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Hip Pain in Medulloblastoma as First Symptom of Extraneural Relapse

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Adult medulloblastoma · Extraneural metastases · Autologous stem cell transplantation

Introduction

Medulloblastoma is a common malignant brain tumor in childhood, but a rare disease amongst adults. The tendency to metastasize along cerebrospinal fluid pathways is well known. Extraneural metastases represent only a small number of recurrences and are associated with a poor outcome. Encouraging results of high-dose chemotherapy followed by autologous stem cell transplantation were reported previously in children with recurrent malignant brain tumors [1].

Case Report

In October 2007, a non-metastatic medulloblastoma of the cerebellum was diagnosed in a 28-year-old man. Following a total tumor resection, he underwent an adjuvant radiochemotherapy until January 2008, based on the experiences of the pediatric HIT '91 protocol [2]. The following magnetic resonance imaging (MRI) scan of the brain showed no residual disease.

In March 2009, he was admitted to the surgical emergency unit because of unbearable pain in the right hip and the lumbar vertebrae, which had intensified over the last weeks. Pain relief could only be achieved by intravenous morphine infusions. At first, the symptoms were thought to be the result of an earlier ski accident; however, a bone fracture could be ruled out following an X-ray.

The laboratory tests revealed anemia, thrombopenia, elevated lactate dehydrogenase (LDH) (13.5 µmol/s l, normally: < 3.75) and alkaline phosphatase levels (4.4 µmol/s l, normally: < 2.15). A pelvic and lumbar MRI scan revealed diffuse mottled signal changes with pathological enhancement after contrast medium (fig. 1). The iliac bone marrow biopsy (figs. 2–4) confirmed the suspicion of an osseous relapse of the medulloblastoma (50% infiltration of the total cellularity). Cerebral recurrence could be excluded by MRI scan.

After histological confirmation of recurrent extraneural medulloblastoma, a polychemotherapy as described by Millot et al. [3] was given.

The chemotherapy consisted of carboplatin 200 mg/m^2 and etoposide 100 mg/m^2 daily for 4 days. After the first course of chemotherapy, the patient was symptom free.

After the second course, stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) and apheresis were performed, followed by positive CD34 selection of 0.96×10^6 CD34+ cells/kg ('in vitro purging').

The staging MRI scan after the third course of chemotherapy revealed diffuse inhomogeneous signal changes. It was unclear whether the signal changes in the MRI scan were due to persistent metastatic disease or due to bone regeneration and remodeling after the eradication of metastatic lesions.

Next, we intensified the therapy with a high-dose chemotherapy protocol, consisting of carboplatin 500 mg/m^2 and etoposide 500 mg/m^2 for 3 days, followed by infusion of the purified autologous hematopoietic stem cells. Hematopoietic regeneration with neutrophils > 0.5/nl and platelets > 20/nl took place within 14 days. Severe infectious complications did not occur. Unfortunately, the patient developed ototoxicity consisting of tinnitus and mild hearing loss.

After complete regeneration of the peripheral blood count, an ambulant maintenance therapy with etoposide per os was initiated. However, after a few weeks, the patient did not want to continue therapy because of gastrointestinal toxicity with nausea, vomiting, and epigastric pain.

The patient is now free of the disease 1 year since the relapse.

Discussion

Medulloblastoma is the most common malignant brain tumor in children, with a peak incidence of 5–8 years. In adults, medulloblastoma is a rare disease, with less than 2% of central nervous system (CNS) malignancies [4]; therefore, they are treated according to pediatric protocols.

The overall survival rate of adult medulloblastoma is high. In the literature, 5-year overall survival rates of 80% [4–7] and 10-year overall survival rates of 60% [5, 6] have been reported. However, relapses occur frequently. The average time to relapse is about 10–26 months after the initial diagnosis [4].

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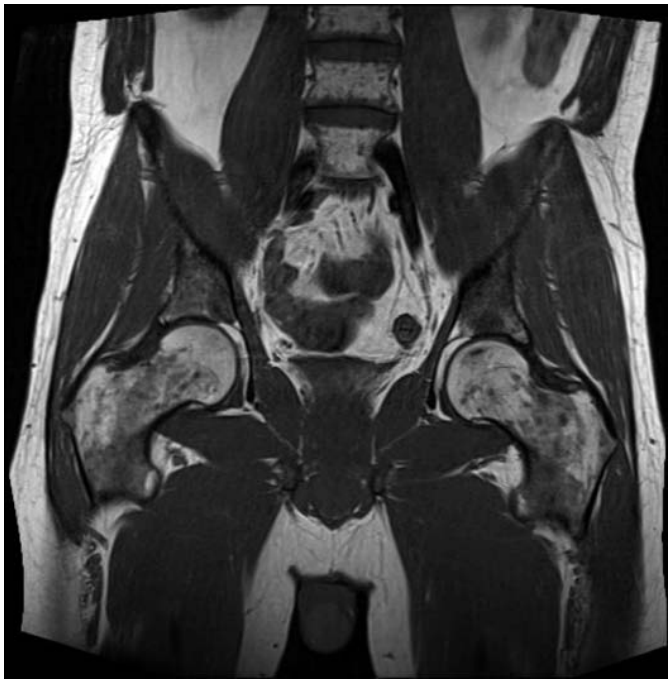

Fig. 1. T1-weighted MRI scan with multiple mottled signal changes in the whole skeleton of the pelvis and pathological enhancement of the contrast medium.

In contrast to infant medulloblastoma, late relapses were often observed in adults [4].

Seeding along cerebrospinal fluid pathways is well known, whereas extraneural metastases have been reported in only 10–15%. They most commonly involve bone, especially pelvis, followed by lymph node, liver and pulmonary metastases [2].

The prognosis for patients with an extraneural relapse is poor, with a median survival of 5–10 months [2]. Nevertheless, there is not yet a generally established therapy for relapse and, instead, individual protocols are normally used.

Medulloblastoma is considered as a very chemotherapy-sensitive tumor. The efficacy of different chemotherapeutics such as carboplatin [8, 9], etoposide [9–11] und thiotepa [9] in the treatment of medulloblastoma has already been demonstrated in previous studies. A few single-center studies demonstrated that the use of high-dose chemotherapy with autologous stem cell support is associated with a favorable response and a potential for long-term survival [3, 9, 12]. For example, Dunkel et al. [9] reported an event-free survival rate of 34% and an overall survival rate of 46% at 3 years in patients with recurrent medulloblastoma after high-dose chemotherapy consisting of carboplatin, thiotepa and etoposide followed by autologous stem cell transplantation.

The idea of purging autologous stem cells to avoid reinfusion of tumor cells seems to be appealing in order to minimize the relapse incidence. Especially in patients with malignant bone marrow infiltration, a contamination of the stem cell product cannot be excluded. This is the reason why we de-

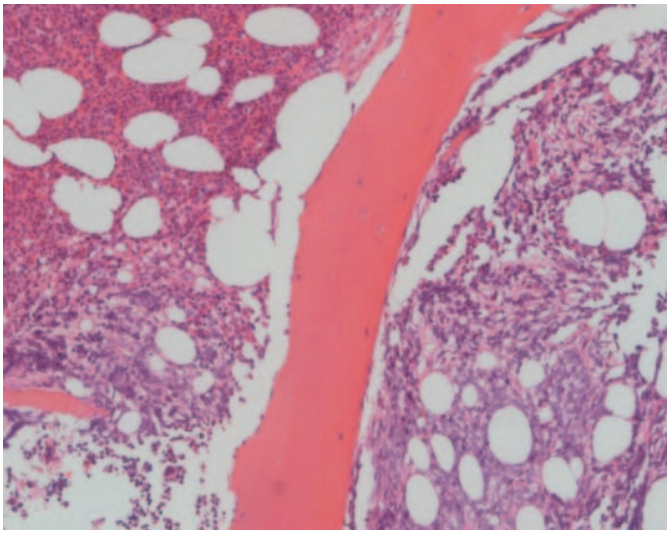

Fig. 2. Hematoxylin/eosin stain (magnification × 20): Area in the lower right corner containing fusiform cells with hyperchromatic nuclei.

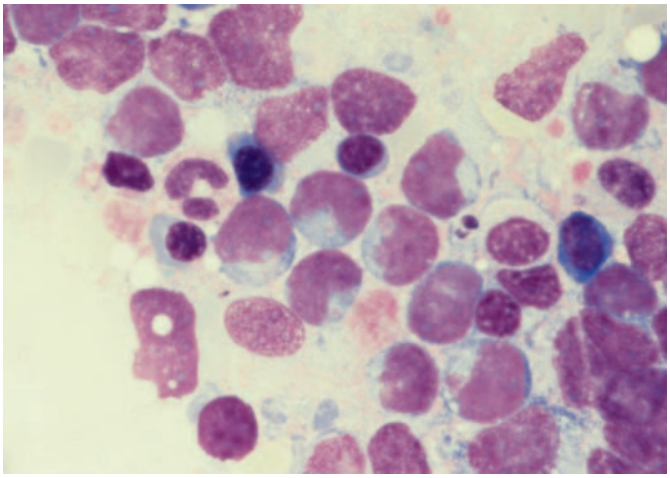

Fig. 3. Bone marrow cytology (Pappenheim, magnification × 60): Marrow infiltration by cells with a large, eccentric-lobed nucleus, containing prominent nucleoli and pale-basophilic cytoplasm.

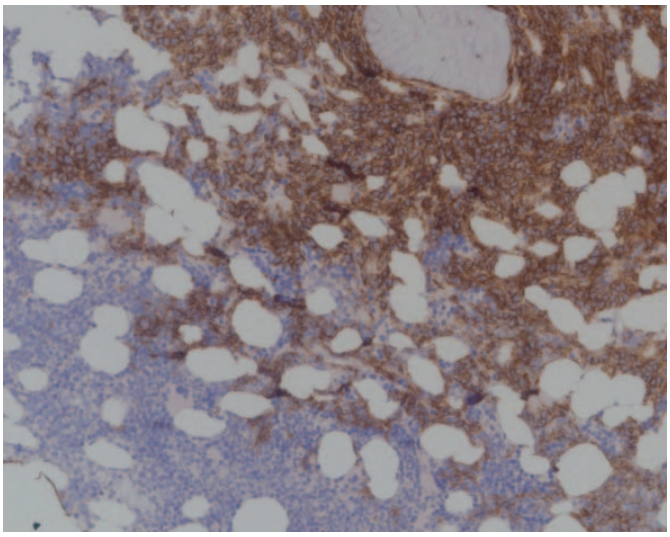

Fig. 4. Immunostaining for CD56 marks the tumor cells (magnification × 10).

cided to use purged autologous stem cells for transplantation in our patient. However, clinical data demonstrating a benefit in survival are lacking, not only for medulloblastoma but also for patients with multiple myeloma or non-Hodgkin's lymphoma [13, 14].

To improve the outcome in patients with medulloblastoma, more efforts in investigating new strategies are needed. Signal transduction inhibitors and immunotherapy have shown disappointing results [15]. Temozolomide, a new oral alkylating chemotherapeutical agent mediating antitumor activity due to DNA methylation, is active against some types of brain tumors [16]. Temozolomide is administered orally; it has a low toxicity profile and could lead to prolonged survival. To define the role of this promising agent in patients with recurrent medulloblastoma more clearly, further investigations in clinical trials are needed. In 2006, a large randomized, multicentric trial (P-HIT-REZ-2005) was opened, comparing the outcome of intravenous chemotherapy with carboplatin/etoposide versus oral chemotherapy with temozolomide in patients with relapsed or refractory brain tumors. The study is currently recruiting participants and the results are expected in a few years.

Conclusions

Bone pain in patients with a history of medulloblastoma should lead us to consider the possibility of extraneural metastases, resulting in appropriate diagnostics. No standard treatment for extraneural relapse in adults is known. Chemotherapy consisting of carboplatin/etoposide followed by a consolidation therapy with high-dose carboplatin/etoposide and autologous purified stem cell transplantation seems to be a promising approach, even in pretreated patients.

Disclosure Statement

The authors declare no conflicts of interest.

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