET [25].The familiar form of DNET can be diagnosis by highlighting the presence of the germlinep.R661P mutation of the fibroblast growth factor receptor 1 (FGFR1) [17]. In one study, the occurrence of exon 9 mutation of the PIK3CA genehas been reported [8].

On the therapeutic level, the gold standard for the treatment remains surgical complete resection. Resection should concern the satellite focal cortical dysplasia when present [9]. Chemotherapy and radiation therapy seem to play no role in the treatment of DNETs. Radiation therapy has been reported in many studies to be associated with a poor overall survival and with a risk of malignant transformation [8]. Target therapy may have an effective place in the treatment of DNETs, by using FGFR1 inhibitors that inhibit the basic fibroblast growth factor-dependent tyrosine kinase activity [8].When complete removal of the tumor is performed, the outcome is favorable in 70% to 90% of cases. In cases of partial surgical resection, recurrences occur, and seizures are only purely controlled[9].

Positive prognostic factors for DNETs include temporal location, younger age, decreased time between onset of epilepsy and surgery, and the absence of cortical dysplasia [14].

Conclusions:-

DNETs are low-grade, benign,non-recurring lesions. They are the second most epileptogenic tumors in the pediatric population and in young adults. Chronic drug-resistant and partial complex seizures remain to be the most classical clinical feature of the disease. The correct diagnosis is based on imaging through computed tomography or magnetic resonance imaging, pathological assessment which can include immunohistochemical and molecular studies.DNET should be considered in cases of intra-axial multinodular lesion. Immunohistochemical and molecular studies should involve CD34, GFAP, IDH1/IDH2, FGFR1, and BRAF. The gold standard of treatment remains to be complete

surgical resection with a favorable outcome, and a complete disappearance of seizures in up to 100% of cases. MRI surveillance is recommended, especially in cases of incomplete resection.

List of figures:

Figure 1: T1 (A), T2 (B), and T1 with gadolinium injection (C) magnetic resonance Imaging (MRI) revealed a 14x12mm, oval-shaped, circumscribed solido-cystic lesion (Red arrow), of the left fronto-parietal lobes cortex. A ring enhancing appearance (Blue arows) could be also identified (C).

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AM, MT, SA and YB carried out the pathological and immunohistochemical studies, drafted the manuscript, participated in the conception and design, acquisition of data, analysis and interpretation of data. BB carried out the imaging data and participated in the acquisition, analysis and interpretation of data. BA and FShave ensured management of the patient andparticipated in the design of the study. All authors contributed to article conception, drafting, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authorsread and approved the final manuscript.

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