Hemangiopericytoma (HPC) is a highly vascular soft-tissue neoplasm of pericytic origin that commonly affects adults in the fifth or sixth decade of life [1]. Only 5–10% of HPC occur in children. Childhood HPC is considered a heterogeneous entity that comprises two distinct clinical syndromes: adult HPC and infantile HPC [2]. Infantile HPC, occurring during the first year of life, is characterized by a more benign course with responsiveness to chemotherapy and even tendency to spontaneous regression. In contrast, the behavior of HPC in children older than 1 year does not appear to differ from adult HPC [2]. In these patients, surgical treatment with curative intention followed by adjuvant radiotherapy seems to be the most important prerequisite of survival. However, the tumor is characterized by a high propensity for local and/or metastatic recurrence, especially if the primary tumor is localized in the meningeal tissues [1]. Survival of patients with extraneural recurrence is very poor, since locally applied treatment modalities are often limited and the response to chemotherapy seems to be disappointing [1]. The high recurrence rate and the bad prognosis of recurrent disease emphasize the importance of a multidisciplinary approach, including innovative treatment strategies.

We report on a previously healthy 13-year-old boy who presented in June 1988 with a 4 month history of headache. Fundoscopy revealed bilateral edema of the papilla, and computed tomography demonstrated a 5-cm expansive lesion arising in the right occipital region. The tumor was surgically removed and histologic evaluation revealed a malignant HPC with typical solid formations of pericytes surrounding vascular spaces (Fig. 1). Chemotherapy was introduced according to the German soft tissue sarcoma study CWS-86 [3]. Simultaneous with the second chemotherapy cycle, hyperfractionated radiotherapy was given to the tumor region for a total dose of 54.4 Gy. Treatment ended and the patient was discharged without evidence of residual disease in August 1989. The subsequent years of follow-up were uneventful and the patient started to study at the university.

In September 1997, the patient was readmitted with low back and left leg pain. X-ray films revealed osteolytic lesions of the sacral bone and of the left femur. Magnetic resonance imaging (MRI) demonstrated a huge tumor in the lumbosacral region (10 × 8.5 × 7 cm) with complete destruction of the left sacrum and infiltration into the surrounding soft tissues (Fig. 2). Further osteolytic lesions were found in the left proximal femur measuring up to 4 cm in diameter (Fig. 3) and in the right scapula (2 cm). Biopsy from the left femur was done, and histopathologic diagnosis was identical to the primary tumor, confirming the diagnosis of recurrent HPC. Peripheral stem cells were harvested after mobilization with cyclophosphamide.

**Interferon Alfa-2a in Recurrent Metastatic Hemangiopericytoma**

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(3 × 1,200 mg/m²) and etoposide (2 × 50 mg/m²), purified by magnet cell sorting (CliniMACS, AmcCell, Bergisch Gladbach, Germany) and cryopreserved. Subsequent chemotherapy was given according to the German treatment protocol CWS-96, including two cycles of CEV (carboplatin 1 × 500 mg/m², epirubicin 1 × 150 mg/m², vincristine 1 × 1.5 mg/m²), one cycle of 1³VA (ifosfamide 3 × 3 g/m², vincristine 1 × 1.5 mg/m², dactinomycin 1 × 1.5 mg/m²), and one cycle of 1³VE (ifosfamide 3 × 3 g/m², vincristine 1.5 mg/m², etoposide 3 × 150 mg/m²).

Concurrent with the third cycle of chemotherapy, fractionated radiotherapy of the metastases (sacrum, femur, scapula) was performed to a total dose of 50 Gy. Since there was no response to combined radiochemotherapy at that time, the decision was made to perform tandem high-dose chemotherapy with autologous peripheral stem cell rescue. In February 1998, the patient received thiotepa (3 × 200 mg/m²) and carboplatin (3 × 500 mg/m²) followed by transfusion of 6.77 × 10⁶/kg CD34⁺ highly purified, autologous, peripheral stem cells. In May 1998, the second conditioning treatment was started, consisting of etoposide (1 × 25 mg/kg) and melphalan (1 × 114 mg/m²) followed by transfusion of 3.8 × 10⁶/kg CD34⁺ highly purified, autologous peripheral stem cells. This multimodal treatment was associated with significant toxicity, including severe mucositis, multiple episodes of septicemia, and prolonged pancytopenia. In June 1998, 4 months after the end of radiotherapy and 1 month after the second autologous peripheral stem cell transplantation, MRI revealed an increase of tumor size in the sacrum (11 × 8.5 × 8 cm) as well as in the femur (4.5 cm). Furthermore, the patient experienced increasing and unbearable low back pain, requiring increasing doses of analgesia. Patient-controlled analgesia (PCA) with intravenous piritramide (Dipidolor®) combined with transdermal application of fentanyl (75 µg for every 3 days) was introduced. However, satisfactory pain control was achieved only with extensive doses of piritramide up to a maximum dose of 380 mg/day. This desperate and terminal clinical situation led to an alternative treatment approach based on inhibition of angiogenesis. In June 1998, after informed consent had been obtained from the patient, antiangiogenic therapy was started with IFN alfa-2a (Roferon, Hoffmann-La Roche SA, Basel, Switzerland) at a dose of 7 MU/m² body surface area, administered subcutaneously three times a week. After 2 months of treatment, IFN was decreased to a maintenance dose of 3 MU/m² subcutaneously three times a week. Treatment with IFN was well tolerated. Within the subsequent 5 months, the amount of analgesia needed could be tapered and finally discontinued in November 1998. During the subsequent years, MRI of the

**Fig. 1.** Sections show uniform oval shaped cells arranged in small nests surrounded by collagen fibers enclosing vascular spaces, consistent with malignant hemangiopericytoma (PAS, 250×).

**Fig. 2.** MRI scan reveals a 10 × 8.5 × 7 cm tumor within the lumbosacral region with complete destruction of the left side of the sacrum and infiltration into the surrounding tissue (arrows).

**Fig. 3.** MRI scan shows an osteolytic lesion in the left proximal femur measuring 4 cm in diameter (arrows).
disease sites was performed at 6-month intervals revealing continuous stable size of the metastatic lesions. In July 1999, thalidomide was introduced as a second antiangiogenic drug at a dose of 100 mg perorally twice a day. Combined therapy with IFN and thalidomide was associated with tolerable and mild toxicity; apart from mild pancytopenia, no other side effects were observed. To date, 3.5 years after initiation of antiangiogenic therapy, there is no evidence of disease progression, and the patient is without any complaints restarting his studies at the university.

**DISCUSSION**

Over the past three decades progress has been made in understanding the importance of angiogenesis for tumor growth and metastasis [4]. Tumor angiogenesis has been identified as a complex multistep process with the involvement of endothelial cells, pericytes, angiogenic stimulators, and inhibitors [4,5]. Numerous proangiogenic cytokines have been discovered to date, of which the most clinically relevant belong to the vascular endothelial growth factors (VEGF) and fibroblast growth factors [4,5]. There is also increasing knowledge about inhibitors of angiogenesis, the best known of them are interferons and angiostatin [5]. Clarification of the specific growth factor interactions underlying the vascular proliferation that accompanies growth of tumor and metastases may lead to the development of new antitumor strategies. IFN slows endothelial migration and proliferation and suppresses the production of the two known angiogenic factors, basic fibroblast growth factor (bFGF) and interleukin-8 [6,7]. In 1989, IFN became the first angiogenesis inhibitor used to treat a child with pulmonary hemangiomatosis [6]. Subsequently, over the past decade, several authors reported the use of IFN to treat infants with life-threatening hemangioma [7,8]. Recently the successful use of IFN in treating a recurrent giant cell tumor, which is another rapidly proliferating vascular lesion, was reported [9].

In our patient, the decision to start antiangiogenic therapy was based on several considerations: (1) despite extremely aggressive radiochemotherapy including tandem high-dose chemotherapy with autologous peripheral stem cell rescue, the patient developed tumor progression resulting in a life-threatening and critical clinical situation; (2) hemangiopericytomas are highly vascular tumors with well-known upregulation of angiogenesis and endothelial growth factors [10]; (3) a report describing the successful use of IFN in two patients with malignant HPC [11]; and (4) positive experience in our institution in the systemic treatment of children with life-endangering hemangiomas [8]. Antiangiogenic therapy with IFN was well tolerated, and the severe low back pain disappeared. Tumor size remained stable reflecting tumor cells being maintained in some kind of dormant state. Thalidomide, another angiogenesis inhibitor currently used in clinical trials, was added as a second antiangiogenic drug in July 1999, in the hope of enhancing the angiogenesis inhibition of IFN. Its effect, if any, cannot be documented in this patient. Antiangiogenic therapy will be continued, in order to maintain stable disease and is not planned to be withdrawn in the near future. Monitoring the levels of vascular growth factors in the urine and/or blood could be a means of defining more exactly treatment intensity and treatment duration. Unfortunately, the assessment of VEGF or other vascular growth factors was not available in our institution at the time IFN therapy was started in our patient.

In summary, increased angiogenesis seems to play an important role in the pathogenesis of malignant HPC. Antiangiogenic therapy seems an attractive and novel treatment option for these patients. Our experience with IFN as second-line treatment is encouraging, and the introduction of antiangiogenic therapy into the first-line therapy of malignant HPC, especially in patients with metastatic disease, should be considered. Another open question is whether serial monitoring of vascular growth factors could be helpful in defining treatment intensity or treatment duration for individual patients. Suitable designed clinical trials and studies of the exact pathophysiology of angiogenesis in hemangiopericytomas are needed.

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