Malignant Hemangiopericytoma: Reports of Two Cases with Different Clinical Course and Review of the Literature

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Geliş Tarihi/Received: 25.12.2012
Kabul Tarihi/Accepted: 28.04.2013

This case report was presented as an electronic poster in 4th Medical Oncology Congress, 21-25 March 2012, Antalya, Turkey (No= EP-314).

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ABSTRACT Hemangiopericytomas are rare vascular tumors with high metastatic potential. Surgery is the mainstay of treatment for nonmetastatic disease. The role of adjuvant therapy is unclear, and the prognosis varies in previous reports. Here, we present two case reports of malignant hemangiopericytoma, one of them originating from retroperitoneum and the other from uterine myometrium. First patient had multiple liver, lung and kidney metastases appearing five months after initial diagnosis. However, he is still alive after 23 months from the first metastasis. Second patient demonstrated an aggressive clinical course despite having initial surgical total excision of the tumor and adjuvant radiotherapy; she had multiple kidney, liver, lung, brain, spleen and thyroid metastases and died 13 months after diagnosis. These tumors usually have an unpredictable prognosis and extremely rare, thus, a consensus on systematic treatment strategy has not yet been identified.

Key Words: Hemangiopericytoma; neoplasm metastasis; chemotherapy, adjuvant


Anahtar Kelimeler: Hemanjioperisitom; tümör metastazı; kemoterapi, adjuvan

Türkiye Klinikleri J Case Rep 2013;21(1):18-23

H emangiopericytoma (HPC) is a rare mesenchymal tumor, which accounts for about 1% of vascular neoplasms. It was first defined by Stout and Murray, in 1942, as a vascular tumor originating from Zimmerman pericytes associated with capillary walls. It occurs most commonly in the skin, soft tissues, muscles of the extremities, retroperitoneum and pelvic fossa, but it may develop wherever capillaries are present. A few numbers of cases originating from uncommon sites such as thoracic cavity, head and neck area, genitourinary tract and cranium are reported in the literature. The most common sites of metastases are the lungs, bone and the liver. Surgery is the mainstay of treatment for the nonmetastatic tumors. For unresectable and metastatic hemangiopericytoma, response to chemotherapy...
is unclear from previous case series. Anthracyclines, Ifosfamide, Etoposide, Cisplatin, Dacarbazine, Actinomycin, Vincristine, Methotrexate are some of the chemotherapeutic agents which were previously experienced by some clinicians. However, it is not possible to accept a standard treatment regimen for these rare tumors due to the lack of randomized studies. Here, we present a report of two cases with different clinical behaviour; one of them with uterine origin and more aggressive behaviour and another, originating from abdominal cavity and a slightly better clinical course.

CASE REPORTS

CASE REPORT # 1

A 44-year-old with abdominal tenderness male was referred to the outpatient clinic of Department of Surgery in May 2010. Physical examination revealed a hard, lobulated solid mass in hypogastrium. Computerized tomography (CT) showed a hypervascular mass with necrotic parts extending from the lower poles of the kidneys to the bladder. Tumoral mass was 22 cm in diameter, and the cleavage between the tumoral mass and adjacent structures were unclear (Figure 1). Further scanning such as colonoscopy, gastroscopy and serum levels of tumor markers (such as CEA, AFP, B-HCG, CA125, CA15-3, CA19-9) were all normal. He underwent a debulking operation in July 2010. Surgical examination revealed a 22x19x6 cm sized, capsulated, yellow-coloured and hypervascular tumoral mass invading the meso of sigmoid colon. It was separated from the adjacent structures and totally extirpated. Microscopic examination showed the tumor cells with typical staghorn pattern (Figure 2) and necrosis. Tumor cells were immunohistochemically positive for vascular marker, CD-34. Due to these pathological findings, a diagnosis of malignant hemangiopericytoma was performed. After the operation, the patient was referred to the outpatient clinic of Department of Medical Oncology. Postoperative CT scan was negative for macroscopic residual disease. A chemotherapy combination, including Ifosfamide and Doxorubicin was planned; however the patient refused to receive the therapy, because of social problems. Five months later, he was admitted to the hospital with complaints of weight loss and nausea. Systemic evaluation with CT scans revealed multiple hypervascular liver metastases, and a solitary metastatic lung nodule. A chemotherapy combination, including Ifosfamide 1.2 g/m² (for consecutive five days) and Doxorubicin 60 mg/m² (day 1) was administered. Each cycle is repeated every 28 days. After six cycles, the number and size of the liver metastases were progressed. Then, Etoposide which was given orally in a dosage of 50 mg/m² (for 14 consecutive days in each 21-day cycles) was initiated. No significant, life-threatening toxicity was observed during this treatment; only grade I leukopenia and grade I stomatitis occurred after second cycle. Response evaluation was performed by
CT scans and stable disease was observed in serial studies. He has received sixth cycle of this therapy last month, and he is still alive after 28 months from initial diagnosis.

Informed consent was taken from the patient.

CASE REPORT # 2

66-year-old female was admitted to the Department of Gynecology with complaints of inguinal tenderness and vaginal hemorrhage. No palpable mass was observed on physical examination. However, ultrasonography and CT imaging showed a 8-10 cm diameter uterine mass. The cytology of endometrial curettage was negative. She underwent total abdominal hysterectomy, salpingo-oophorectomy, lymph node dissection and peritoneal washing. In the surgical examination, uterine wall was mobile and normal in size. On gross macroscopic examination, uterine cavity was irregular and hemorrhagic. Tissue section from the superficial region of the myometrium was observed as in solid tumor pattern. Microscopical examination showed tumor cells as a typical hemangiopericytic (staghorn) pattern (Figure 2) with diffuse necrosis (Figure 3a). Immunohistochemical staining was diffusely positive with CD-34 (Figure 3b), focally positive with desmin and actin. The invasion of myometrium by tumor cells was observed and the proliferation labeling index, Ki-67 was 40% (Figure 4a-b). Lymph node examination and abdominal washing cytology were negative for malignancy. Due to the diffuse myometrial invasion, external radiotherapy (total dose: 45 Gy, 1.8 Gy for 25 fractions) and intracavitary brachytherapy (total doses: 21 Gy, 7 Gy for 3 fractions) were delivered. However, six months after diagnosis, she was admitted to an emergency service with complaints of headache and nausea. Magnetic resonance imaging (MRI) of the brain showed a large suboccipital intracerebral hematoma and multiple hemorrhagic masses with vasogenic edema in the frontal, temporal and parietal lobes of the brain (Figure 5). She underwent craniotomy and hematoma was aspirated. Corticosteroids and mannitol were delivered to relief symptoms of brain edema and whole-brain irradiation was performed for five consecutive days (totally 20 Gy, 4 Gy for 5 fractions). In addition, chest and abdomen CT showed multiple hypodense metastatic lesions in spleen, kidneys, liver and lungs (Figure 5). After brain radiotherapy, she received a combination regimen, CYVADIC [including Cyclophosphamide 500 mg/m², day 1-Vincristine 1 mg/m², day 1- Dacarbazine 250 mg/m² from day 1-5-Doxorubicin 50 mg/m², day1] in each 21-day cycle. After 7 months of a progression-free interval, she was admitted to an emergency service due to the acute paralysis of her right arm. MRI and CT imaging showed progression in all metastatic sites (including brain,
spleen, liver and lungs) and a new metastatic lesion in the thyroid gland was detected. She received reirradiation for brain metastases for five days (total dose: 20 Gy, 4 Gy for 5 fractions). Then, Etoposide 50 mg/m² (orally for 14 days in each 21-day cycle) was administered. However, she died fifteen days after the initiation of this therapy due to rapid disease progression and brain edema.

**DISCUSSION**

Hemangiopericytoma is a rare mesenchymal tumor; it represents 2–3% of all soft tissue sarcomas and 1% of all vascular tumors. HPC is principally an adult tumor; median age at diagnosis is reported as 45 years in previous series. Most tumors present as slow-growing masses with non-specific symptoms. However, hypoglycemia, hypertension or gynecomastia due to secretion of insulin-like growth factor and renin are some of the reported paraneoplastic syndromes.

World Health Organisation (WHO) classification defines the term ‘haemangiopericytoma’ as a variety of tumors, which show a thin-walled branching vascular pattern (staghorn pattern) and resemble cellular areas of solitary fibrous tumors (SFTs). Soft-tissue tumors with HPC-like growth patterns has been recently divided into three categories: 1. Solitary fibrous tumor group with its variants, 2. Lesions showing clear evidence of myoid/pericytic differentiation and corresponding to “true” HPCs (myopericytoma/glomangiopericytoma and a subset of sinonasal HPCs), 3. Neoplasms that occasionally display HPC-like features (e.g. synovial sarcoma). The diagnosis of malignant HPC is recognized by cellularity, increased mitotic rate, hemorrhage and necrosis. HPCs demonstrate immunohistochemically positivity for CD34, vimentin and type IV collagen and negativity for S-100 protein, neuron specific enolase, factor VIII related antigen, carcinoembryonic antigen, desmin,
laminin, and cytokeratin. Prior to the routine use of immunohistochemistry in the diagnosis of HPC, misinterpretation for synovial sarcoma was common. However, unlike HPC, synovial sarcomas are often immunoreactive for both keratins and epithelial membrane antigen (EMA).

These tumors can occur anywhere in the body; the most common localizations are lower extremities, pelvis and head and neck. Uterine HPCs are extremely rare when compared to that of the abdominal cavity or extremities; a few numbers of cases with uterine HPCs are reported in the literature. Prognosis of uterine HPCs is reported as better than the HPCs of other sites. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the mainstay of treatment of uterine sarcomas, including HPCs. Adjuvant radiation therapy has historically been of little survival value, but it appears to improve local control and may delay recurrence. Regarding adjuvant chemotherapy, there is little evidence in the literature supporting its use except for carcinosarcomas. Thyroid metastasis of malignant HPC is also very rare. Only one patient with thyroid metastasis from HPC is reported in the literature. Cranium is another primary origin of HPC. However, intracranial localization of HPC (meningeal-HPC, M-HPC) is extremely rare when compared to other sites. Unlike most primary intracranial tumors, M-HPC metastasizes to extra-neural sites, most commonly to the bone, liver, and lungs. M-HPCs are usually seen as hyperdense lesions in CT and MR imaging. Our patient with uterine HPC relapsed five months after initial diagnosis despite receipt of adjuvant radiotherapy. The patient developed multiple visceral metastases, including infrequent sites, such as thyroid gland and brain. Metastatic lesions were hypervascular in MRI and were presented with synchronous hematoma at initial diagnosis. As the brain metastases were multiple, and they appeared at the same time with other visceral metastases (five months after diagnosis of uterine HPC), rather than M-HPC, we concluded that the brain lesions were also from uterine origin.

Due to its vascularity, it is capable of local recurrence and distant metastases; lungs and bone are the most common sites of metastases. However, the prognosis is favorable despite high locally and distant recurrence rates in patients with HPC. Various chemotherapeutic agents have been used for the treatment of metastatic disease. Doxorubicin, alone or in combination (frequently with ifosfamide), appears to be the most effective agent with response rates up to 50%. Other drugs, such as cyclophosphamide, vincristine, methotrexate, actinomycin and DTIC, may demonstrate some anti-tumoral activity, but due to the small patient populations and because these drugs are frequently used in combinations, it is not possible to apply a standard protocol based on the results of previous studies.

Thus, no consensus has been reached regarding the most appropriate treatment.

The VEGF-VEGFR and PDGFR pathway, both have a major role in angiogenesis, and have been proposed as potential therapeutic targets in HPC within the past few years. Interferon-alfa and thalidomide, tyrosine kinase inhibitors such as sunitinib, sorafenib or dasatinib are some of the anti-angiogenic agents that have been established to induce partial responses and disease stability. The effect of metronomic chemotherapy in HPC was evaluated in a small retrospective study only, which administered metronomic temozolomide in combination with anti-VEGF therapy (bevacizumab) and was found as a clinically beneficial regimen. The efficacy of etoposide, a topoisomerase II inhibitor, was examined in a single-center study which administered 2 cycles of intravenous etoposide as sequential salvage therapy in combination with other cytotoxics in M-HPC patients. However, in the literature, there has not yet been published a study on the efficacy of oral etoposide given in metronomic schedule for HPC. This report also provides an evidence for the efficacy of metronomic etoposide in HPC. Both of our patients received metronomic etoposide as salvage chemotherapy after first-line anthracycline based combination regimen. The first patient achieved stable response, and the other progressed during the first cycle. The combination of metronomic etoposide with an anti-angiogenic agent (a tyrosine kinase inhibitor or bevacizumab) might be a better option than single agent, etoposide. However, due to the lack of the prospective and/or randomized studies, we do not
know the best initial treatment option in metastatic HPC.

Ten-year survival has been reported from 47% to 70%.

Time interval from the diagnosis of HPC until the development of metastases ranges from 1-14 years in previous reports suggesting the longer survival times in these patients. In the current report, our patients developed distant metastases after five and six months from surgery respectively. One of them rapidly progressed despite receipt of a major combination of chemotherapeutic and died 13 months after initial diagnosis. The other patient demonstrated a slightly better clinical course than the female patient and has been alive since 28 months from initial diagnosis despite having massive metastatic lesions in liver and lung. Thus, clinical course and chemotherapy response of HPCs are different and there is not any standart treatment strategy for these tumors yet. However, targeted antiangiogenic therapy in combination with metronomic cytotoxic chemotherapy may be a better option for these patients due to the little toxicity in metronomic chemotherapy compared with standart combination regimens and established activity of VEGFR and PDGFR pathways in HPC.

REFERENCES