Eur J Med Res (2006) 11: 462-466

Multifocal Epithelioid Hemangioendothelioma: Case Report of a Clinical Chamaeleon

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Abstract
Epithelioid hemangioendothelioma is an extremely rare vascular bone tumor with a slow growth and poor prognosis. The term was designed to describe neoplasms that had an appearance in between hemangiomas and sarcomas. Various synonyms for epithelioid hemangioendothelioma are used clinically: low grade anaplastic angiosarcoma, cellular hemangioma, histiocytoid hemangioma and angioendothelioma. However, it represents 1% of all vascular neoplasms and is locally aggressive. We report the course of disease of a 47-year-old man who presented to our clinic with unspecific abdominal and back pain. Radiological findings revealed multiple lesions in the spine as well as liver and spleen involvement. Tumor histology of the bone and liver biopsies confirmed the diagnosis of epithelioid hemangioendothelioma. Although treatment was initiated with thalidomide, the patient developed multiple organ dysfunction syndrome (MODS) and succumbed to his disease. This case report may contribute to the data on clinical findings and natural history of this rare tumor.

Key words: epithelioid hemangioendothelioma, multifocal tumor growth, multiple organ dysfunction syndrome, sarcoma, angioendothelioma, hystiocytoid hemangioma, anaplastic angiosarcoma, hemangioma, thalidomide

Background

Hemangioendothelioma is a rare tumor entity with an intermediately aggressive biological appearance in between the benign hemangioma and the highly malignant angiosarcoma [1]. Hemangioendothelioma is considered to be a low-grade malignant vascular tumor. It can occur in every age but has its maximum distribution in patients with an average age of fifty years. Its etiology and risk factors are not known. Clinically, hemangioendothelioma is most frequently diagnosed with primary lesions located in the liver, lung, gastrointestinal tract, head and neck, heart, central nervous system [2] or bone [3, 4]. With regard to the location of the primary tumor, a difference in gender distribution is seen. Primary hemangioendothelioma in the liver and lung are more common in female patients in contrast to hemangioendothelioma of the bone and soft tissues, which have an equal sex distribution [1]. Most commonly affected bones include the skull, vertebrae and long bones [1, 2]. The appearance of this extremely rare tumor can be solitary, multifocal in the same bone, or polyostotic [6]. The radiologic findings are rather non-specific [5]. In general, the lesions may be medullary or cortical and are typically of osteolytic nature with variance in the degree of peripheral sclerosis. A purely osteolytic appearance, osteolytic lesions have been found to either expand or remain stationary, can occur [6] and cortical erosion is not uncommon [5]. Therefore, one of the multiple sequelae of hemangioendothelioma is a pathologic fracture due to erosion and destabilization of the cortical bone. The coarse trabecular pattern, or honeycomb pattern, is suggestive of a vascular tumor [2]. In native X-ray studies, multiple smaller erosions of cortical bone are often referred to as "moth-eaten" or "soap-bubble" patterns. Local tumor growth may also extend into adjacent soft tissue [5]. Periosteal reaction is uncommon in untreated cases without a pathological fracture [5]. Differential diagnoses include metastasic disease, carcinoma, malignant melanoma or multiple myeloma, but it has to be kept in mind that due to the heterogenous clinical appearance of hemangioendothelioma, a broad spectrum of differential diagnoses must be considered and carefully evaluated [5]. Therefore, a meticulous and multidisciplinary approach in both diagnosis and treatment is crucial for the survival and outcome of the patient. In our institution, patients with soft tissue tumors are evaluated by a multidisciplinary tumor board, biopsies are taken and reference histologies are sent to at least one more cooperating tumor center. Since soft tissue tumors even of the same entity frequently demonstrate a heterogenous and often misleading histologic and radiographic picture, this strategy ensures validity to a difficult diagnosis and ultimately adds on to an effective treatment of the patient.

Case Report:

A 47-year-old caucasian male was referred to our clinic in June 2003. His chief complaints included paraparesis and an unspecific abdominal and back pain. The

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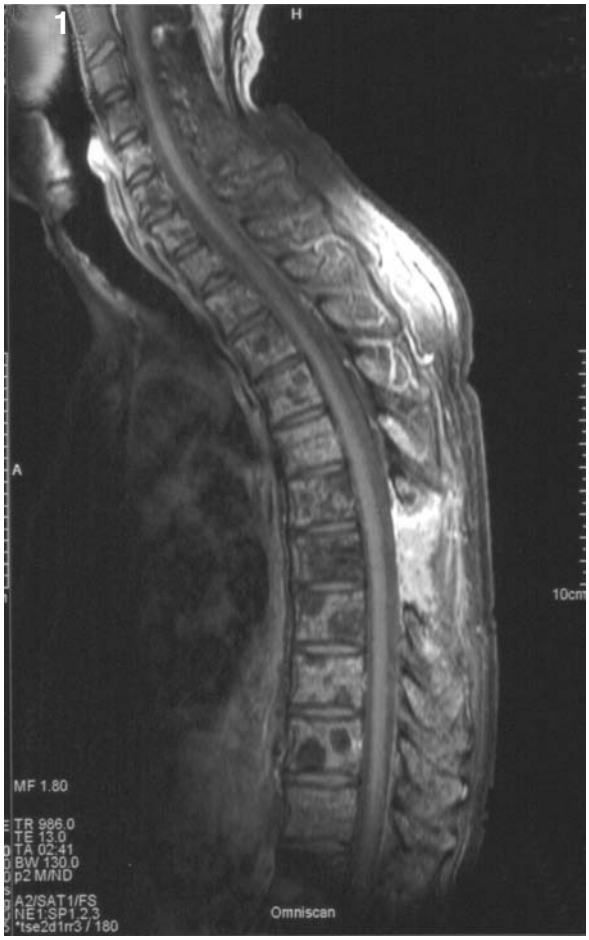

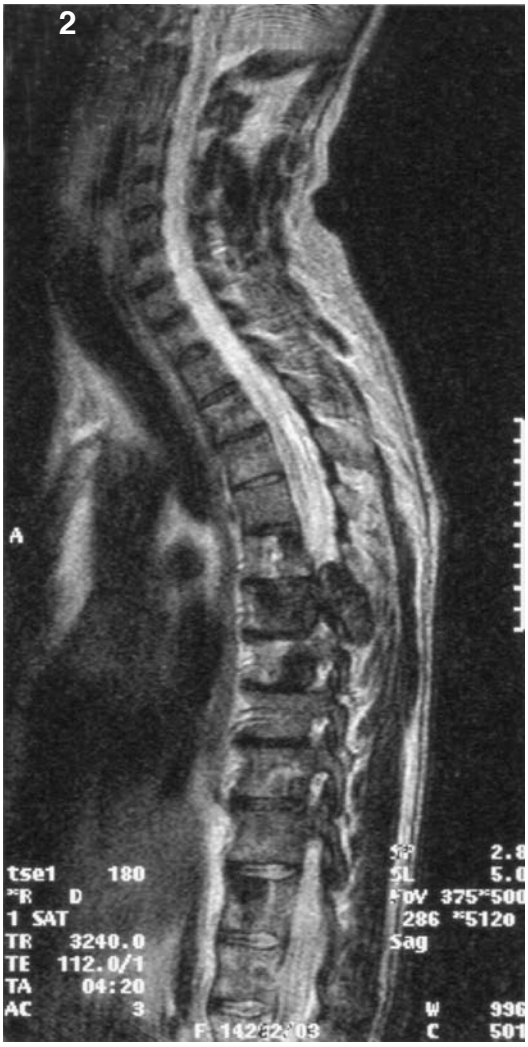

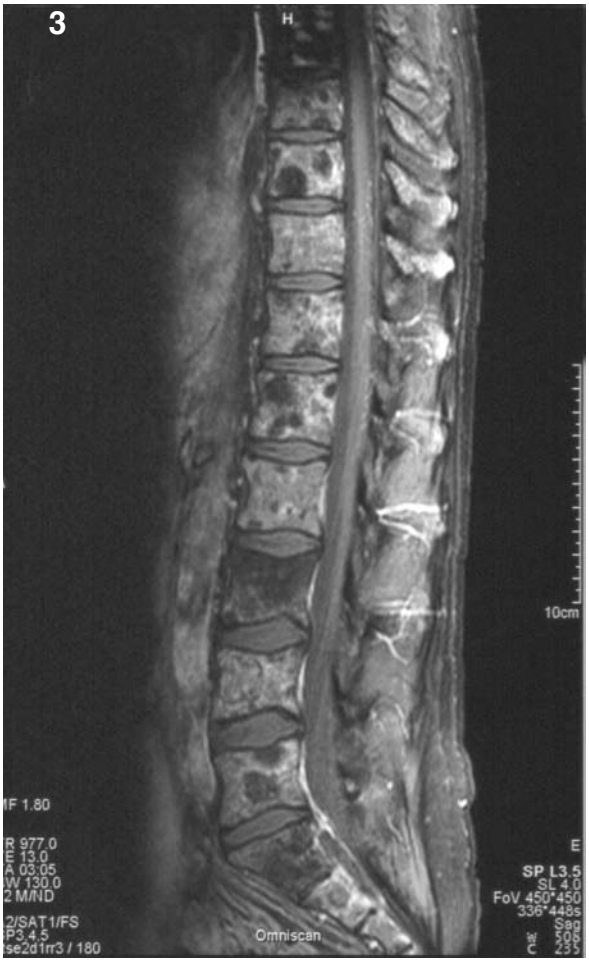

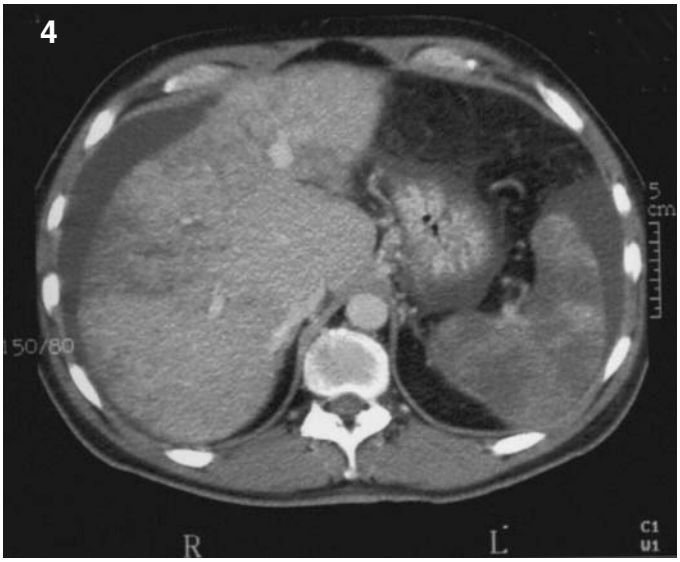

Fig. 1. Lateral radiograph of the cervical spine.

Fig. 2. Axial CT of the cervical spine.

Fig. 3. Sagittal T2 MRI of the cervical spine.

Fig. 4. CT of the liver.

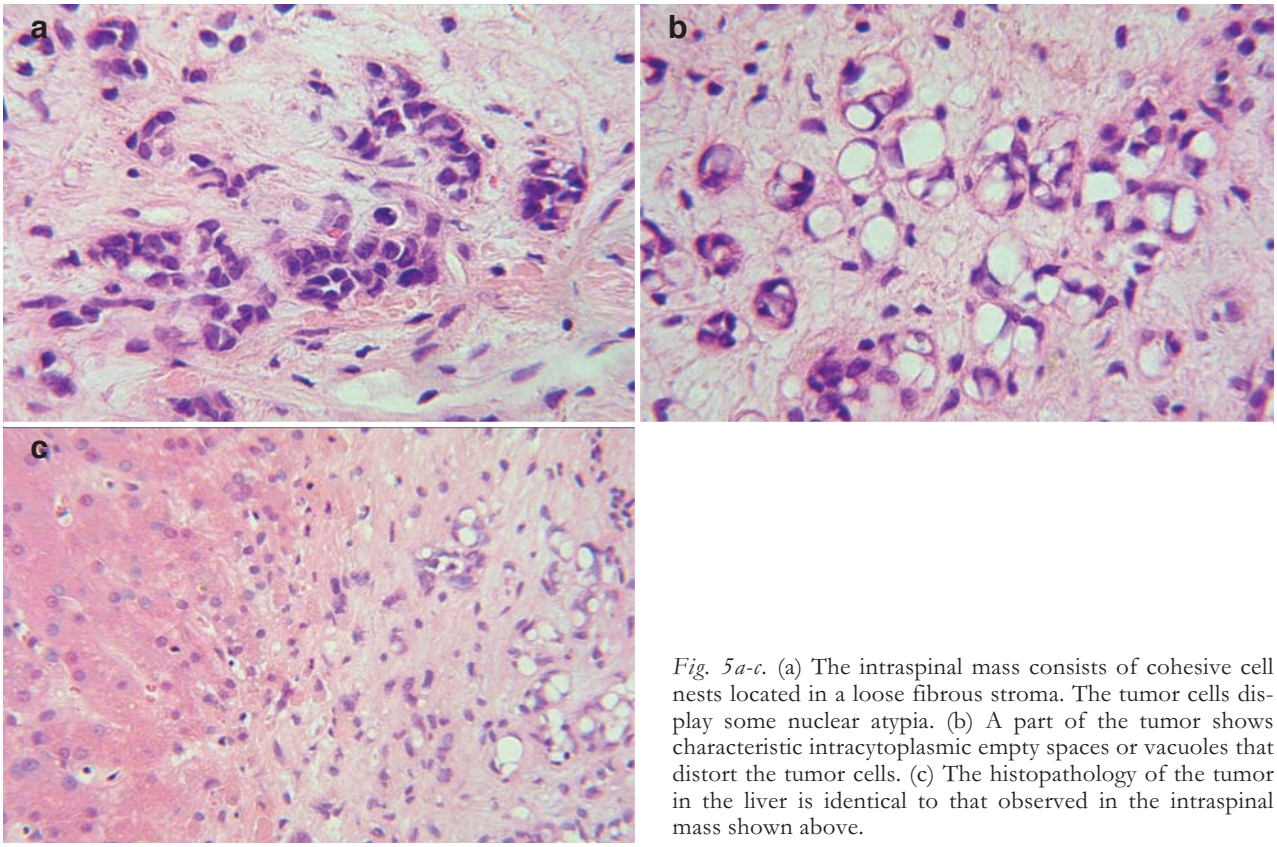

Fig. 5a-c. (a) The intraspinal mass consists of cohesive cell nests located in a loose fibrous stroma. The tumor cells display some nuclear atypia. (b) A part of the tumor shows characteristic intracytoplasmic empty spaces or vacuoles that distort the tumor cells. (c) The histopathology of the tumor in the liver is identical to that observed in the intraspinal mass shown above.

onset of symptoms was two years earlier with a steady progression in severity. Otherwise, patient history and physical examination did not contribute to a conclusive working diagnosis. The patient underwent computed tomography (CT) scanning and magnetic resonance imaging (MRI) of the spine and the abdomen which revealed not only a vertebral body destruction at the level of Th7 with compression of the myelon, but also multiple osteolytic lesions in the spine in particular at the thoracal and lumbal level, and also in the os sacrum (Figs. 1-3). A metastatic disease or multiple myeloma was presumed. The patient was referred to the Department of Neurosurgery for tumor debulking and decompression of the thoracic spinal cord. At exploration, virtually the entire spine appeared to be black. Histological examination of the small bone fragments appeared to be difficult. The tissue specimens displayed a fibrous stroma rich in capillary structures as well as some small, sharply circumscribed aggregates of rounded cells in the stroma. Very few such cells had a vacuolated cytoplasm, but did not appear to contain mucin in the Alcianblue staining. The fibrous stroma was full of hemosiderin deposits in the Prussian blue staining, indicative of numerous older microbleedings. Capillary structures and the few cell aggregates stained immunopositive with the established endothelial cell surface markers CD31 and CD34; they did not react with a large panel of cytokeratin antibodies nor with the malignant melanoma markers HMB-45 and S100. The proliferation index measured by staining with Ki67 (MIB-1) was very low. The initial diagnosis was intra-osseous hemangioendothelioma, but review by a consultant for osteopathology lead to the diagnosis of skeletal angiomatosis.

Due to the diagnosis of a benign disease, no chemotherapy or radiation therapy was performed.

Several months later, the patient developed liver failure and was admitted to the Medical Intensive Care Unit. Physical examination revealed a large amount of peritoneal ascites. Microbiologic analysis revealed infection with Staphylococcus aureus spp. Radiographically, CT scanning showed signs interpreted as "liver cirrhosis" with occlusion of the splenic vein (V. lienalis), infarction of the spleen and concomitant portal hypertension (Fig. 4). Gastroesophageal endoscopy was carried out and showed esophageal varicosis grade II. A second histology of the intraspinal mass and a liver biopsy were performed. Small tissue samples from the intraspinal mass appeared to clearly show a tumor, consisting of small solid cell aggregates accompanied by a loose fibrous stroma. There was nuclear atypia (Fig. 5a). A part of the tumor cells displayed intracellular lumina, recognizable as clear spaces or 'vacuoles' that distort the cells (Fig. 5b). The tumor examined in the liver biopsy showed an essentially identical histopathology (Fig. 5c). The tumor cells reacted immunohistochemically with the endothelial cell surface markers CD31 (Fig. 6a) and CD34 (Fig. 6b); they did not react with cytokeratin antibodies (Fig. 6c). The proliferative activity in the tumor was low, as demonstrated in the Ki67 (MIB-1) immunostaining (Fig. 6d). The diagnosis of epithelioid hemangioendothelioma was established. In the further clinical course ascites was punctured and drained several times. Intravenous antibiotic treatment according to the antibiogram was

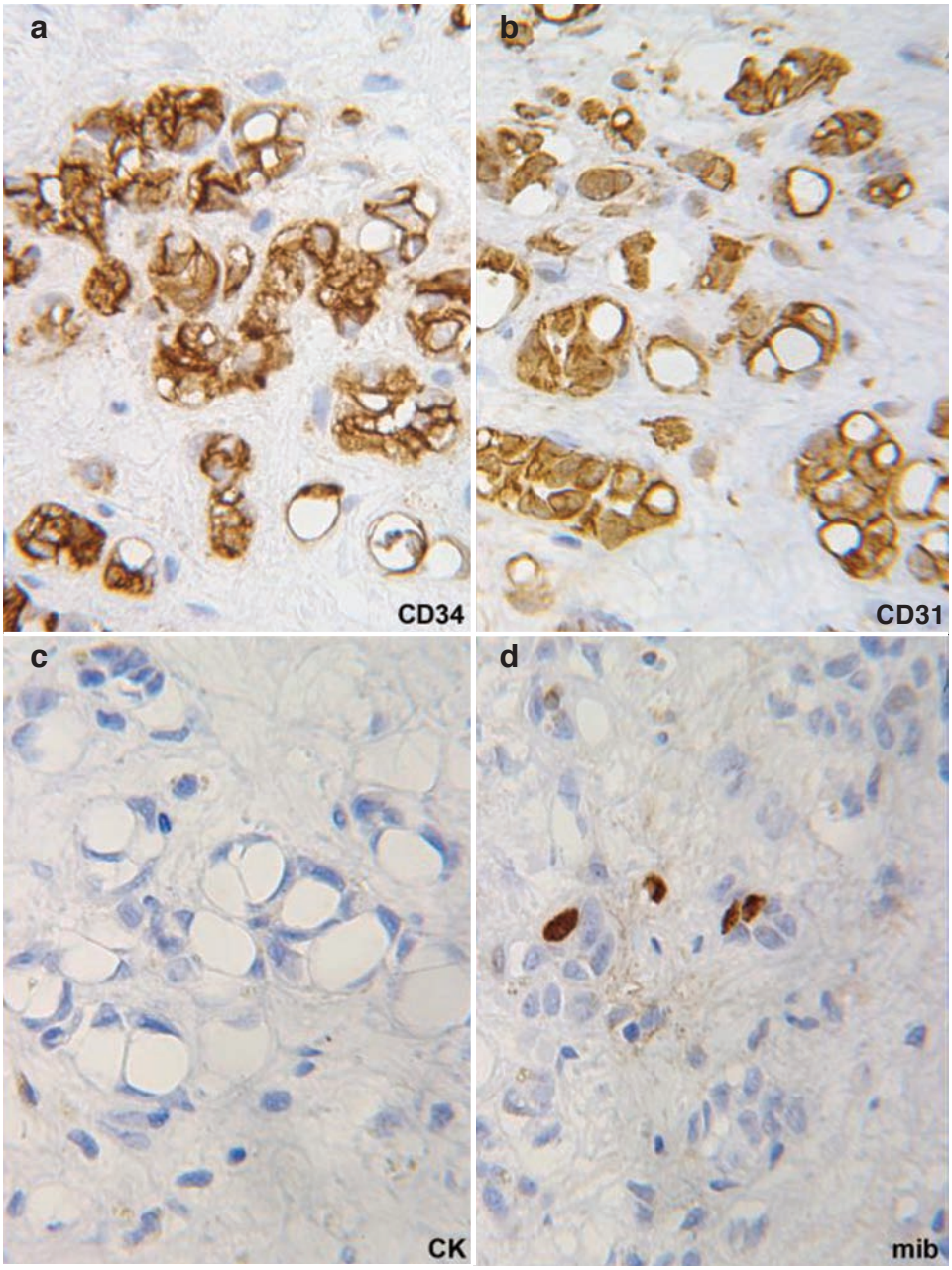

Fig.6 a-d. Many tumor cells stain intensely with the endothelial cell surface antibodies CD34 (a) and CD31 (b); they do not react with cytokeratin marker CK8 (c). The proliferative activity in the tumor is low, as shown in the Ki67 staining (d).

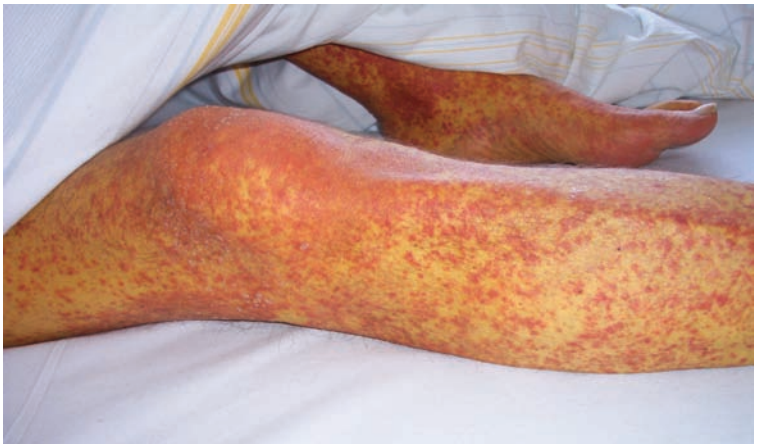

Fig. 7. Urticaria after thalidomid medication.

initiated. Furthermore, thalidomide treatment was given. During the course of the treatment, the patient developed a generalized allergic reaction (urticaria) (Fig. 7) and increased fatigue. Several weeks later the patient developed multiple organ dysfunction syndrome and succumbed to his disease.

Discussion

Hemangioendothelioma is an extremely rare tumor. This tumor entity was initially classified as benign but case reports have shown a locally invasive tumor growth with a vasculogenic component. Generally, the prognosis seems to be better than angiosarcoma, with a mortality rate up to 20%. The local recurrence rate has been determined in literature as 10-15 % and metastasizing disease is found in up to 20-30% of the cases. However, the risk factors are still unknown. Generally, hemangioendothelioma has been diagnosed in patients of all age groups, but a peak incidence rate was found to be at an average age of 50 years. Since no general pattern of organ distribution is seen, primary lesions have been described to occur in the liver, spleen, lung, bone and also in soft tissue. A hemangioendothelioma must be taken into consideration when a vasculogenic tumor/space-occupying lesion is diagnosed, and further evaluation is needed in order to a) establish the diagnosis of a neoplastic lesion and b) to differentiate this tumor from other vascular tumors. Therefore, the diagnostic finding has to be done in a multidisciplinary board. Besides radiographic studies such as plain x-ray studies, CT scanning and MR imaging, tumor biopsies are a cornerstone in the diagnosis of hemangioendothelioma. Once a tumor biopsy has been performed (ideally, the biopsy should be obtained using the wide excision technique with sufficient safety margins), a number of different stains are performed and examined. Since there is no known specific surface protein or tumor marker for hemangioendothelioma, the synopsy of the various diagnostic elements is important. To minimize diagnostic error, reference histologies should be sent to another institution/facility. Immunohistochemistry staining is positive for endothelial cell surface markers CD31 and CD34 (30 % positive for Cytokeratine). Standard treatment options include first-line surgical resection (wide excision). However a curative surgical intervention could not be performed in our patient due to the extent of disease, so he underwent initial surgical debulking and a course of palliative treatment. Thalidomide was given 200 mg p.o. as an experimental drug, because of the vasculogenic component of this tumor but had to be discontinued because of side effects (fatigue and generalized urticaria). Since there were no data available on chemotherapy for this disease and the patient was in a very poor condition after malignant hemangioendothelioma was diagnosed, no chemotherapy was carried out. Although the tumor aspect in repetitive spine CT and MRI scans remained stationary for several months, the patient developed metastasizing disease (liver, spleen) and succumbed to his disease. In summary, this case report shows the intricacies and pitfalls in diagnosis and treatment of hemangioendothelioma and further adds on to the existing database on the course of disease, therapy and outcome of epitheloid hemangioendothelioma.

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Received: August 16, 2006 / Accepted: September 7, 2006

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