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RESEARCH ARTICLE

PINEAL CHORIOCARCINOMA: CASE REPORT AND LITERATURE REVIEW

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Abstract

Primary pineal choriocarcinoma is a very rare brain tumour. It represents only 1% of all primary intracranial neoplasms in adults, secretes human chorionic gonadotropin and has a poor prognosis. It mainly affects young males. Magnetic Resonance Imaging (MRI) data is suggestive of the diagnosis; however, confirmation is obtained through pathological assessment. Sometimes biopsy can be avoided if tumour markers are elevated. The treatment is multimodal based on the combination of three therapeutic modalities: surgery, radiation therapyand chemotherapy. The prognosis is related to the completeness of excision, and the extent of irradiation. In our work, we report a 38-year-old man diagnosed with localized pineal choriocarcinoma. At first chemotherapy was performed, followed by radiotherapy by the technique of Irradiation nwith Volumetric Intensity Modulation by Arc Therapy in stereotactic conditions, a dose of 40 Gy in 10 fractions of 4 Gy delivered at the tumour site. The therapeutic follow-up was marked by a very good tolerance of the treatment. The MRI evaluation after 3 months showed a total regression of the tumour process. The patient was followed for 18 months, he remained healthy without any side effects of the treatment and without any neurological deficit, and the results of all six-monthly follow-up brain MRI carried out during 18 months were satisfactory, in favour of a complete remission. A literature review is conducted to identify similar studies that document primary pineal choriocarcinomas.

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Introduction:-

Intracranial germ cell tumours are rare tumours, accounting for less than 7% of all gonadic and extragonadic germ cell tumours [1, 2].

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They are of extraneural origin but are encountered in the central nervous system (CNS) following the aberrant migration of primordial germ cells during embryogenesis. These tumours are usually located on the midline and occur in the pineal region in 2/3 of cases [3, 8]. The histological classification distinguishes between two main categories: germinomas and non- seminomatous germ cell tumours (NSGCT) [1].

Primary pineal choriocarcinoma (CCPP) is one of the very rare categories of NSGCT [1,2,12]. It is the most aggressive form of trophoblastic disease [1, 2, 6].

The pathological study confirms the diagnosis. However, the contribution of tumour imaging and markers is considerable and can even dispense from biopsy [4, 12].

The objective of this work was to focus on this rare entity of germ cell tumours. The literature is used to discuss diagnostic and treatment suggestions to provide a factual basis for treatment in adult patients with CCPP.

Observation:-

We report a 38-year-old man with no pathological history, who was consulted for progressive aggravation of frontal headaches developing over the past year, associated with vomiting, rotatory vertigo and episodes of comitial crises. The clinical examination at admission revealed an intracranial hypertension syndrome (ICHT) with decreased visual acuity and no other associated neurological or general signs. The patient had a performance status index of 1, a body surface area of 1.89 m^2 and a body mass index of 25.7.

Brain MRI revealed an expansive midline process measuring 30x22x18 mm; centered on the pineal gland and extending along the walls of the 3rd ventricle (V3), especially to the left, gaining Sylvius's aqueduct. This process was associated with active tri-ventricular moderate hydrocephalus (Figure 1).

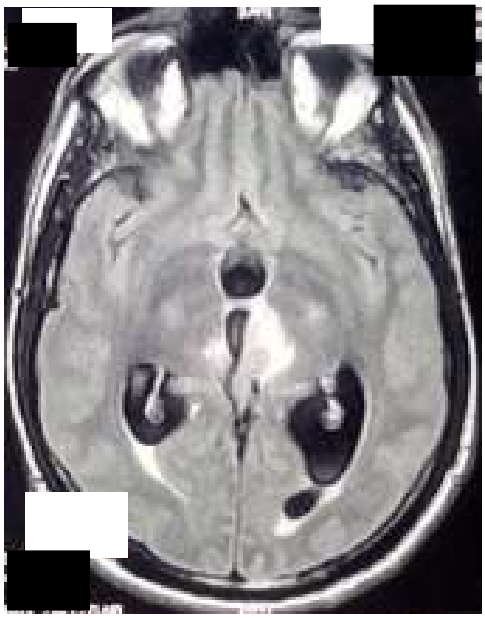

Figure 1:- Brain MRI. Axial sections; showing an expansive process of the midline measuring 30x22x18 mm; centered on the pineal gland; extending along the walls of the 3rd ventricle (V3), especially to the left, gaining the Sylvius aqueduct associated with a moderate tri-active ventricular hydrocephalus.

The patient had undergone an emergency ventriculoperitoneal derivation (VPD). As part of the diagnostic workup, a β-HCG assay was performed in the blood and cerebrospinal fluid (CSF). It was positive in the blood to a level of 0.94 ng/ml. Alphafoetoprotein (AFP) was at 3.21 ng/ml in blood, and < 2.7 ng/ml in CSF.

The anatomopathological result of CSF showed the presence of numerous lymphocytes. No cytological signs of malignancy have been identified.

After discussion in a multidisciplinary consultation meeting, we recommended a first chemotherapy based on Etoposide (190 mg on day 1 (D1), and D2) + Actinomycin (0.5 mg IV per day at D1, D2) associated with methotrexate 180 mg IV bolus then 360 mg SG 5% over 12 hours + Folinic Acid 15 mg per os over 12 hours, in four courses at an interval of 3 weeks. The radiological evaluation by brain MRI showed a significant regression of the pineal gland tumour process, measuring 9.7 mm/6.6 mm/3.2 mm versus 30 mm/22 mm/18 mm with the disappearance of the peri-lesional edema and hydrocephalus (Figure 2).

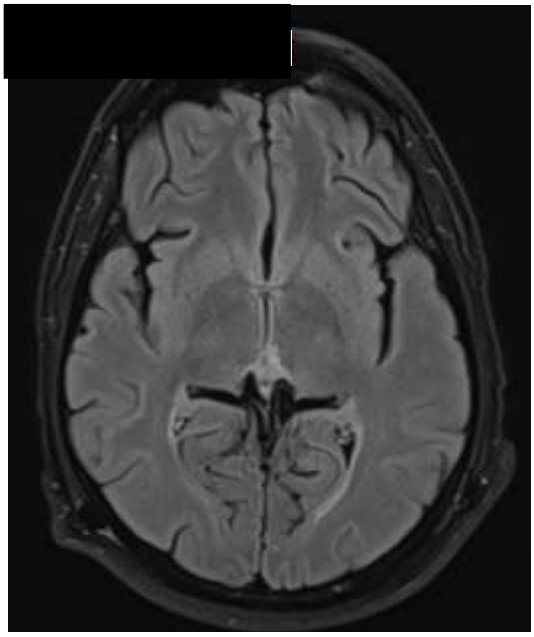

Figure 2:- Axial section of FLAIR sequence MRI; showing clear regression of the midline lesion process centred on the pineal gland, measuring 9.7 mm x 6.6 mm x 3.2 mm.

The case was discussed again in the multidisciplinary consultation meeting and the decision was to do radiotherapy. We performed a fusion of CT and MRI images; we precisely delineated the tumour volume with the neighbouring organs at risk (figure 3). The patient underwent radiotherapy using the VMAT technique (Volumetric Intensity Modulated Arc Therapy) in stereotactic conditions on the tumour. He received a dose of 40 Gy, in 4Gyhypofractionation. (Figure 4).

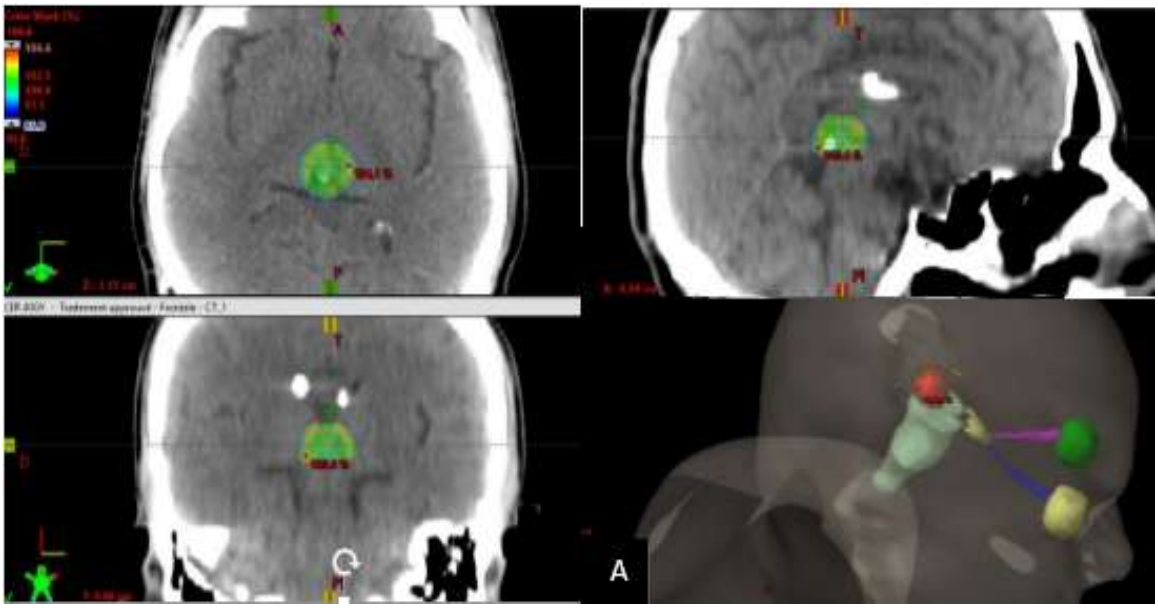

Figure 3:-Prescription isodoses of our patient.

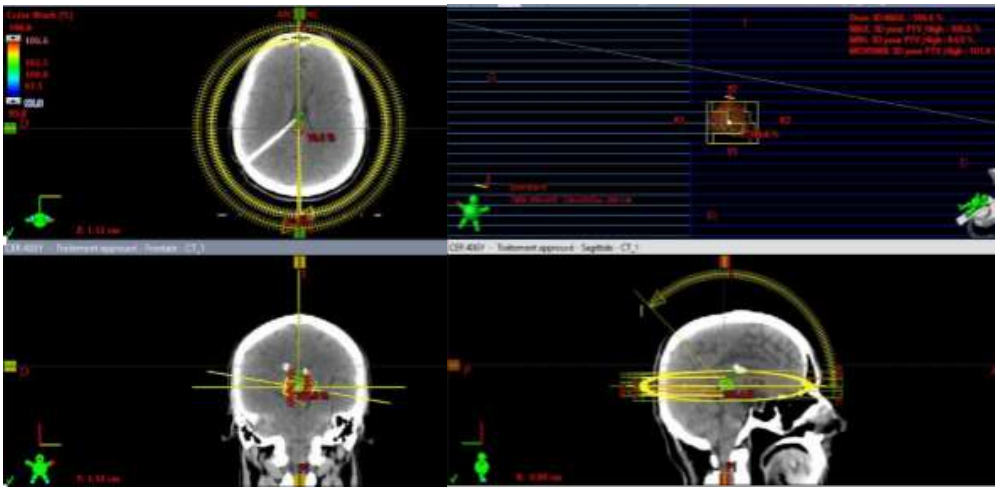

Figure 4:-Iconography of our patient's treatment plan for irradiation by the VMAT technique: non-coplanar arcs converging on the isocenter.

The therapeutic follow-up was marked by a very good tolerance of the treatment. A follow-up brain MRI was performed after three months in favour of a complete remission (Figure 5). Also, the results of all six-monthly follow-up brain MRI carried out during 18 months were satisfactory.

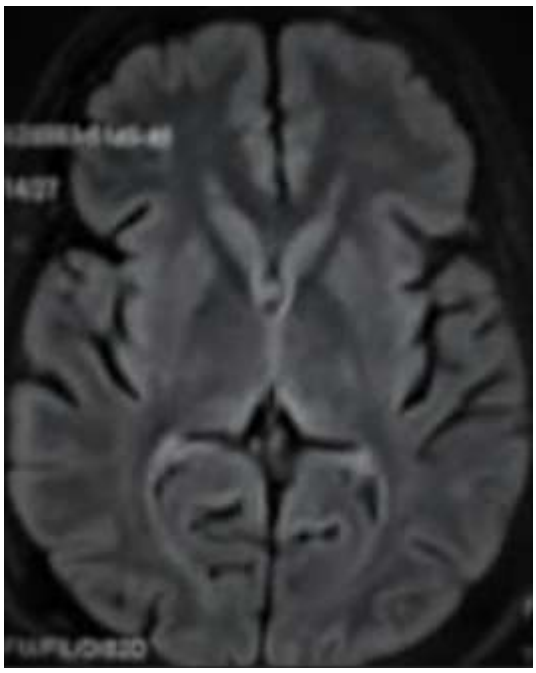

Figure 5:- Axial section in T1 sequence MRI after Gadolinium injection; shows no signal anomaly.

Discussion:-

Primary pineal choriocarcinoma (PPCC) represents 1% of all primary intracranial neoplasms in young adults, less than 5% of all pineal tumours [6], and constitutes 3-5% of primary intracranial germ cell tumours [1,6]. It predominantly affects young males (3-22 years), with a male predominance and a sex ratio of 74.19 [1, 2].

Clinically, pineal tumours usually cause obstructive hydrocephalus, due to their location [1], and are responsible for the signs of ICHT in 25-50% of cases [2]. Neuro-ophthalmologic and neuroendocrine signs may be present, on the other hand; signs of early puberty are seen if the tumour occurred at a young age [1].

The contribution of imaging in the diagnosis of NSGCTs is considerable. In some published studies [2], PPCCs have been described on computed tomography (CT) scan as ovoid tumours, generally showing heterogeneous enhancement after contrast administration, slightly hyperdense and relatively well defined with lobulated margins, centred in the pineal region [2]. However, MRI is the imaging modality of choice 12], and it allows a better characterization of the tumour than CT [2]. The haemorrhagic component is a typical feature of PPCC; due to its vascularity which is important [1, 2, 12]. Yet; it correlates with a poor prognosis [2].

The macroscopic appearance of PPCC corresponds to a brown granular tumour and is almost always hemorrhagic and necrotic due to the presence of stromal vascular channels [1,2]. The presence of cytotrophoblastic cells and syncytiotrophoblasts are characteristic on microscopic examination [6]. However, biopsy is very often avoided due to the location of the tumour and especially its haemorrhagic nature [6]. In addition, the search for tumour markers in blood and CSF is systematic [3, 7, 12], their positivity with suggestive imaging is sufficient to retain the diagnosis [2, 12]. They are also useful for follow-up [1, 12]. Indeed, this is the attitude we followed in our reported case. In our case, we did not perform a biopsy of the tumour, to avoid the risk of early mortality due to tumourhaemorrhage. And we retained the diagnosis of PPCC in front of MRI findings and β-HCG positivity in blood.

PPCCs can disseminate to the ventricular cavities, brain parenchyma, subarachnoid spaces and give locoregional metastasis (15%) [1, 12]. The assessment of extension should include spinal MRI, as well as cytological analysis of the CSF at the spinal level and in the shunt system [4, 12]. Positive CSF cytology is generally considered as metastasis, even if the spinal cord MRI is normal [5]. The metastatic form is a poor prognostic factor [6]. In our case, CSF cytology was normal, as well as spinal cord MRI.

At present, the therapeutic strategy for this type of tumouris better codified. The goal of treatment is to achieve complete remission and improve quality of life. The choice of treatment depends on the patient's age, performance status, tumour size, locoregional extension, metastatic spread and finally the different guidelines. [7].

Surgery is difficult due the deep location of these tumours. In some studies, surgery was limited to CSF shunting to control ICHT in case of hydrocephalus. However, the morbidity rate is currently reduced thanks to the development of microsurgical techniques for diagnostic purposes [3, 7]. Neuroendoscopy offers the possibility to perform the biopsy, collect the CSF, and the treatment of the tumor whose standard is the complete surgical removal [3, 7] at the same time.

Some authors suggest that multimodal treatment based on chemotherapy, radiotherapy and tumour resection offers the best chance to treat PPCC [2, 9]. The study of Shinoda J et al demonstrated the efficacy of triple therapy, especially if surgery is complete [9].

Dual therapy combining chemotherapy and radiotherapy without surgery is an effective therapeutic option in the management of these tumours, while avoiding the complications associated with surgery, especially if it is partial. Kim et al [6] reported a successful therapy with synchronous chemotherapy and radiotherapy without surgery. This was followed by three consecutive courses of chemotherapy. This strategy resulted in regression of 63% of tumours, with clinical improvement in patients, with no progression over almost 2 years of follow-up (Table 1).

A phase II study was conducted by the Japanese Intracranial Germ Cell Tumour Study Group [11], which showed that the combination of postoperative radiotherapy and adjuvant chemotherapy had superior results compared with radiotherapy alone in terms of overall survival and comorbidity. In this study, they reported a 2-year survival rate of 67.7% and 46.5% respectively. These results are similar to those of the study by Y Matsukado et al [11]. In addition, the rate of hematogenous or CSF metastatic dissemination was 45% in patients treated with postoperative irradiation [11].

Table 1:- Literature review of therapeutic modalities undertaken by different schools. [6, 11].

Author	Treatment strategy			Survival rate at 2 years
Kim et al	CMT + synchronous RTH without surgery, followed by Three consecutive courses of CMT	**Protocol**		No progression after almost 2 years of follow-up.
		IfosfamideCisplatineEtoposide,	Whole brain, 30 Gy/15 Fr; Boost de 30 Gy/15 Fr	
Phase II study - Japanese Intracranial Germ Cell Tumor Study Group	Post-operative RTH and adjuvant CMT)	Cisplatine, Vinblastine Bleomycine (PVB)	-	67,7%
	Postoperative RTH alone	-	-	46,5 %
Y Matsukado et al [11]	CMT associated with RTH	Cisplatine, Vinblastine Bleomycine	-	69,8 %
	Postoperative RTH alone	-	-	46,5 %

The results of the third international study on central nervous system (CNS) germ cell tumours concluded that chemotherapy alone, including intensive chemotherapy was more toxic and less effective than regimens containing radiotherapy [10]. Whereas; radiation therapy may induce long-term complications, including intellectual deterioration [7]. The focus of clinical trials has been on reducing radiotherapy volumes and mitigating late toxicity. The addition of chemotherapy to radiotherapy reduces the dose and volume to be irradiated, therefore; it minimizes side effects without decreasing the cure rate [10], and increases the sensitivity of these tumours to radiotherapy, with a benefit in survival [7].

Furthermore, the morbidity associated with radiotherapy can be avoided by the use of modern techniques. Thanks to technological innovation, more performance has been achieved in the treatment of these tumours. By comparing the dosimetric results of IMRT and 3D conformal radiotherapy (3DCR). dM. J. CHEN et al concluded that the extent of radiation therapy has an impact on overall survival.

The irradiation of the whole neuraxis with a Boost on the tumour bed brings a survival benefit with a rate of 100% at 2 years and 5 years; while this rate is reduced to 50% at 5 years in case of cranio spinal radiation (CSR), these results are superior to those of irradiation localized in the tumour bed (59% at 2 years and 5 years) [4] (Table 2). However, the risk of morbidity related to irradiation is frequent due to medium- and long-term sequelae, especially neuropsychological and spinal. It is correlated to the volumes irradiated. Calaminus et al, has shown that CSR could be avoided without increasing relapse outside the radiotherapy field in localized NSGCT. Chemotherapy and CSR remain the standard for metastatic disease [4, 13].

J. Guyotat proposed primary chemotherapy. In case of complete response, irradiation of the tumour bed, or combined with CSR in case of meningeal dissemination is performed. In case of residues, at the end of chemotherapy, an ablative surgery of the residue is indicated [7].

The authors of the SIOP-CNS-GCT 96 trial, also opted for platinum-based chemotherapy followed by focal irradiation for non-metastatic PPCC cases, and CSR with Boost in all MRI-visible tumour sites for cases with metastases. Therefore, they suggested irradiation of the ventricles, since the majority of relapses after focal irradiation occur in the periventricular zone [4, 7]. A dose of 24 Gy to the ventricular system with a 16 Gy boost to the tumour seems to be sufficient to decrease the incidence of these relapses.

The concept of irradiation of the ventricles has been introduced recently, since it is the main site of relapse. The SFOP (French Society of Pediatric Oncology) has centrally analysed all relapses. It concluded that relapses at the local and/or ventricular level are more frequent than at the spinal level [7].

Table 2:- Literature review on therapeutic modalities undertaken by different schools. (Continued).

Author		**Treatment strategy**	**Volume and dose of radiotherapy**	**Overall survival**	
				A 2 Years	A 5 Years
dM. J. CHEN et al [4].	-	CMT and RTH	Whole brain + Boost on the tumor bed	100%	100%
			Cranio spinal	100%	50%
			localized to the tumor	59%	59%
J. Guyotat [7].	Localized CCPP	CMT first Cisplatin/ etoposide/ifosfamide). Followed by RTH if complete response.	localized to the tumor (55 Gy)		
	Disseminated CCPP		CSR (30 Gy)		
The trial SIOP-CNS-GCT 96 [4, 7].	Localized CCPP	CMT followed by RTH	Localized to the tumor 54 Gy.		
	Disseminated CCPP		CSR of 30 Gy + Boost of 24 Gy in all tumor sites visible on MRI + 24 Gy in the ventricular system + a Boost of 16 Gy on the tumor.		

Our patient presented a localized form, and had a first chemotherapy, which induced a tumour regression of more than 65%. Followed by irradiation at the tumour site with a dose of 40 Gy in 10 fractions of 4Gy. The results of our strategy were satisfactory, and no short- and medium-term side effects were reported.

Prognostically, Matsutani et al classified PPCCs in the poor prognosis group [8]. These tumours have a poor survival rate compared to other germ cell tumours. [9]. Shinoda et al observed that the median survival time of PPCC was 22 months, the one- and two-year survival rate was 61.2% and 49.8%, respectively [9], as well as the three- and five-year survival rate was 45.8% [6]. A better prognosis correlates with male gender compared to the female population according to the study of T.Jiang et al [6].

Recent cellular and molecular evidence suggests that intracranial germ cell tumours may result from the transformation of endogenous brain cells [10]. Matsutani et al stated that there are new perspectives in terms of molecular biology for malignant germ cell tumours [8]. Molecular study of intracranial germ cell tumours suggests roles for CCND2, RB1, and PRDM14 in their pathogenesis and finds KIT/RAS and AKT1/mTOR pathways as new therapeutic targets in the future [8,10].

Conclusion:-

The diagnostic strategy of PPCC is currently well-established. A lot of work has been done to standardize the therapeutic protocols; different protocols have been proposed by the authors. However, previous studies are limited by the small number of cases, the short follow-up and the incomplete follow-up of the patients. The management of these tumours is multidisciplinary, combining total excisional surgery if possible, chemotherapy and radiotherapy. For localized forms; the target volumes to be irradiated concern the tumour and the ventricular system, the association of spinal irradiation in disseminated forms is strongly suggested. In our experience we have advocated neoadjuvant chemotherapy followed by irradiation of the tumour volume, with good clinical and radiological evolution. The therapeutic follow-up was marked by a very good clinical and radiological evolution. The MRI evaluation after 3 months showed a total regression of the tumour process. The patient was followed for 18 months, he remained healthy without any neurological deficit, and the results of all six-monthly follow-up brain MRI carried out during 18 months were satisfactory, in favour of a complete remission.

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List of abbreviations :

PPCC: Primitive Pineal Choriocarcinoma.
CNS: Central Nervous System
DVP :Ventriculo-Peritoneal derivation.
NSGCT: Non Seminomatous Germ Cell Tumors
HCG : Human Chorionic Gonadotropin
AFP:Alphafoetoprotein
RCM:Pluridisciplinary Concertation Meeting
PPCC :Primitifpinéalchoriocarcinoma
CSF : Cerebrospinal fluid
MRI: Magnetic Resonance Imaging
ICHT : Intracranial Hypertension
EEG : Electroencephalogram
VMAT : Volumetric Intensity Modulated Arc Therapy
CSR: cranio spinal radiation
PVB: Cisplatin, Vinblastine and Bleomycin
3DCR: 3D Conformational Radiotherapy.

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