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Medulloblastoma with myogenic differentiation: long-term survival in a patient treated with aggressive combination therapy and autologous stem cell transplantation

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Abstract

Medulloblastoma with myogenic differentiation (MMD) is a rare and aggressive variant of medulloblastoma, occurring predominantly in children. There have been only two case reports of long-term survival previously published. We report a case of long-term disease-free survival in a 21-year-old diagnosed with MMD.

Keywords

Medulloblastoma with myogenic differentiation; Medullomyoblastoma; Autologous stem cell rescue

Introduction

Medulloblastoma with myogenic differentiation (MMD, also called medullomyoblastoma) is an aggressive cerebellar malignancy, first described by Marinesco and Goldstein in 1933 [1]. To date, 63 cases have been reported in the literature, in contrast to medulloblastoma which affects approximately 350 children in the United States each year. MMD is diagnosed histologically when myoblastic components are seen alongside primitive neuroectodermal components. The majority of patients affected by MMD are children under the age of ten [2–4]. However, cases in adults have been reported, the oldest being 40 years [5–7].

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Conflict of interest None.

The prognosis in patients with MMD is poor, with few patients surviving more than 3 years from diagnosis [3]. Two cases of long-term survival have been reported in children [2, 8], but there are no reports of long-term survival in an adult. We present a case of a 21-year-old diagnosed with MMD in 1999 treated with aggressive combination therapy who remains a long-term disease-free survivor 11 years following his diagnosis.

Case report

In June 1999, a 21 year old male presented with an 8-month history of dizziness and impaired balance. These symptoms worsened on extension of his neck and had become considerably worse over the preceding 2 months. Past medical history was unremarkable and there was no significant family history. On examination, the patient held his head tilted to the left. Otherwise his examination was entirely normal. There was no papilledema, nystagmus, diplopia, dysmetria, dysdiadochokinesis or intention tremor. Magnetic resonance imaging (MRI) of the brain demonstrated a 3×2.5 cm posterior fossa mass that was contrast enhancing following the administration of gadolinium (Fig. 1). The tumor was excised using a sub-occipital craniotomy and microsurgical resection with frameless stereotaxy. Gross total resection (GTR) was achieved. Microscopically a small round blue cell neoplasm was seen with additional areas of eosinophilic cells that had cross-striations and were immunoreactive for desmin and smooth muscle actin (Fig. 2). Ki-67 staining was approximately 10%. Based on these findings, the diagnosis of MMD was made. Cytogenetic analysis of the tumor was attempted, but the specimen was uninformative. Recently, the original sample was re-stained in an effort to determine immunoreactivity to myoglobin but the remaining specimen in the block was limited and the result was inconclusive. A spinal MRI and lumbar puncture obtained 10 days postoperatively did not demonstrate neuraxis dissemination.

The patient was consented to receive chemo-radiotherapy followed by adjuvant chemotherapy with the first part of the therapy following Pediatric Oncology Group (POG) study POG 9631. The therapy was as follows:

- Suboccipital craniotomy and microsurgical GTR
- Craniospinal radiotherapy (3,600 cGy) with a boost to a total dose of 5,580 cGy to the posterior fossa. Concomitant VP-16 (50 mg/m²/day po $\times$ 21 days followed by a 7 day break and then repeated)
- 4 week break
- Cisplatin (90 mg/m²/day IV on day one of each cycle) and VP-16 (50 mg/m²/day po $\times$ 21 days beginning on day one of each cycles) for two cycles
- Cyclophosphamide (4 g/m²/day IV $\times$ 1) followed by stem cell mobilization and harvest
- Cisplatin (90 mg/m²/day IV on day one of each cycle) and VP-16 (50 mg/m²/day po $\times$ 21 days beginning on day one of each cycles) for one additional cycle.
- Cyclophosphamide (1.5 g/m²/day IV on days one and two) and vincristine (1.5 mg/m²/day, days one and eight) for two cycles

- Preparative regimen consisting of:
- Carboplatin 725 mg/m²/day for 3 days, day -6 to -4
- VP-16 800 mg/m²/day for 3 days, day -6 to -4
- Cyclophosphamide via continuous IV infusion 2.5 mg/kg/h for 60 h beginning day -4
- Stem cell rescue 2.78×10^6 CD34+ stem cells/kg on day zero
- G-CSF 10 mcg/kg/day starting on day +1

The patient tolerated the therapy fairly well. He was admitted twice for fever and neutropenia and experienced some common transient therapeutic side effects, such as jaw pain secondary to vincristine. Long-term, the patient complained of reduction in his short-term memory which was attributed to craniospinal irradiation. Over time this has improved. The patient elected to receive no further MRI studies after his April 2004 MRI which continued to show complete clinical remission, which is an option offered to patients at the 5-year follow-up. He remains alive and clinically free of disease now 11 years from his initial presentation.

Discussion

Medulloblastoma with myogenic differentiation (MMD) is a rare and aggressive malignant neoplasm seen predominantly in children. The tumor most commonly originates from the cerebellar vermis, although other sites include the cerebellar hemispheres [2] and the cerebello-pontine angle [9]. The histogenesis of MMD is contentious. Briefly, current hypotheses include MMD arising as part of a malignant teratoma [3, 10], myoblastic differentiation of primitive neuroectodermal cells [11, 12] and secondary myoblastic differentiation of mesenchymal or endothelial cells near or within a primitive neuroectodermal tumor [13, 14]. MMD appears to have similar genetic features to the range of other medulloblastoma variants (e.g., large cell/anaplastic, desmoplastic) [15], reflecting the decision to reclassify this tumor in the 2007 World Health Organization (WHO) Classification of Tumours from medulloblastoma to MMD [16, 17].

However, despite the apparent genetic similarities, the reported outcomes of patients with MMD treated with surgery followed by radiation and/or chemotherapy have been very poor. The majority of patients have survived less than 1 year from diagnosis [5]. The longest reported survival in a patient treated with either radiotherapy or chemotherapy alone is 4 years [18]. It is difficult to compare the prognosis with the large cell/anaplastic variant of medulloblastoma given the paucity of cases. However, the presumption has been that the outcome should be somewhat more favorable for MMD than the large cell/anaplastic variant.

More recent publications have reported the use of combination therapy. Helton et al. [2] describe five children treated with combination therapy. This consisted of gross total resection (GTR), cranio-spinal irradiation (CSI) and varying combination chemotherapy. Two out of five patients died of their disease and a third patient died of secondary acute

lymphoblastic leukemia. Death occurred within 2 years of diagnosis in all three cases. The other two patients were disease-free at 23 and 92 months. Helton et al. [2] also reported a case of long-term survival following two episodes of local disease recurrence in a child initially treated with GTR and CSI, without chemotherapy. Following recurrence, further surgery was performed and combination chemotherapy administered. The patient was found to be disease-free at 187 months post-diagnosis. In a separate report an 8-year-old boy was diagnosed in 1999 and treated following GTR, CSI and 6 cycles of combination chemotherapy and was disease-free 11 years after diagnosis [8].

The published literature to date suggests that aggressive combination therapy offers the best chance of extended disease-free control. The long-term survival of our patient supports this hypothesis. A brief report published in *Pediatric Blood and Cancer* in 2006 outlined a case of MMD in a 23 month old male with comparable use of aggressive combination therapy and favorable results with complete remission at 2 years. In contrast to our treatment, Nozza et al. [19] treated with two consecutive stem cell transplants and subsequent CSI.

Trying to determine if there are prognostic factors that impact on survival is difficult given the paucity of cases and the inability to study outcomes prospectively. Extent of resection is likely important since GTR is generally associated with a better outcome in virtually all pediatric neurooncology studies. MMD presents exceptionally rarely in adulthood and it is reasonable to consider whether this has a prognostic effect. Two case reports in adults with MMD demonstrated survival of less than 1 month [5] and less than 3 years [3]. The findings of these authors provide no evidence to suggest there is any prognostic advantage to presentation in adulthood. Our patient also had a protracted symptomatic prodrome before diagnosis and it is necessary to contemplate whether this could be related to his positive outcome, suggesting a slower growing tumor. The duration of symptoms prior to diagnosis is typically short, mostly 3 months or less (Rao et al. 1990) [5]. However, longer symptomatic periods prior to diagnosis have been reported and have not been associated with improved long-term survival. In our case, histopathology demonstrated smooth muscle actin positive cross-striated eosinophilic cells consistent with leiomyoblastic MMD. Case reports show that rhabdomyoblastic differentiation predominates in MMD but smooth muscle differentiation has been seen previously and does not seem to be associated with an improved outcome [4, 20–22].

In summary, we present a case of MMD in a 21-year-old with long-term survival following aggressive combination therapy. The rarity of MMD limits our understanding of this tumor to single case reports and small case series but it appears that GTR followed by aggressive combination therapy, including consideration of autologous stem cell rescue might offer an improved outlook for such patients.

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Fig. 1.
MRI images: **a** Preoperative post-contrast T1 image. **b** Postoperative post-contrast T1 image

Fig. 2.
Histopathology: **a** H&E staining demonstrating striated muscle fibers. **b**
Immunohistochemistry of tumor demonstrating desmin positivity