Complete Response to PD-L1 Targeted Treatment in a Patient with Anaplastic Papillary Tumor of the Pineal Region

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Abstract

An adult female patient underwent repeated neurosurgical procedures, radiosurgery, radiation therapy and chemotherapy for a recurrent and metastatic anaplastic papillary tumor of the pineal region. For a radiographically assured new relapse, she was treated with the anti-death receptor one antibody pembrolizumab given infused at a dose of 2mg/kg every two weeks. Within a week, the tumor manifestations of the patient shrank continuously and she achieved complete remission which remained stable since now more than a year. The therapy was discontinued after eighteen months. The report of efficacy of cancer immune therapy in an advanced patient shows a treatment opportunity in this orphan disease.

Introduction

Parenchymal tumors arising from the pineal gland are very rare, affect mainly adult women and usually can be cured by total surgical removal [1-4]. Malignant tumors of the pineal gland however, preferentially occur in children or young adults, tend to spread through the cerebrospinal fluid and may show an aggressive clinical course [5-7].

Here we report the course of an anaplastic papillary tumor of the pineal region in a female patient that already started with increased mitotic activity evolving through multiple recurrences to a rapidly growing, metastatic tumor. Interestingly, the patient achieved complete remission after therapy with the immune checkpoint inhibitor pembrolizumab.

Case Presentation

37-year-old women underwent MR imaging because of double vision and headache. No history of major diseases or allergies was stated. The MRI showed a cystic tumor in the pineal region leading to obstructive hydrocephalus which was removed by an endoscopic ventriculo-cisternotomy. Histologic examination showed a papillary tumor of the pineal gland with less than 5% of cells positive for Ki-67 immunohistochemistry (Figure 1). In 2010, a locally recurrent tumor was resected, showing 34% of cells positive for Ki-67. Due to this increased mitotic activity and proliferation rate the tumor was rated as anaplastic tumor, WHO grade III. Subsequently, the patient underwent focal fractionated radiotherapy with 1.8 Gy/ fraction up to 54 Gy and concomitant and adjuvant chemotherapy with Temozolomide, in analogy to the standard of care therapy for malignant gliomas (Stupp 2005) [8]. Three years later, metastatic spread to the left trigonal zone, the right hemisphere of the cerebellum and on the vermis and a spinal metastasis at Th9 were detected. The spinal tumor was resected and treated with a local radiotherapeutic boost. The intracranial metatases were treated by Gamma Knife radiosurgery and the patient underwent four cycles of systemic chemotherapy with cisplatin (25mg/m² days 1-4), etoposide (40mg/m², days 1-4) repeated after 28 days and intrathecal etoposide and intrathecal liposomal cytarabine (4 cycles each) by an Ommaya reservoir [9,10]. One year later, in December 2014, a new cerebellar metastasis was
treated by radiosurgery and in January 2015, resection of two new metastases in the cerebellum was performed. Tumor tissue from this fifth surgery was analyzed, using a panel of tests composed from immunohistochemistry, FISH analysis and genetic sequencing of 70 potential drug targets [11]. This analysis failed to show a druggable target or expression of death receptor ligand 1 (PD-L1). Still, we informed the patient about potential benefits and risks of treatment with an antibody directed to programmed death receptor-1 (PD-1) and started with this therapy within an accelerated access program in 2015 [12]. The patient started treatment with 2mg/kg pembrolizumab every two weeks intravenously in March 2015. Six weeks later, the patient complained about jerking of legs, dizziness and dysphasia. MRI showed again contrast enhancing lesions at the previous tumor sites spinal and a new tumor in the fourth ventricle. Palliative radiotherapy was started and immune therapy was continued. The symptoms improved and vanished. MRI controls done every three months showed stable disease, then shrinking and disappearance of the tumor formations. The patient achieved complete remission with stabilization of her clinical condition, allowing independence in ADL and IADL (Figure 2).

**Discussion**

This patient achieved complete remission of an aggressive papillary tumor of the pineal region after multiple recurrences under treatment with the PD-L1 inhibitor pembrolizumab. Retrospectively, the last episode of recurrence, treated with radiotherapy was almost certainly a pseudoprogression after the start of the immune therapy – happily the patient recovered and remained in stable clinical condition which allows her an independent life since this episode of clinical worsening. As papillary tumors of the pineal region are extremely rare tumors in adults, the favorable outcome in this patient should prompt the use of immune therapy in pinealoblastomas earlier in the future.

Of note, the tumor responded to targeted PD-L1 treatment in the absence of any significant PD-L1 immune-expression by the tumor cells [13-16]. This conflicting result prompted us to retrospectively assess the expression of mismatch repair proteins before and after treatment with temozolomide. In fact, none of the examined lesions showed evidence for mismatch repair deficiency [17-19]. Still, as pembrolizumab has been recently approved also for tumors with high microsatellite instability we might speculate that this might be
the reason for complete response in our patient. However, so far, germline DNA has not been available for definite confirmation.

References


