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Complete Response to Radiotherapy in a Pineal Parenchymal Tumor of Intermediate Differentiation

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Abstract

Background and Importance: Approximately 20 percent of parenchymal pineal tumors (PPT) arise from the epithelial cells and are extremely rare, especially in adults, accounting for less than 1 percent of all primary brain tumors in Europe and North America. PPT of intermediate differentiation (PPTID) was recognized as a new entity and introduced in the 2007 WHO classification, corresponding to grades II (GII) or III (GIII). Previous studies had suggested its potentially aggressive behavior and tendency for cerebrospinal fluid seeding. A standard treatment for these tumors has not yet been defined. The gross total surgical resection is indicated whenever technically feasible and the impact of adjuvant radiotherapy and chemotherapy is not established. In fact, little is known about the radiation and chemotherapy sensitivity of these tumors.

Clinical Presentation: We describe a case of a recurrent PPTID (G II, Ki67:10%) which underwent to an endoscopic third ventriculostomy, biopsy and a two conformal radiation therapy course (25 fractions of 180 cGy over 4 weeks and, 3 fractions of 180 cGy, total of 5400cGy). After that, the patient was completely asymptomatic and an MRI revealed no residual mass. There was no sign of relapse by the 27-months follow-up.

Conclusion: Given the paucity of good clinical evidence for a standard therapy and the fact that the currently PPTID treatment is experience-based, we conclude that radiotherapy can be considered as suitable possibility of primary treatment. Due to its rarity, prospective multi-institutional studies should be arranged to establish the optimal PPTID management.

Keywords: Pineal parenchymal tumor; Intermediate differentiation; Radiotherapy treatment

Background and Importance

Approximately 20 percent of PPT arises from the epithelial cells and are extremely rare, accounted for less than 1 percent of all primary brain tumors in Europe and North America. PPTID was introduced into the WHO classification in 2007 as an intermediate-grade malignancy (GII or III) and constitutes approximately 10% of all PPTs. Currently there is none randomized controlled trials or systematic reviews assessing the effectiveness of surgical and non-surgical treatment for them. Although surgical resection is considered the gold standard treatment, the optimal management of PPTIDs has not been defined yet. The role of chemotherapy is uncertain and radiotherapy is often indicated as an adjuvant treatment. In fact, the little knowledge about the effectiveness of surgical and non-surgical treatment for PPTID comes from series of cases reported. We describe a case of a recurrent unresectable PPTID that presented a complete response to Three-dimensional conformal radiation therapy (3D-CRT), without recurrence or any adverse effects until the 27-months follow-up.

Case Report

This report is about a 43-year-old female patient that presented initially with headache, dizziness, visual abnormalities and unstable gait in January 2010, without other co-morbidities. Her brain magnetic resonance imaging (MRI) revealed an obstructive hydrocephalus because of a large mass in the pineal gland. She underwent to an endoscopic third ventriculostomy and biopsy. Pathology revealed a PPTID. As symptoms improved, she remained under observation with no further treatment until February 2013, when her symptoms reappeared. At that time, a team of neurosurgeons attempted surgical resection, but the procedure had to be interrupted due to massive intraoperative bleeding. Pathological report confirmed same findings as before, with a Ki67 of 10% (Figures 1 and 2). In May 2013 the patient was referred to our hospital for treatment. At that time, her MRI showed a 6.4 × 3.5 × 2.9 cm midline mass presenting high T2/FLAIR

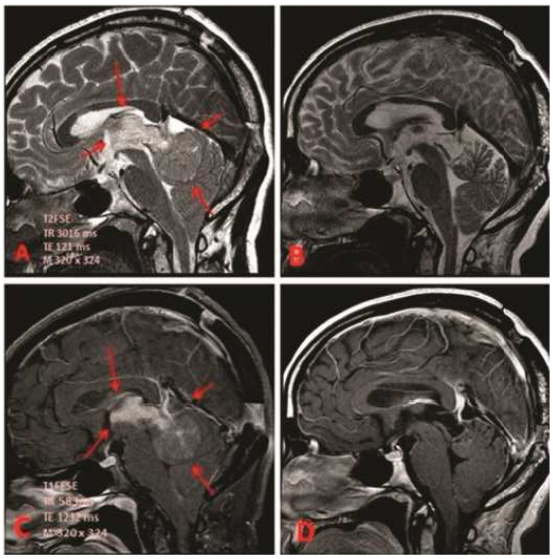

Figure1: Complete response of the tumor to the 3D radiotherapy.

The 1.5-T MRI done prior to the 3D-CRT demonstrates a midline mass (arrows) with mostly hyperintense signal on T2FSE (A) and heterogeneous contrast enhancement on T1W1 sequences (C). The MRI on the twentieth month follow up confirms a lasting and complete response to the 3D-CRT (B, D).

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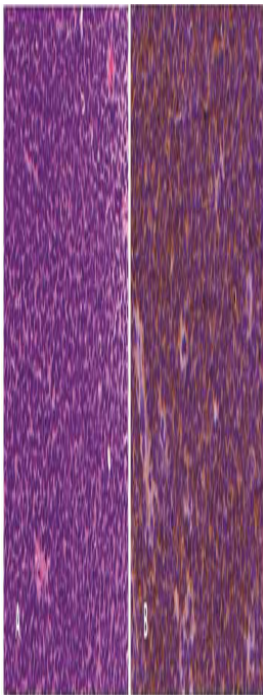

Figure 2: Histopathologic features: A) H&E stained section, B) Immunohistochemistry section.

The neoplasm was homogeneously composed of diffuse sheets of small to medium sized cells, which had a barely discernible cytoplasm and a rounded nucleus with salt and pepper chromatin and subtle nucleoli(us) (A) . In particular areas, small rosettes were identified. Mitotic figures counting reached 2 mitoses per 10 high-power microscopic fields. No coagulative necrosis, calcification or cystic areas were observed. Features of pineocytoma or pineblastoma were not identified microscopically in the material examined, and no brain parenchyma invasion was observed in the specimen. Immunohistochemically, the neoplasm expressed synaptophysin and chromogranin A diffusely (B). Ki-67 (MIB-1) was positive in about 5-10% of the neoplastic cells.

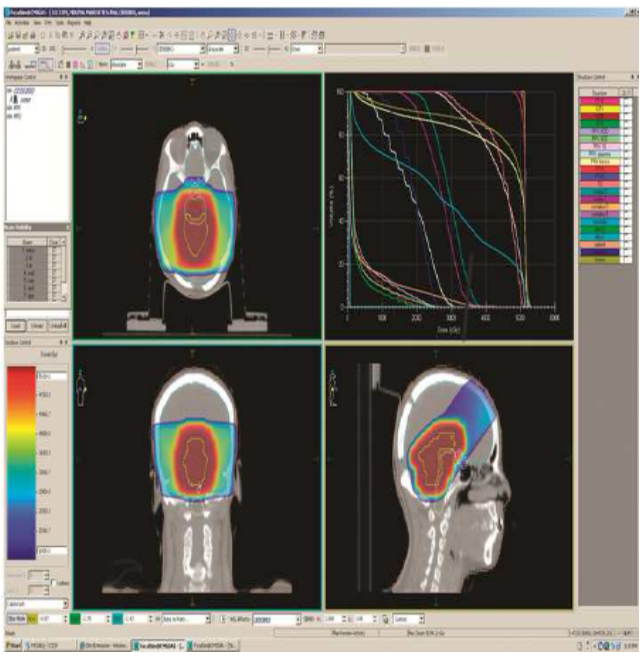

Figure 3: Three-Dimensional conformal radiation therapy plan. Radiation fields arrangement and isodoses distribution.

signal and a heterogeneous contrast enhancement in T1W1 sequences at the pineal gland topography, occupying the third ventricle and quadrigeminal plate cistern, compressing the central lobule and culmen of the cerebellum, forth ventricle and cerebral aqueduct (Figures 1 and 2). A cerebrospinal fluid lumbar puncture, as well as spinal axis MRI was completely normal. The patient adamantly refused another surgical resection attempt and was referred to radiotherapy. She underwent 3D-CRT in 25 fractions of 180 cGy over 5 weeks (4500 cGy) to the ventricular system and a boost of 540cGy in 5 fractions to the tumor, adding up to a total dose of 5040 cGy (Figure 3). Her symptoms completely resolved at about four months following completion of radiotherapy. Her first follow-up MRI showed a complete response. She persists symptom free so far (27 months after radiotherapy) and her latest MRI has showed no evidence of remaining tumor (Figures 1b and 1d).

Discussion

Approximately 20 percent of PPT arise from the epithelial cells and are extremely rare, especially in adults, accounting for less than 1 percent of all primary brain tumors in Europe and North America [1-3]. Symptoms at presentation vary according to the tumor aggressiveness and the most common are headache, vision abnormalities, nausea, vomiting and impaired gait. MRI is the most useful method to identify the tumor and delineate its relationship to adjacent structures [4-10]. PPTIDs are usually heterogeneously hypointense on T1WI and heterogeneously hyperintense on T2WI, and show strong heterogeneous or uniform enhancement following contrast administration [9-11]. Histopathological diagnosis is always desirable prior to therapy and tissue samples can be obtained through stereotactic biopsy, neuroendoscopic or open surgery. The PPT cells stain positive for neuron specific enolase and synaptophysin on immunohistochestry, demonstrating their neuroendocrine nature. PPTID has an intermediate degree of malignancy compared with pineocytomas (PC) and pineoblastomas (PB) and no definite hystopathological grading criteria has been established yet [1,2,12-16]. The PC does not usually present mitotic figures and often expresses neurofilament protein (NFP), while PPTID presents up to 6 mitoses per 10 high-power microscopic fields and expresses NFP irregularly [12,13]. The PB presents numerous mitotic figures, focal NFP and necrosis. There are recognized hybrid cases (PC-PPTID and PPTID-PB) supporting the idea of a spectrum among these neoplasm and reinforcing the difficulty of conceiving a grading methodology that predicts biological behavior and prognosis consistently [12,13-17]. proposed a prognostic grading for PPTs including four grades: grade I (GI) for PC, grade GIV (GIV) for PB and GII and III for PPTID, with GII being defined as having fewer than six mitotic figures and positive immunolabelling of NFP, and GIII being define as having six or more mitotic figures or fewer than six mitotic figures but without immunostains for NFP [13,14]. In a large retrospective case control study, survival rates were far better for PPTIDs than for PBs and also was reported that GIII had a much more aggressive biologic behavior compared with GII [8,12,16]. However, the most reliable prognostic factors are the presence of leptomeningeal or spinal metastases and extension of surgical resection [8,12-17]. This latter procedure has still been acknowledged as the most effective or the gold standard therapy [2-8]. Despite of this, the optimal management (including adjuvant therapy) remains unclear [2-4]. Currently, there is no standard systemic therapy, no randomized controlled trials and none systematic reviews assessing the effectiveness of surgical and non-surgical treatment for PPTID. A few large-scale studies have reviewed long-term results of different treatment approaches ranging from surgery or external irradiation alone to combined treatment with surgery, radiotherapy or chemotherapy, but they have been no

definitive conclusions [6,14-18]. The surgery plays a pivotal role in relieving the local mass effect and providing a maximal tissue sample for histological analysis. Although gross total resection is associated with better local control, the correlation between the extent of resection and survival is questionable [8,19,20]. In spite of advancements in neurosurgical techniques, the mortality and permanent morbidity rates may be as high as 4-7% and 10% respectively [20].The role of chemotherapy is uncertain. A number of schemes using combined agents, such as procarbazine, lamostine, vincristine, etoposide, cis-platinum, carboplatinum, hydroxyurea, nimustine, cyclophosphamide, ifosfamide, bleomycin, ACNU and interferon beta, have showed some positive action [5-8,18,19,21-24]. Li et al. [25] have detected a mutation of epidermal growth factor receptor in PPTID tumors and have suggested that molecular-targeted therapies, in addition to chemotherapy, may be a viable treatment option for PPTID tumors [24,25]. Radiation therapy have been frequently indicated as adjuvant treatment for any remaining tumor after surgery or recurrence. It has been performed as external conventional radiotherapy, gamma-knife radiosurgery or brachytherapy [21,22,23]. Despite of this, the role of craniospinal and whole-ventricular irradiation for patients with PPID remains to be determined [24]. Almost all patients in the previous reports were relative long-time survivors and practically all different treatment approaches have presented some late adverse effects as neurocognitive disorders. It is believed that toxicity of cranial irradiation and the concurrent or subsequent administration of neurotoxic chemotherapy (while the blood brain barrier is disrupted) are some of the crucial factors involved in the injury [24]. Considering the potential neurotoxic effects of the treatment and the expected survival time (even after experiencing a recurrence), the combined approach should be carefully considered, depending on the patient's pathological characteristics and disease extent. The exception is about patients with cerebrospinal dissemination that should receive wide irradiation fields, such as craniospinal and whole-ventricular irradiation, combined with sequential chemotherapy. The patient reported here had a complete and durable response to the 3D-CRT performed as a single modality of treatment, without any late adverse effects. This report has significant limitations. Firstly we described only a case of PPTID patient treated successfully with 3D-CRT and secondly, 27 months is a relatively short follow-up of this disease. Although we can't develop any conclusion, this report is in according to previous studies that have suggested the highly radiosensibility of PPDIT and supporting the idea of adding radiotherapy in protocols of PPTID treatment as adjuvant or primary therapy.

Conclusion

Although the PPTID has a potentially aggressive behavior and tendency for cerebrospinal fluid seeding, the expected survival time is relatively long. Currently the PPTID treatment is experience-based and surgical resection is considered the kmxzsey treatment. The role of chemotherapy still remains uncertain and radiotherapy is often indicated as an adjuvant treatment to any remaining tumor after surgery, recurrence or cerebrospinal dissemination. Given the rarity of this disease prospective multi-institutional studies should be arranged as soon as possible to establish the optimal PPTID management.

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