

INTRACRANIAL GERM CELL TUMOR IN THE PINEAL REGION: A CASE REPORT
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ABSTRACT

Germ cell tumors (GCTs) represent a rare entity. The gonads are the primary site for their development, but due to developmental anomaly, it can be seen in extragonadal location. Intracranial CGTs arise more often in midline structure like the pineal gland and the suprasellar region, of both children and young adults. They represent $\approx 0,5\%$ of all primary tumors. However, intracranial CGTs are often of mixed histological types (Mixed GCTs). We report a 11 years-old of CGTs in the pineal region. The literature is reviewed and the management is discussed in this paper.

KEYWORDS: Pineal gland, germ cell tumors, child, Parinaud's syndrome.

INTRODUCTION

Intracranial germ cell tumors are rare, representing less than 5% of all central nervous system tumors in Western series,^[1] and more in East Asia. It occurs more in the pineal gland, with a male predominance. The most frequent age is 10 to 12 years.

The pathogenesis is unknown. Some theories are trying to explain it, like "The germ cell theory" which suggests that cell tumors arise from primordial germ cells that aberrantly migrated and undergone malignant transformation.^[2] Recent investigations comparing the genomic alterations in GCTs found similar copy number alterations whether the GCT was systemic or central nervous system (CNS) based.^[3] Classically, classification is based on histology; but many others factors are increasingly used for both diagnosis and classification, like: tumor markers, mitotic activity, cytogenetic and molecular genetic findings.

90% of cases occur before age 20 years. They are classified into germinomatous ($\approx 2/3$ of cases) and nongerminomatous germ cell tumors, including teratoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, or mixed malignant germ cell tumors (MMGCT), according to the World Health Organization (W.H.O).^[4] In Europe and Asia, we classify them into secreting and non-secreting tumors, depend on levels of tumor markers (*beta-human chorionic gonadotropin* -HCG- and *alpha-fetoprotein* -AFP-) in serum and/or cerebrospinal fluid (CSF).^[2] Diagnosis is based on clinical signs, tumors markers, neuroimaging, and often

requires a biopsy. In the case of characteristic increased tumor markers in the serum and/or CSF, biopsy is not performed.

The optimal treatment remains controversial, especially the use of chemotherapy and protocols of radiotherapy (volume treated, dose).^[5] Despite good results with combination therapy (surgery, radiation, chemotherapy), the treatment options are not consensual, and no one of them is clearly accepted as standard therapy.

CASE REPORT

A 11 years-old male without a past medical history presented to "Child hospital" due to vomiting, bilateral blindness, headache, and a progressive development of diplopia. A neurological examination revealed a *Parinaud's Syndrome* with a facial paralysis. An initial brain magnetic resonance (MRI) revealed a pineal region tumor with obstructive hydrocephalus (Fig.1). Emergency ventriculoperitoneal shunt (VPS) was performed in Neurological department.

His serum beta-human chorionic gonadotropin (HCG) was 102, 34 UI/l and CSF alpha-fetoprotein (AFP) was > 190 U.I/l. Serum AFP was 1,7 ng/ml, AFP CSF was $< 0,5$ ng/ml. According to several European and Asian groups, this tumor was considered as secreting. 2 CSF cytology were realized, the first one was (+) and the second one (-). An MRI of the spine was negative. A brain CT scan showed a $44 \times 37 \times 41$ mm tumor of the pineal region (Fig.2).

The patient received neoadjuvant chemotherapy (Ifosfamide, Cisplatin, Etoposide). He completed 3 cycles, which were adapted to his neurological status: aphasia, swallowing disorder, convulsive crisis. Then he was referred to neurosurgery department for a surgical treatment, but it was dismissed. After chemotherapy, he began to neurologically recover, his tumor markers normalized (serum HCG was 2,5 m U.I/ml, AFP was 1,92 ng/ml). The tumor size remains stable, a brain MRI showed non-reducing size of the pineal tumor, with a triventricular dilatation (Fig.3, 4). The patient received a radiotherapy to craniospinal axis (30 Gy, 2 Gy per fraction), and a boost dose of 24 Gy was irradiated to the tumor using volumetric modulated arc therapy (VMAT) (Fig. 5, 6).

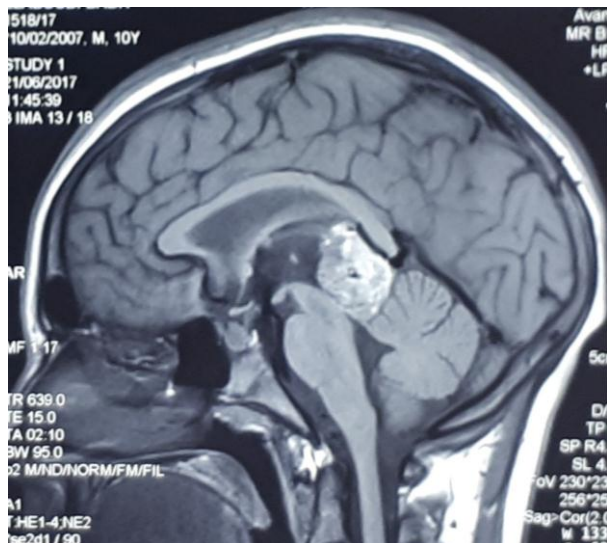


Fig. 1: Initial MRI (sagittal plan) revealing a pineal region tumor with obstructive hydrocephalus.

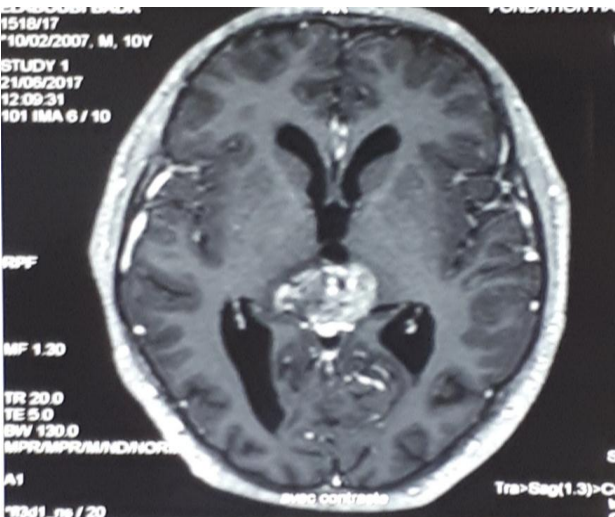


Fig. 2: A brain CT scan showing a pineal region tumor.

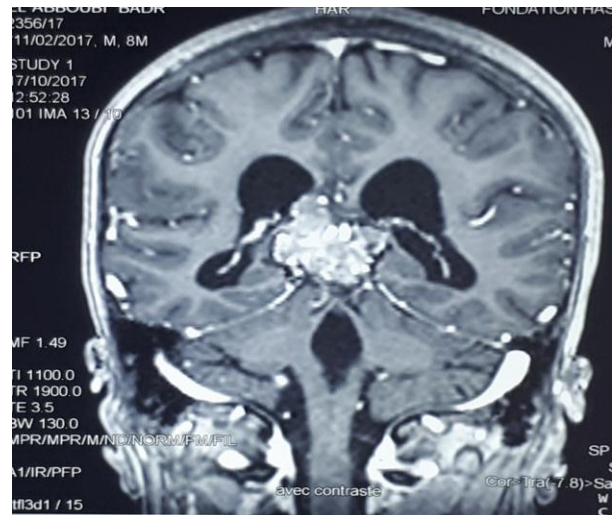


Fig. 3: Post-chemotherapy enhanced coronal MRI scans showing the tumor in the pineal region.

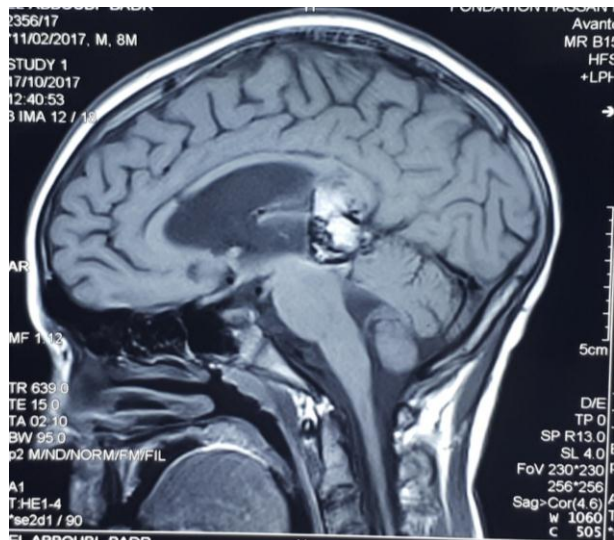
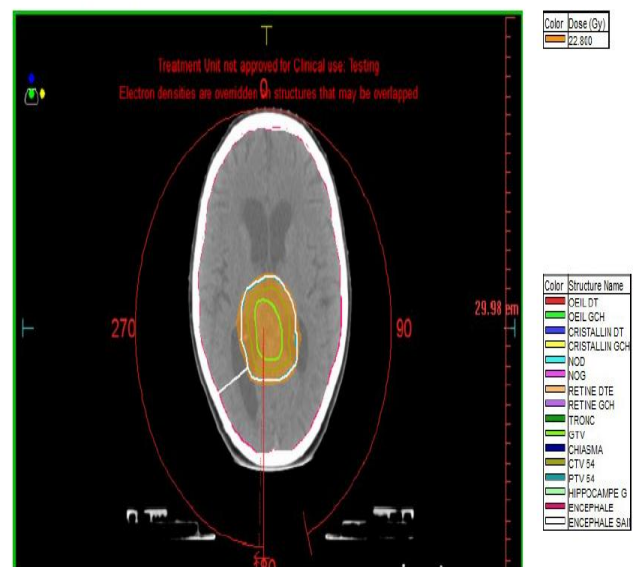


Fig. 4: Enhanced sagittal MRI scan demonstrating 44x37x41 mm heterogeneously pineal region tumor.



(a)

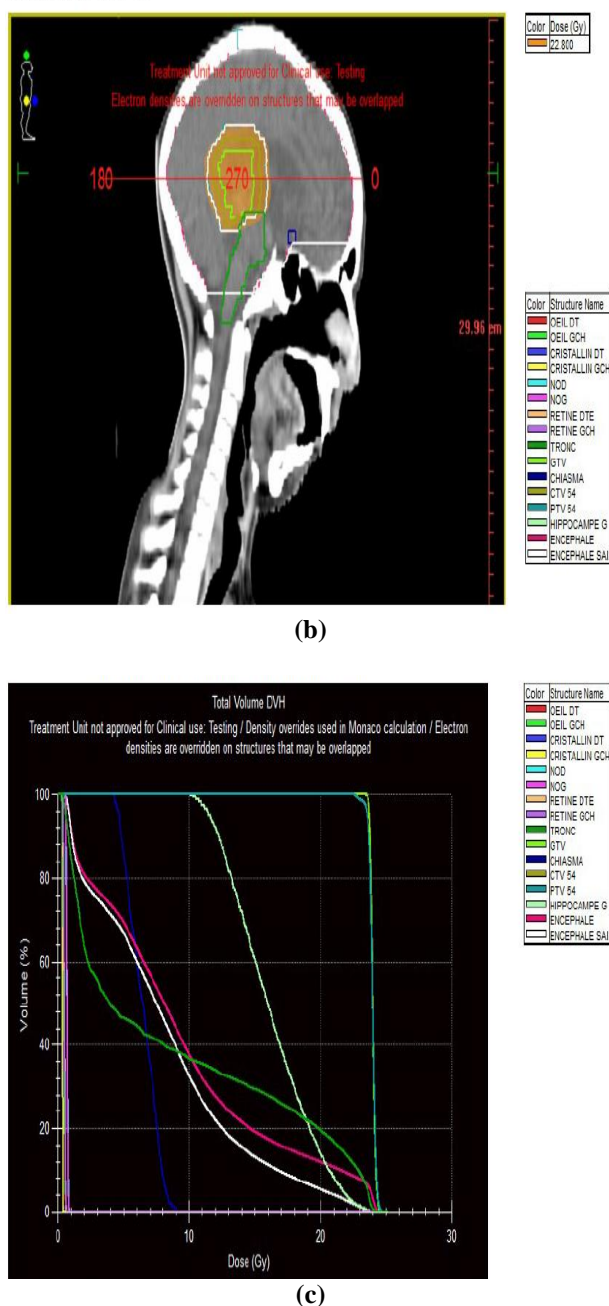


Fig. 5: Axial (a), sagittal (b) treatment plan and DVH-based plan (c) for the boost irradiation.

DISCUSSION

Primary brain tumors, including GCTs, are a diverse group of diseases that represent the most common solid tumors of childhood. Intracranial GCTs is a rare subset of these tumors, pineal region tumors represent 0.5-1.6% of all intracranial tumors. 90% of them occur before age of 20 years (11 years-old in our case), and more frequently in pineal gland and suprasellar cistern, with a male predominance.^[6] GCT are more common in Asia than western countries (11% of pediatric tumors),^[1] especially in far east Asian countries including Japan. Actually, we can't estimate the exact incidence of extragonadal GCT, because of the limited series existing and few cases reported in literature.

Classifications of extragonadal GCTs follow those adopted for neoplasms of germ cell origin involving the testis and ovary. Intracranial GCTs histology is similar to GCTs classification elsewhere in other locations. The World Health Organization (W.H.O) classified intracranial GCTs into the following groups:^[4] Germinoma, Embryonal carcinoma, Yolk sac tumor, Choriocarcinoma, Teratoma (mature; immature), Teratoma with malignant transformation, Mixed GCT. They are classified into germinomatous and nongerminomatous GCT. In Europe and Asia, they are broadly classified into secreting and non-secreting tumors, depending on elevation of tumor markers in serum and/or CSF.^[7] There are many tumor markers usually secreted by these tumors, but HCG and AFP are the most used for diagnosis purposes and monitoring of a therapeutic response or tumor recurrence.^[7]

Pineal tumors present with non-specific symptoms including an intracranial pressure and diplopia related to tectal and aqueductal compression. A Parinaud's syndrome (vertical gaze impairment, convergence nystagmus, and light-near pupillary response dissociation), headache, nausea and vomiting could be observed when the masse is localized in pineal region or posterior third ventricular region.^[8] In our case, these two factors were observed. Patients with pineal region tumors usually have a shorter history of symptoms, with weeks to months of symptoms.

Genetic alterations observed in CNS GCTs are largely unknown. Some research showed some frequent imbalances in CGT, particularly in chromosomes 1,8,12,13,18 and X. Cytogenetics abnormalities on chromosome 12, like gains of 12p or isochromosome 12p are frequent in intracranial CGTs.^[9] Gains of chromosomes X are observed in most of intracranial CGTs cases. Recently, p14 and c-kit gene were associated with some intracranial germinomas.

Neurological profiles of intracranial GCTs are largely nonspecific,^[10] but some characteristics can be helpful. Germinomas usually appears as homogenous solid tumor, with isointensity on T1-weighted images and hypointensity on T2- images. On MRI, GCTs other than teratoma usually appears as hypo- to isointense solid masse on T1-weighted images, iso- to hyperintense on T2-images with prominent contrast enhancement. Nongerminomatous GCTs show heterogeneous enhancement. Intratumoral hemorrhage is particularly characteristic of choriocarcinoma and mixed tumors with choriocarcinomatous elements.

There is no clinical staging system validated for GCTs.^[11] The staging evaluation of CNS CGTs includes MRI, lumbar cerebrospinal fluid (CSF), when it's medically permissible, for the measurement of tumor markers.^[12] Patients with negative CSF cytology and localized tumor are considered M0 (metastatic negative), while patients with positive CSF cytology or with drop

metastasis are M+ (metastatic positive). This staging is very important because M+ patients could receive higher total dose and extended fields of radiation. Our patient was M+.

The management of intracranial GCTs and choice of optimal treatment remains controversial. Specific treatment protocols have not been established.^[13] When it's permissible, surgery must be complete because small pieces of tissue may not represent the histology of the tumor, germinoma shows high radiosensitivity as an example. Thus, radiation alone seems to be an efficient treatment. The craniospinal irradiation (CRS) was considered for many years as a Gold standard of treatment of GCTS germinomas. Due to adverse effects on central nervous system (CNS) developing, and late neurological detrimental effects of CSR (especially for young patients), CRS is recommended only in case of M+ patients (at MRI and/or CSF analysis), like in our case,^[14] and more efforts are being made to reduce more the radiation fields as much as possible.^[15] Actually, the multimodality therapy (surgery, radiation, chemotherapy) is the most recommended. Chemotherapy take an important role in the treatment of intracranial GCTs, however there is no standardized protocol (dosage duration of treatment,.). Many chemotherapeutic agents were selected and used for intracranial GCTs, based on gonadal GCT treatment, like: Methotrexate, ACNU, vinblastine, vincristine, bleomycin, etoposide, Ifosfamide and carboplatin/cisplatin. Actually, many institutions around the world prefer to use cisplatin, etoposide and Ifosfamide, as seen for our patient; however, the administration schedule is not clearly established.^[16] Many trials and studies are trying to optimize pre-radiation chemotherapy and give lower dose of radiation and fields size, to get a more effective management of intracranial GCTs. The multimodality therapy is showing good results, but there are no standard approaches at this moment.^[17]

In conclusion, the neoadjuvant chemotherapy (3drugs) followed by radiation therapy (CSR or reduced fields) seems to be reasonable and acceptable.

CONCLUSION

Intracranial CGTs tumors are rare, the pineal region is rare localization for young children, most often male infants. The most common type of relapse is local recurrence at the primary site, in almost 70% of the cases. There is no standard approaches. Adequate diagnosis and treatment regimens are still under debate and remains controversial. A neoadjuvant chemotherapy followed by "large volume" or reduced filed radiation therapy seems to be reasonable, as seen in many trials. But the protocol treatment remains controversial, especially about the volume treated and dose received.

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