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Review Article

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EXCLUSIVE RADIOTHERAPY SUITABLE FOR SEMINOMATOUS TUMORS OF THE CENTRAL NERVOUS SYSTEM: REPORT OF A CASE AND REVIEW OF THE LITERATURE

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ABSTRACT

Primary cerebral seminomatous germ cell tumors are rare. They are located preferentially in medial structures, often in the pineal region. They most often affect children or young adults, with a predominance in the second decade of life. The management of intracranial germ cell tumors is not consensual. But exclusive external radiotherapy would be effective with a reduced dose in a limited brain volume. It is in this context that we report our clinical case from a patient with a primary seminoma of the pineal gland that responded well to exclusive external radiotherapy without neurological morbidity. **Résumé:** Les tumeurs germinales séminomateuses cérébrales primitives sont rares. Elles sont localisées préférentiellement aux structures médianes, souvent région pinéale. Elles touchent le plus souvent l'enfant ou l'adulte jeune avec une prédominance au cours de la 2ème décennie. La prise en charge des tumeurs germinales intracrâniennes n'est pas consensuelle. Mais la radiothérapie externe exclusive serait efficace avec une dose réduite dans un volume cérébral limité. C'est dans ce contexte que nous rapportons notre cas clinique à partir d'un patient présentant un séminome primitif de la glande pinéale ayant bien répondu à la radiothérapie externe exclusive sans morbidité neurologique.

INTRODUCTION

Germ cell tumors are embryonic tumors located mainly in the gonads. Their cerebral localization is rare. They represent less than 1% of intracranial neoplasms.[1, 2, 3, 4]

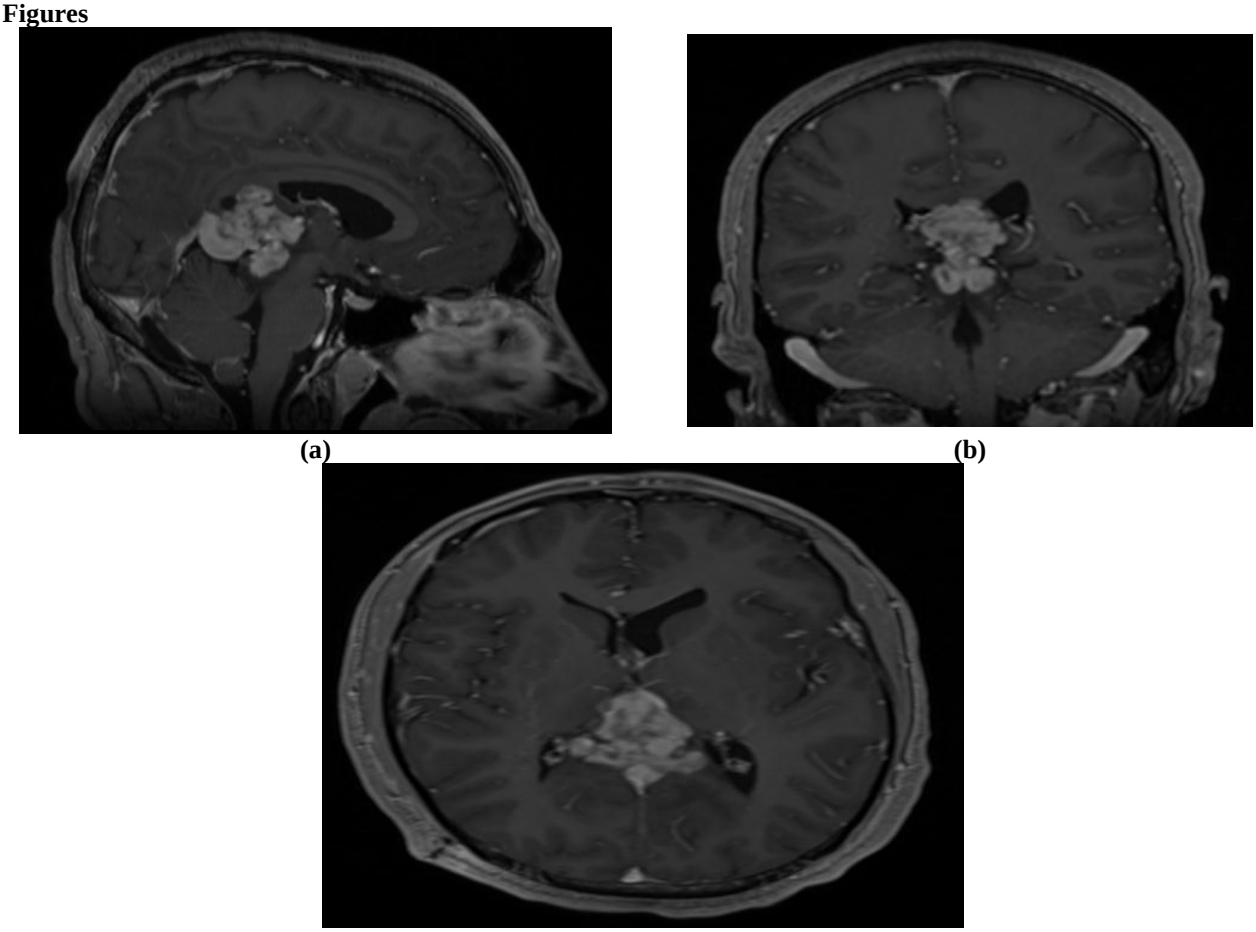
A distinction is made between seminomatous germ cell tumors (germinomas) and non-seminomatous germ cell tumors (mature teratomas, immature teratomas, yolk cell tumors, choriocarcinomas).[5,6] Germinomas are located preferentially in medial structures, often the pineal and suprasellar regions (40% of cases), occasionally the thalamus.[7, 6, 8, 9, 10] They tend to affect young men and children.[11, 12] Their prognosis is very favorable, as they usually prove to be highly chemosensitive and radiosensitive[11, 7, 13] However, there is still no consensus on the therapeutic strategy.

PATIENT AND OBSERVATION

A 28-year-old man with no prior history was admitted to the emergency room in October 2015 for a picture of intracranial hypertension with horizontal diplopia. CT scan and brain MRI demonstrated a pineal region tumor lesion of 35 mm long axis with triventricular hydrocephalus (Figure 1). The patient first underwent a ventriculoperitoneal shunt and then a stereotactic biopsy. The biopsy was concluded to be a pure seminomatous tumor. Tumor markers (alpha-fetoprotein, HCG, and LDH) and cerebrospinal fluid (CSF) cytology were normal. Spinal cord MRI was normal.

The patient was treated with 3D exclusive radiotherapy on a limited volume including the tumor and the ventricular system. The tumor associated with the ventricular system received a dose of 22 Gy in five weekly fractions and 2 Gy per session. Then an additional 24 Gy was delivered to the tumor bed (Figures 2 and 3). The evolution was marked by a complete clinical and radiological remission at 5 years after diagnosis and without signs of toxicity (Figures 4 and 5).

Figures



(a) **(b)**

(c)

Figure 1: Initial T1 MRI (sagittal (a), coronal (b), axial section (c)) showing a tumor in the pineal region with obstructive hydrocephalus.

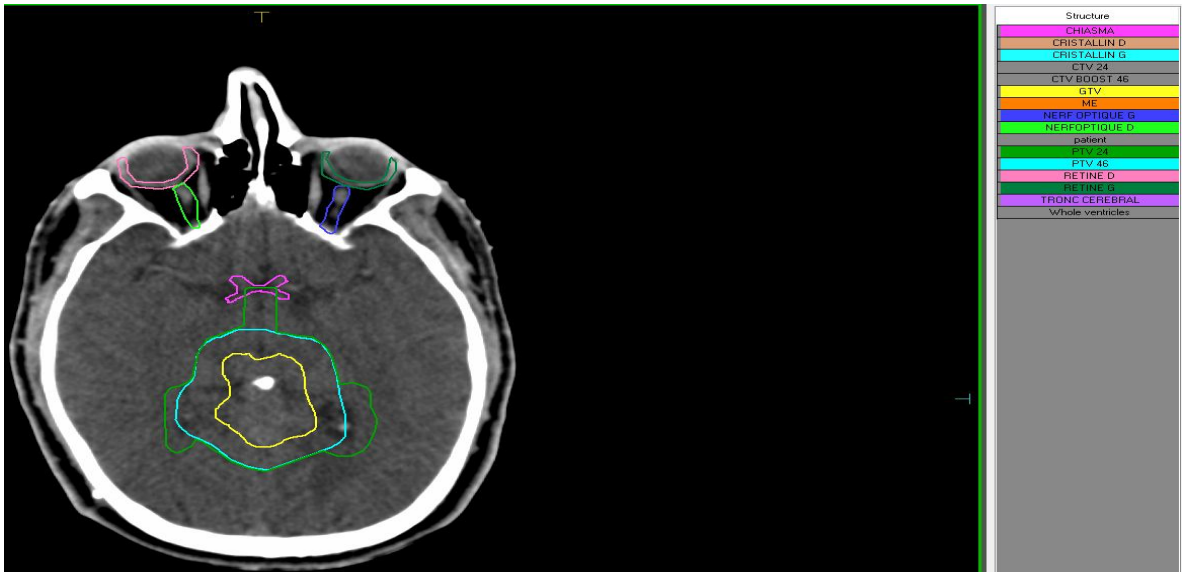


Figure 2: Delineation of target volumes. GTV T (in Yellow), PTV T 24 (2 cm around the PTV T with the inclusion of the ventricular system in Green), PTV T 46 (2 cm around the PTV T only in Blue).

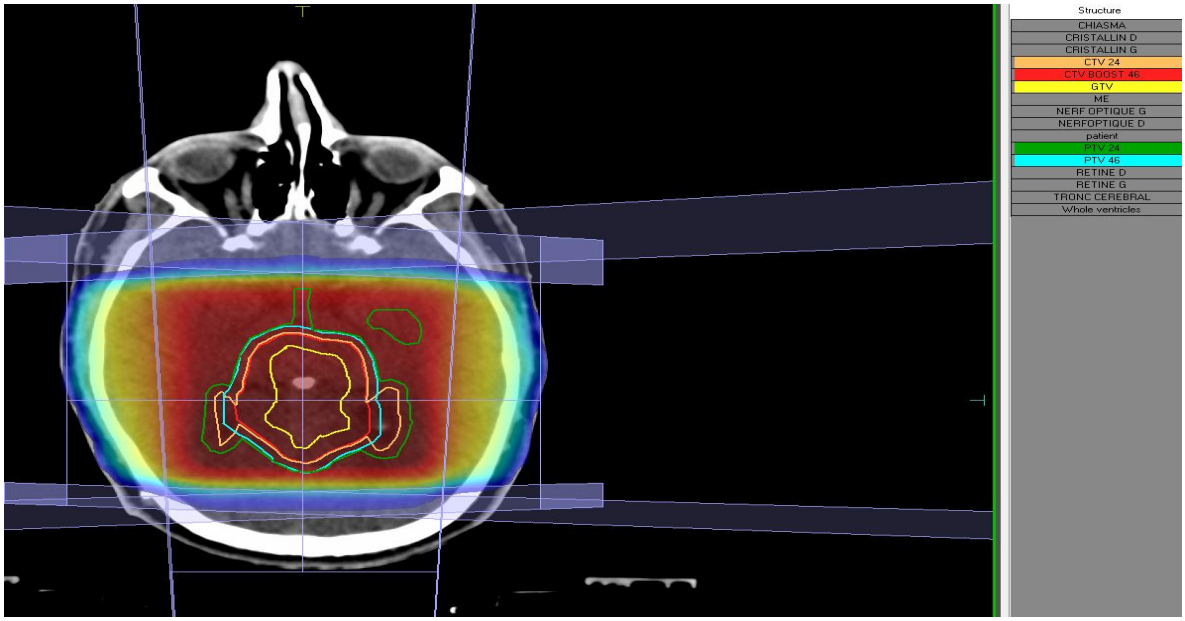


Figure 3: Axial treatment plan for irradiation of target volumes PTV T 24 (in Green taking 24 Gy) and PTV T 46 (in Blue taking 46 Gy).

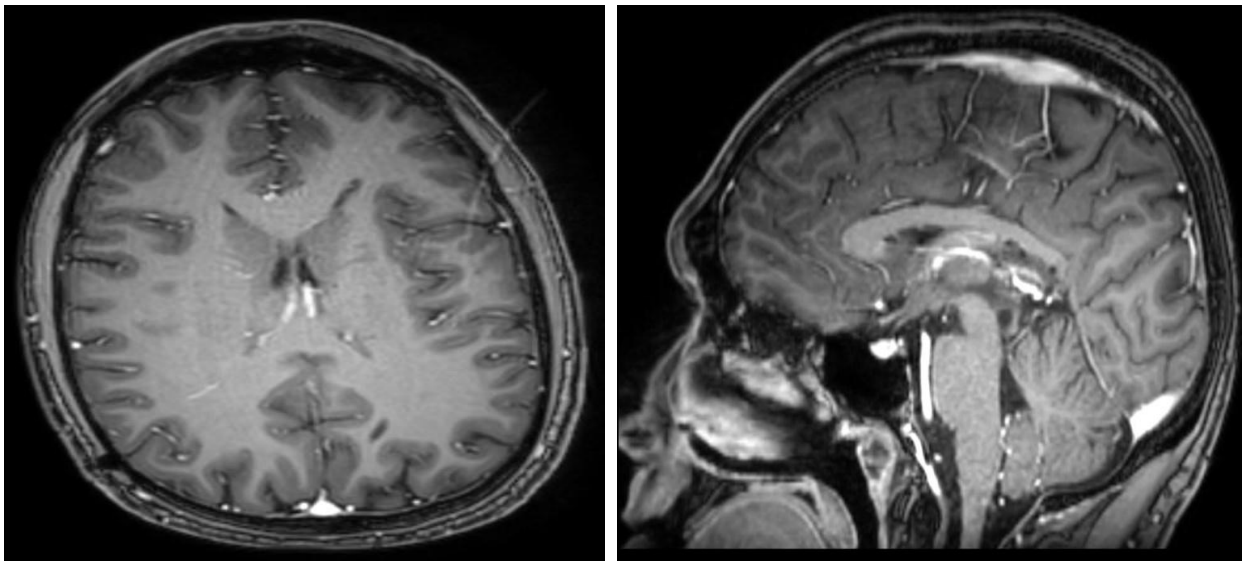


Figure 4: Post-radiotherapy control MRI (Sagittal and Axial section) at 2 years showing a visible tumor absence of the pineal region and absence of dilation of the ventricular system.

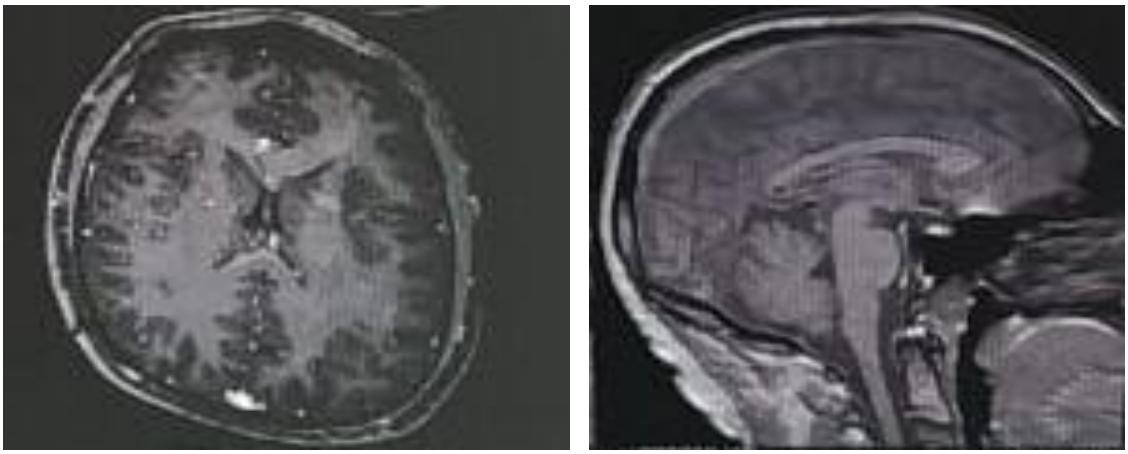


Figure 5: Post-radiotherapy control MRI (Sagittal and Axial section) at 5 years still showing a stable aspect of the pineal region without visible tumor localization.

DISCUSSION

Germ cell tumors are mainly located in gonads. Their location in the brain is rare. These tumors represent less than 1% of all brain tumors.[1, 2, 3, 4] However, for unknown reasons, this rate is about 4% in Japan.[14, 15, 16] Germinomas, also known as pure seminomas, account for 60% of brain germ cell tumors. These germinomas affect children and young adults with a predominance in the 2nd decade (45%).[17] The predominance of males is clear with a sex ratio of 2/1.[18] Our male patient was 28 years old in our case.

The histogenesis of brain germ cell tumors is still debated. Strictly extraneural in origin, germinomas are developed along the midline, particularly in the pineal and suprasellar regions. But they are of variable differentiation and malignancy. Primordial germ cells, precursors of germ cells, are located in the extraembryonic mesoderm. These primordial germ cells migrate along the dorsal mesentery to the genital ridges. They will be then, at the origin of the gonads. On their migration path during embryogenesis, they can develop in the pineal region as well as at the anterior end of the third ventricle. In this pineal region, germinomas manifest macroscopically months or years after the onset of diabetes insipidus. The tumor is most often located in the pineal region (50% of pineal tumors) or in the suprasellar and hypothalamic region (35% of cases). An intrasellar localization is possible but rare and the association of intrasellar germinoma and pineal germinoma has already been reported.[19, 20 - 22, 23]

The clinical expression is presented in different forms of clinical signs. It includes an intracranial hypertension syndrome related to compression of the aqueduct of Sylvius or the 3rd ventricle, occulomotor disorders and in particular Parinaud's syndrome due to compression of the superior colliculi, as well as an endocrine syndrome due to infundibular compression explaining diabetes insipidus, or potomania due to stimulation of the hypothalamus.[23] Intracranial hypertension and oculomotor disorders were observed in our case.

Brain imaging provides considerable support for diagnosis. The brain scan shows a well-limited, homogeneous, round or lobulated, iso- or hyperdense mass in the pineal or suprasellar region. And it enhances after injection of contrast. Its interest has decreased since the advent of MRI. However, the brain scan is still the first examination requested when faced with a picture of intracranial hypertension. Brain MRI is the best diagnostic test. It allows differentiating a normal pineal gland from a pineal tumor knowing that the size of the pineal gland measures between 5 and 10 mm in its long axis and 1 to 4.5 mm in thickness.[24] The germinoma usually appears as a well-limited mass, iso-signal in T1 and iso- or hyper signal in T2, taking up gadolinium homogeneously. However, this appearance is not specific and does not allow differentiation between the histological types of epiphyseal tumors,[25, 26]

Histology is the fundamental requirement for prognosis and therapeutic conduct.[14] And this histological evidence has become easy to obtain with an acceptable morbidity rate of about 5%.[14, 16, 26] And it is possible thanks to the progress of neurosurgical techniques in stereotactic conditions.[14] A stereotactic biopsy allows eliminating differential diagnoses. These differential diagnoses are mainly non-seminomatous intracranial germ cell tumors and pineal parenchymal tumors (pineocytomas and pineoblastomas).[27] In the past, trial radiotherapy was recommended. It should be abandoned nowadays, in favor of biopsy, given the risk of irradiating benign or non-radiosensitive tumors.[1, 28] In our case, the diagnosis was on histological evidence after stereotactic biopsy.

The diagnosis of certainty is based on histological data. On the other hand, the recent diagnostic means represented by tumor markers (beta-HCG or αFP) and modern imaging, can lead to a sufficient presumption to start a treatment. Detection in blood or cerebrospinal fluid of beta-HCG or αFP, even in small amounts, is sufficient to make the diagnosis of a germ cell tumor. In germinoma, tumor markers are usually negative. Nevertheless, a moderate elevation of beta-HCG is possible.[1]

Cerebrospinal fluid cytology should be performed routinely to detect neoplastic cells. However, its sensitivity remains to be discussed. Positivity at the lumbar level indicates metastatic evolution. This requires an adapted treatment.

The surgery of these tumors is laborious because of their location. The pineal gland can be accessed through the occiput. Nevertheless, a complete removal is made difficult by the depth of the tumor.[14] However, between 60% and 90% of patients with pineal region tumors require derivation because of symptomatic hydrocephalus.[29, 30] In frail patients or those with poor prognosis tumors, bypass may be the only surgical treatment offered.

Intracranial seminomas remain the most radiosensitive brain tumors. Thus they can be cured by radiotherapy alone. Radiotherapy symbolizes the historical treatment.[31, 32, 14] The recommendations for radiotherapy have constantly evolved. They aim to optimize the volume to be irradiated and also the dose to be delivered in order to reduce the risk of medium and long-term sequelae. Thus, in the early 1990s, radiotherapy was based on craniospinal irradiation of 30 Gy in 15 fractions and three weeks, then 20 Gy in 10 fractions and two weeks in the tumor bed.[1,31,33] With this irradiation technique, long-term survival rates were 85-100% depending on the series.[7,32] Unfortunately, delayed toxicity dominated by cognitive impairment and growth retardation, and endocrine failure in children have been noted. The frequency and severity of these complications

seemed to be more severe the younger the patient and the higher the radiation dose.[34]

Currently, the optimal brain volume to irradiate remains a debate. It varies according to the authors. As spinal irradiation used to be systematic.[7, 8, 35, 26], some authors suggest reserving it for patients whose cytological examination of the cerebrospinal fluid reveals the presence of tumor cells[35, 36], or who have multifocal tumors or tumors with ventricular invasion.[37, 38, 39, 36] Thus, in a series of 40 patients, Harrigan-Hardenbergh et al. compared the results of whole-brain irradiation with a complement on the tumor bed, associated or not with acraniospinal irradiation. The median dose delivered to the brain was 32.4 Gy (15 to 44.37 Gy). There was no difference in recurrence-free survival rate between those who had and those who had not received radiation to the spinal axis. Other authors have recommended limiting the dose delivered to the entire brain to 25 Gy and that of the tumor bed complement to 20 Gy.[3] According to Haddock et al. in a retrospective series, partial brain irradiation is associated with an increased rate of cerebrospinal relapse. The five-year disease-free survival rate was 29% after partial brain irradiation versus 50% after total brain irradiation and even 100% after cerebrospinal irradiation.[2] On the other hand, Fuller et al. showed in a review of 208 cases in the literature that the risk of meningeal relapse was low if the germinoma was localized, 3-9% after craniospinal radiotherapy, 6-10% after whole-brain irradiation, and 8-20% after focused irradiation, with no significant difference between these relapse rates.[40] Similarly, Shibamoto et al. showed that the relapse rate was not higher between local and large volume irradiation.[10] Also, Chirato et al, recommend irradiating a limited volume but including the whole ventricular system.[36] Partial irradiation of the brain volume allows a significant reduction of irradiated healthy tissue compared to irradiation of the entire brain and thus a potential benefit in terms of late toxicity.[41]

The dose is another topic of discussion. The dose of 50 Gy was frequently recommended to treat the primary tumor.[40, 2, 10, 36] This dose was adopted empirically based on the side effects of radiotherapy on healthy brain tissue.[36] However, although the risk rate of cerebral necrosis does not exceed 0.5% for a dose of 50 Gy, other severe complications may develop, namely cognitive disorders and endocrine insufficiency.[36, 28] On the other hand, if testicular germinomas (histologically identical to intracranial germinomas), can be cured by a dose of 25 - 35 Gy[36], the question is why such a dose requirement for such a radiosensitive tumor? Therefore, in some studies, authors have tried to analyze a dose reduction using an irradiation dose lower than 50 Gy.[36] Shibamoto et al, proved that the control rate was the same for patients receiving 40 - 45 Gy and 50 Gy or more[36] However, the toxicity appears to be much higher for doses above 50 Gy. According to Shibamoto et al., it would be reasonable to reduce the dose to 40 - 45 Gy, at least for tumors less than 4 cm in diameter. Shirato et al. recommended a dose of 40 Gy since the control rate was not improved with doses above 40 Gy. On the other hand, recurrences were noted in patients who received less than 35 Gy.[42] But Fuller et al. did not find a correlation between dose and disease-free survival or overall survival.[40] And Haddock et al[2], stated that there was a correlation between doses above 40 Gy and better local control. The 10-year overall survival rate after exclusive radiotherapy has been estimated to be between 83 and 100%.[31, 2, 42, 26]

A second alternative treatment approach is based on neoadjuvant chemotherapy followed by radiotherapy. On the other hand, when chemotherapy is combined with radiotherapy, the results appear to be significantly better than exclusive chemotherapy.[1, 44, 31] This association was initially described by Alen et al.[44] According to the results published in the literature, it would seem that chemotherapy could reduce the doses and volumes of irradiation and also the late toxicity of the treatment.[44, 31, 14, 45] The largest study confirming this alternative treatment approach is the prospective phase II trial. This trial, conducted in Japan, included 130 patients with intracranial seminoma. Patients received three cycles of carboplatin and etoposide before 24 Gy of radiation to the initial affected site. This treatment regimen resulted in a five-year overall survival rate of 97.8% and a recurrence-free survival rate of 90.8%.[46] Typically, this combination involves three to four courses of BEP followed by 40 Gy of radiation to the tumor site (25 Gy to the craniospinal axis if the disease is diffuse). The five-year recurrence-free survival rate was 90%.[7, 31] The results are the same as those of exclusive radiotherapy.[1, 31] Despite these excellent results, only the phase III trial initiated under the support of the Children's Oncology Group compares exclusive radiotherapy of 24 Gy to the entire brain and 45 Gy to the tumor bed with neoadjuvant chemotherapy of two cycles of carboplatin and etoposide and two cycles of cyclophosphamide and cisplatin followed by radiotherapy of 24 Gy to the initial affected site. This phase III trial will be able to definitively confirm the equivalence of the combination therapy and its lower delayed toxicity.[39, 12]

CONCLUSION

Seminomas of the pineal gland are rare tumors with a good prognosis. However, this rarity explains the difficulty of conducting randomized studies to establish a consensual therapeutic strategy.

Irradiation in a localized volume with a dose of 40 - 45 Gy appears to be effective if there are no tumor cells in the cerebrospinal fluid and with a reduction of toxicity.

Our patient received exclusive radiotherapy on a limited brain volume including the tumor and the ventricular system up to a dose of 22 Gy with five weekly fractions of 2 Gy per session. Then a 24 Gy complement in the tumor bed. The evolution was marked by a complete

clinical and radiological remission at 5 years after the diagnosis and without any sign of toxicity.

Conflicts of interest
Authors do not declare any conflict of interest.

Authors' contributions
All authors contributed to the writing of this manuscript and approved the final version.

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