Malignant Hemangiopericytoma

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Abstract
Hemangiopericytomas (HPC) are malignant vascular tumors arising from mesenchymal cells with pericytic differentiation. HPC immumnohistochemical profile is uncertain and diagnosis is usually controversial. Differential diagnosis from synovial sarcoma, mesenchymal chondrosarcoma, fibrous histiocytoma, and solitary fibrous tumor is a major medical challenge. The existence of this particular disease type is even sometimes questioned, and systematic review of pathological slides is essential. Two subtypes of hemangiopericytomas have been described: infantile HPC in infants under 1 year, and adult disease in children over 1 year and adults. HPC is a rare tumor of adult life (fifth decade) and pediatric cases account for approximately 3% of all soft tissue sarcomas in this age group. These tumors usually develop in the limbs, the pelvis, or the head and neck, and mostly in muscle tissue. Surgery remains the mainstay treatment. However, prognosis being usually favorable, the use of mutilating surgical procedures should be restrained. Adjuvant chemotherapy is an option in case of unresectable, life-threatening tumors, particularly in the infantile subtype. Adjuvant radiation therapy is appropriate for patients with high grade tumors or incomplete resections. Late relapses may occur and require long-term follow-up. Cytogenetic abnormalities (translocations) have been found in some hemangiopericytomas.

Keywords
Hemangiopericytoma, vascular tumor, differential diagnosis, treatment, prognosis.

Disease name and synonyms
Hemangiopericytoma (HPC)

Diagnosis criteria / Definition
Initially described by Stout and Murray in 1942 (Stout and Murray 1942), hemangiopericytoma is a soft tissue tumor derived from mesenchymal cells with pericytic differentiation (Enzinger and Weiss 1995). Disease can either be benign or malignant. Two types have been described: infantile HPC and adult disease. Although infantile HPC is usually described together with the adult type, it deserves separate consideration because of its different histological presentation and clinical behavior.

Microscopic characteristics are the so-called pericytoma pattern with tightly packed cells around ramifying thin-walled and endothelial-lined vascular channels ranging from small capillary-sized vessels to large gaping sinusoidal spaces (Enzinger and Weiss 1995).

Distinction between low-grade and high-grade lesions is difficult on the basis of histological parameters (Enzinger and Weiss 1995; Coffin 1997). Combining factors such as mitotic activity, cellularity, hemorrhage, and necrosis, may prove informative for assigning a grade to the tumor.
Soft tissue hemangiopericytoma is a controversial pathologic entity. The relative non-specificity of the characteristic branching capillary pattern and the cytological features of the constituent cells, in addition to the lack of a distinct immunohistochemical staining profile, has resulted in uncertainty and absence of consensus regarding this subgroup of tumors.

Differential diagnosis
Malignant HPC has been classified as a soft tissue tumor, but is likely to be over-diagnosed. The problem of histological confusion with other soft tissue tumors, such as solitary fibrous tumor, fibrous histiocytoma, synovial sarcoma and mesenchymal chondrosarcoma, arises from the shared hemangiopericytoma-like vascularity of all these tumors (Enzinger and Weiss 1995; Erlandson and Woodruff 1998). Moreover, lesions formerly known as infantile HPC fall within the spectrum of infantile myofibromatosis (Mentzel *et al* 1994). Nielsen and Folpe have described a benign variant of HPC, designated lipomatous hemangiopericytoma, with a mixed histology of both mature adipocytes and hemangiopericytoma (Nielsen *et al* 1995; Folpe *et al* 1999; Espat *et al* 2002).
Immunohistochemistry is of limited help in the identification of neoplastic pericytes and hence in the direct recognition of HPC. Cell markers focally present in normal pericytes, such as Desmin and muscle actins, are infrequently found in HPC neoplastic cells. Greater success has been reported using antibodies against factors XIIIa (Nemes 1992) and CD34 (van de Rijn *et al* 1994), although they are usually immunohistochemically mute for muscle markers. Approximately two thirds of primary monophasic synovial sarcomas have a positive phenotype for keratins and/or epithelial membrane antigen (EMA). However, HPC usually does not express EMA and has not been reported to stain for keratins (Espat *et al* 2002).
Additional evidence for determining whether a HPC-like tumor is a synovial sarcoma is available from cytogenetic studies. Over 80% of synovial sarcomas have a specific t(x;18)(p11.2;q11.2) rearrangement (Turc-Carel *et al* 1986, 1987), as demonstrated by cytogenetics, fluorescence in-situ hybridization and molecular genetics using a reverse transcriptase-polymerase chain reaction for the detection of the SYT-SSX1 or SYT-SSX2 fusion transcripts (Fligman *et al* 1995).
Finally, apart from particular entities such as meningeal HPC or HPC of the nasal fossa, all tumors diagnosed as hemangiopericytomas should be histologically reviewed in order to rule out other tumor types.

Frequency
HPC is a rare tumor of adult life (fifth decade) and is uncommon in children. Pediatric cases account for less than 10% of all HPC (Enzinger and Smith 1976) and approximately 3% of all soft tissue sarcomas in this age group.

Clinical description
HPC is usually a deep soft tissue mass with insidious growth. The tumor may occur anywhere in the body, the most common anatomic locations being the lower extremities, the pelvis, and the head and neck (Enzinger and Weiss 1995). Most HPC tumors are deep-seated and are found in muscle tissue. Dermal and subcutaneous HPC are much less common.
Clinical presentation is non-specific. Pain is a late symptom associated with an enlarging mass. However the symptoms vary depending on the site of disease. Most tumors present as a slowly growing mass that may cause intestinal or urinary symptoms in the abdomen. Occasional cases are associated with hypoglycemia due to the secretion of insulin-like growth factor (Karnak *et al* 2001).
Radiographic findings are not specific; they consist of a well-circumscribed, radiopaque soft tissue mass that often displaces neighboring structures. Cystic changes are common, but calcification is rare and usually concern large tumors of long duration.
Two distinct clinical entities have been described: the adult type in adults and children older than 1 year, and the infantile type occurring in the first year of life.
Most infantile HPCs are considered congenital; they represent about one third of all pediatric HPC (Ferrari *et al* 2001). Clinical features and behavior are particular, with subcutis and oral cavity locations; multifocal and metastatic forms are reported, as well as good response to chemotherapy and occasional spontaneous regressions (see “Management including treatment”). Prognosis is usually favorable (Coffin 1997).
Prognosis is usually worse in the adult type. In a study of 106 HPC cases with available follow-up information for 93 patients, the reported 10-year-survival rate was 70% (Enzinger and Smith 1976). Mac Master reported 60 patients of whom 48% had died of disease (Mc Master *et al*1975). In Auguste series, 53% of the 19 patients developed pulmonary metastases with 59% and

47% overall survival at 5 and 10 years, respectively (Auguste *et al* 1982).
Recently, Espat *et al*. reported 93% and 86% two- and five-year overall survival rates, respectively. However, the authors used a multimodal pathological review to exclude other soft tissue tumors histologically mimicking HPC (Espat *et al* 2002).
Conventional malignant HPC is capable of both local recurrence and distant metastases, but has low disease-associated mortality (Espat *et al* 2002). The most common sites of secondary disease are the lungs and bones (Kauffman and Stout 1960; Enzinger and Smith 1976). The reported incidence of metastases varies from approximately 10% to 60%, depending on the diagnostic criteria and the therapy.
Local and distant relapses after prolonged disease-free interval have been reported (Spitz *et al* 1998), suggesting a mandatory long-term follow-up (Ferrari *et al* 2001).

Management including treatment
In adults, complete surgical resection remains the mainstay of treatment. In Espat's report, patients undergoing complete tumor resection showed a 100% survival rate at five years (Espat *et al* 2002). However, considering the favorable outcome in this disease, some authors caution against operations that may potentially cause loss of function or are limb threatening. Pre-operative ligation of afferent vessels or vascular embolization might help reduce the menace of operative hemorrhage (Pandey *et al* 1997). Both chemotherapy and radiotherapy seem effective and are recommended in all patients with incomplete resection and/or large, locally invasive tumors.
The role of adjuvant radiotherapy after incomplete removal of the tumor seems established (Miser *et al* 1997). Different data suggested a benefit of radiotherapy for local control of both gross residual tumors and microscopic incomplete excision (Mira *et al* 1977; Jha *et al* 1987; Staples *et al* 1990). Literature surveys demonstrated that surgery and postoperative radiotherapy with 50 Gy or more resulted in significantly improved local control compared to surgery alone (p=0.02) (Someya *et al* 2001).
Since HPC in pediatric ages is so rare, only few publication reports or data about its clinical management are available (Kauffman and Stout 1960; Atkinson *et al* 1984; Ferrari *et al* 2001). Surgical resection is the mainstay of treatment. The infantile subtype is characterized by high response to chemotherapy when required in case of unresectable, life-threatening tumors (Del Rosario and Saleh 1997). Responses to chemotherapy have been reported with vincristine, cyclophosphamide, doxorubicin, dactinomycin, methotrexate, mitoxantrone and other alkylating agents (Ortega *et al* 1971; Wong and Yagoda 1978). Considering the high chemoresponsiveness of these tumors, as well as the early age of patients, less toxic chemotherapeutic regimens that limit use of anthracyclines and/or alkylating-agents should be investigated. Due to the rarity of these tumors, there is an insufficient number of patients for conducting the randomized trials that are needed to confirm the role of adjuvant chemotherapy in this disease.
Radiotherapy should be discussed, but the indications are limited because of the age of the patients.

Genetic counseling
Cytogenetic abnormalities have been found in some hemangiopericytomas. Most HPC are near-diploid, and breakpoints in 12q13, 12q24 and 19q13 seem to be common, with recurrent t(12;19)(q13;q13) translocations (Mandahl *et al* 1993; Mitelman *et al* 2002; Hallen *et al* 2002).

Unresolved questions
Of all vascular tumors, the diagnosis of hemangiopericytoma is one of the most controversial. Doubt has even been raised as to its existence as a specific tumor type (Fletcher 1994).

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