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

Malign Hemanjioperisitoma: Değişik Klinik Seyirli İki Olgu ve Literatürün Gözden Geçirilmesi

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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

ÖZET Hemanjioperisitomlar yüksek metastatik potansiyeli olan ve nadir görülen vasküler tümörlerdir. Lokalize hastalıkta cerrahi, ana tedavi şeklini oluşturur. Adjuvan tedavinin rolü net değildir ve kaynaklarda prognozu değişken olarak bildirilmektedir. Bu yazıda, biri retroperitondan, diğeri uterus miyometriumundan kaynaklanan iki malign hemanjioperisitom olgusu sunulmuştur. İlk hasta tanıdan 5 ay sonra gelişen yaygın karaciğer, akciğer ve böbrek metastazlarına rağmen, ilk metastaz gelişiminden 23 ay sonra halen hayattadır. Diğer hastada ise, tümörün ilk planda cerrahi olarak total eksizyonu yapılmasına ve adjuvan radyoterapi verilmesine rağmen, çok sayıda böbrek, karaciğer, akciğer, beyin, dalak ve tiroid gibi çoklu organlarda metastaz gelişmiş ve tanıdan yalnızca 13 ay sonra ölmüştür. Bu tümörlerin oldukça nadir görülmesi ve prognozlarının değişken olması nedeniyle, henüz sistemik tedavi stratejisi üzerinde görüş birliği yoktur.

Anahtar Kelimeler: Hemanjiyoperisitom; tümör metastazı; kemoterapi, adjuvan

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

Hemangiopericytoma (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.[1] 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.[2-5] 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 chemotheurapeutic agents which were previously experienced by some clinicians.[6-8] 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 out-patient 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 clivage between the tumoral mass and adjacent structures were unclear (Figure1). 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

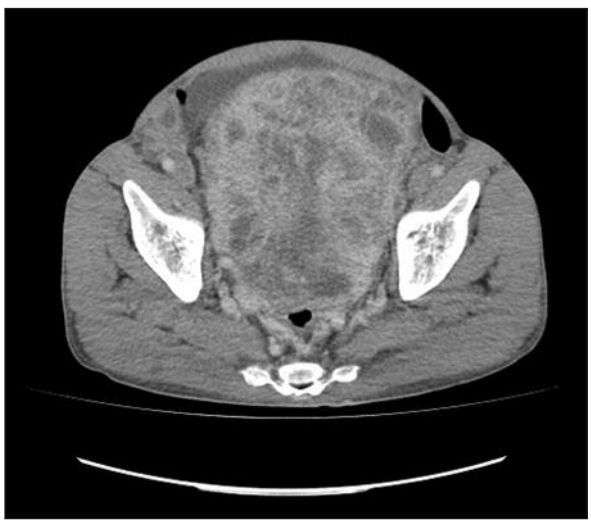

FIGURE 1: CT scan showing the huge necrotic abdominal mass.

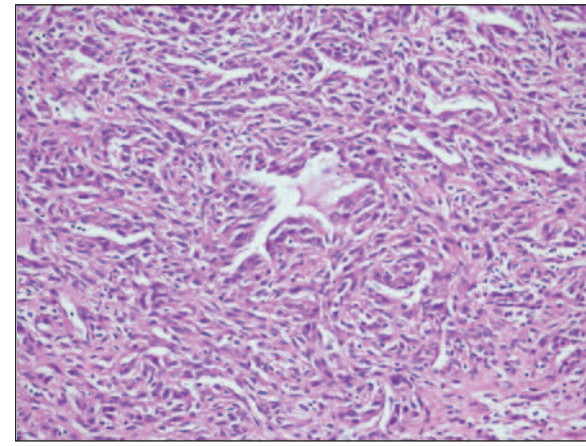

FIGURE 2: Typical hemangiopericytic (or staghorn) pattern of the tumor [Hematoxylen-Eosin, x400].
(See color figure at http://www.turkiyeklinikleri.com/journal/turkiye-klinikleri-journal-of-case-reports/1300-0284/tr-index.html)

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

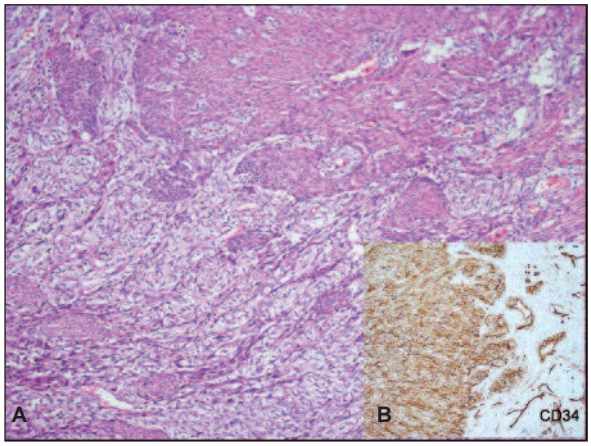

FIGURE 3: A) The appearance of tumor cells with areas of diffuse necrosis and invasion of normal myometrium [Hematoxylen-Eosin, x40].

B) The appearance of myometrial invasion with tumor cells [Hematoxylen-Eosin, x40] and immunohistochemically positivity for CD-34 [X200].

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CT scans and stable diease 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-oopherectomy, 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/m^2, day 1-Vincristine 1 mg/m^2, day 1- Dacarbazine 250 mg/m^2 from day 1-5-Doxorubicin 50 mg/m^2, 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,

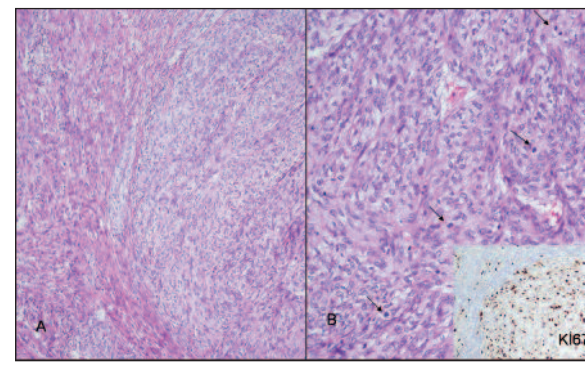

FIGURE 4: A) Tumoral focus invading myometrium [Hematoxylen-Eosin, x100]

B) Pleomorphic tumor cells with high mitotic index in larger magnification [Hematoxylen-Eosin, x400] and immunohistochemical strong positivity for Ki-67.

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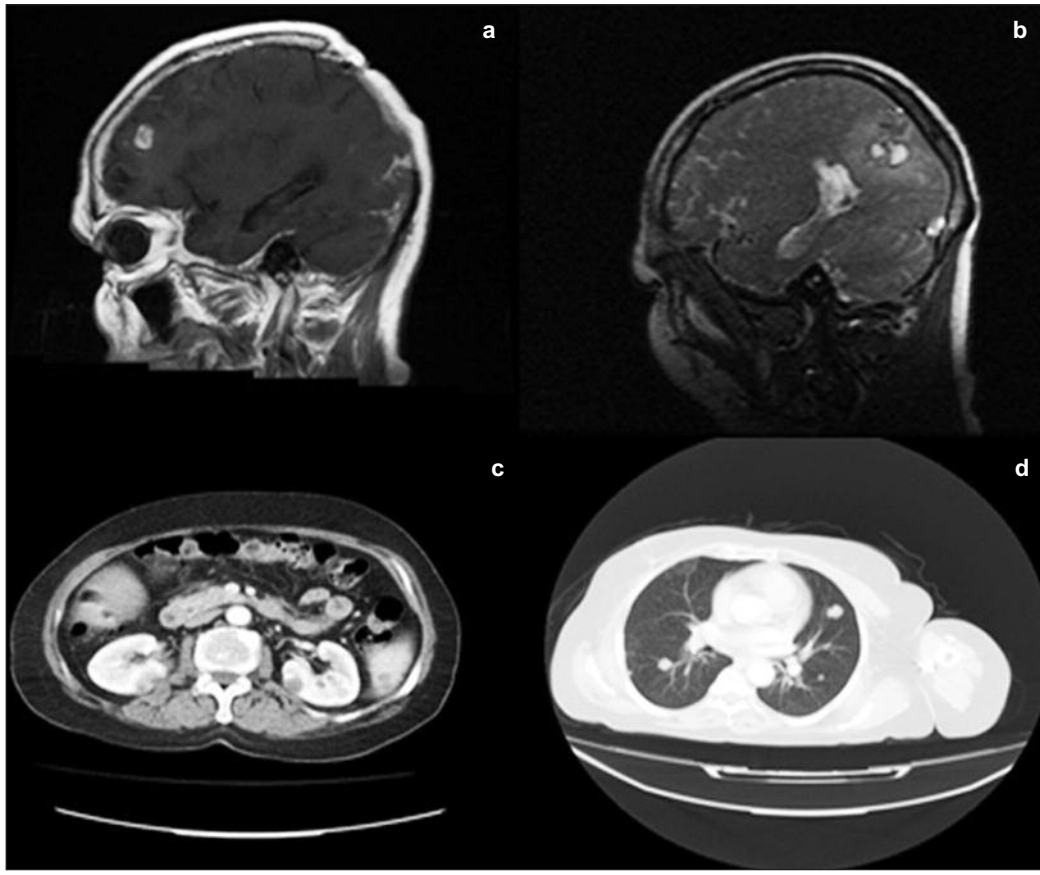

FIGURE 5: Hyperintense metastatic lesions in frontal, temporal and parietal lobes of the brain in magnetic resonance imaging **(a, b)** and the appearence of liver, lung and spleen metastases in computed tomography imaging **(c, d)**.

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.[8,9] 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.[10,11]

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).[12] 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).[13] 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.[12] 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).[14-16]

These tumors can occur anywhere in the body; the most common localizations are lower extremities, pelvis and head and neck.[17] 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.[18] 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.[18] Thyroid metastasis of malignant HPC is also very rare. Only one patient with thyroid metastasis from HPC is reported in the literature.[19] 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 extraneural sites, most commonly to the bone, liver, and lungs. M-HPCs are usually seen as hyperdense lesions in CT and MR imaging.[20] 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 metastasic 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.[6,21] 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.[22-24] Interferon-alfa and thalidomide,[25] tyrosine kinase inhibitors such as sunitinib,[26,27] sorafenib[27] or dasatinib[28] 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.[7] 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%.[8,20,29] 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.[8] 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 chemotherapeutics 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

1. Stout AP, Murray MR. Hemangiopericytoma: a vascular tumor featuring Zimmermann's pericytes. Ann Surg 1942;116(1):26-33.
2. Chnaris A, Barbetakis N, Efstathiou A, Fessatidis I. Primary mediastinal hemangiopericytoma. World J Surg Oncol 2006;4:23.
3. Das AK, Gans BJ. hemangioperıcytoma of oral cavity: review of literature and report of case. J Oral Surg 1965;23:456-60.
4. Wong VV, O'Brien O, De Tavernier M. Bilateral malignant ovarian haemangiopericytoma. J Obstet Gynaecol 2011;31(1):98-9.
5. Rutkowski MJ, Jian BJ, Bloch O, Chen C, Sughrue ME, Tihan T, et al. Intracranial hemangiopericytoma: clinical experience and treatment considerations in a modern series of 40 adult patients. Cancer 2012;118(6): 1628-36.
6. Wong PP, Yagoda A. Chemotherapy of malignant hemangiopericytoma. Cancer 1978; 41(4):1256-60.
7. Chamberlain MC, Glantz MJ. Sequential salvage chemotherapy for recurrent intracranial hemangiopericytoma. Neurosurgery 2008; 63(4):720-6; author reply 726-7.
8. Espat NJ, Lewis JJ, Leung D, Woodruff JM, Antonescu CR, Shia J, et al. Conventional hemangiopericytoma: modern analysis of outcome. Cancer 2002;95(8):1746-51.
9. Enzinger FM, Smith BH. Hemangiopericytoma. An analysis of 106 cases. Hum Pathol 1976 ;7(1):61-82.
10. Derakhshani P, Neubauer S, Braun M, Heidenreich A, Engelmann U. Giant retroperitoneal hemangiopericytoma with paraneoplastic gynecomastia. Case report and literature review. Urol Int 1999;62(4):223-5.
11. Kruskal JB, Kane RA. Paraneoplastic hypoglycemia associated with a hepatic hemangiopericytoma. J Ultrasound Med 2002;21(8): 927-32.
12. Enzinger FM, Weiss SW. Soft Tissue Tumors. 5th ed. New York: Mosby Year Book; 2008. p.1-1120.
13. Knösel T, Schulz B, Katenkamp K, Katenkamp D, Petersen I. [Solitary fibrous tumor and haemangiopericytoma: what is new?]. Pathologe 2010;31(2):123-8.
14. Corson JM, Weiss LM, Banks-Schlegel SP, Pinkus GS. Keratin proteins and carcinoembryonic antigen in synovial sarcomas: an immunohistochemical study of 24 cases. Hum Pathol 1984;15(7):615-21.
15. Abenoza P, Manivel JC, Swanson PE, Wick MR. Synovial sarcoma: ultrastructural study and immunohistochemical analysis by a combined peroxidase-antiperoxidase/avidin-bio-tin-peroxidase complex procedure. Hum Pathol 1986;17(11): 1107-15.
16. Ordóñez NG, Mahfouz SM, Mackay B. Synovial sarcoma: an immunohistochemical and ultrastructural study. Hum Pathol 1990;21(7): 733 -49.
17. Eken KG, Tanrıverdi O, Özağarı A, Kabuk-çuoğlu F. [Renal hemangiopericytoma: a case report and current approach to hemangioperiocytoma-solitary fibrous tumor]. Turkiye Klinikleri J Med Sci 2012;32(5):1423-8.
18. Zagouri F, Dimopoulos AM, Fotiou S, Kouloulias V, Papadimitriou CA. Treatment of early uterine sarcomas: disentangling adjuvant modalities. World J Surg Oncol 2009;7:38.
19. Proietti A, Sartori C, Torregrossa L, Vitti P, Aghababyan A, Fregoli L, et al. A case of metastatic haemangiopericytoma to the thyroid gland: Case report and literature review. Oncol Lett 2012;3(6):1255-8.
20. Soyuer S, Chang EL, Selek U, McCutcheon IE, Maor MH. Intracranial meningeal hemangiopericytoma: the role of radiotherapy: report of 29 cases and review of the literature. Cancer 2004;100(7):1491-7.
21. Galanis E, Buckner JC, Scheithauer BW, Kimmel DW, Schomberg PJ, Piepgras DG. Management of recurrent meningeal hemangiopericytoma. Cancer 1998;82(10): 1915-20.
22. Park MS, Ravi V, Araujo DM. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma, and hemangiopericytoma/solitary fibrous tumor. Curr Opin Oncol 2010;22(4):351-5.
23. Dietzmann K, von Bossanyi P, Warich-Kirches M, Kirches E, Synowitz HJ, Firsching R. Immunohistochemical detection of vascular growth factors in angiomatous and atypical meningiomas, as well as hemangiopericytomas. Pathol Res Pract 1997;193(7):503-10.
24. Delgado M, Pérez-Ruiz E, Alcalde J, Pérez D, Villatoro R, Rueda A. Anti-angiogenic treatment (sunitinib) for disseminated malignant haemangiopericytoma: a case study and review of the literature. Case Rep Oncol 2011;4(1):55-9.
25. Kirn DH, Kramer A. Long-term freedom from disease progression with interferon alfa therapy in two patients with malignant hemangiopericytoma. J Natl Cancer Inst 1996; 88(11):764-5.
26. Mulamalla K, Truskinovsky AM, Dudek AZ. Rare case of hemangiopericytoma responds to sunitinib. Transl Res 2008;151(3):129-33.
27. Domont J, Massard C, Lassau N, Armand JP, Le Cesne A, Soria JC. Hemangiopericytoma and antiangiogenic therapy: clinical benefit of antiangiogenic therapy (sorafenib and sunitinib) in relapsed malignant haemangioperyctoma /solitary fibrous tumour. Invest New Drugs 2010;28(2):199-202.
28. Peters KB, McLendon R, Morse MA, Vredenburgh JJ. Treatment of Recurrent Intracranial Hemangiopericytoma with SRC-Related Tyrosine Kinase Targeted Therapy: A Case Report. Case Rep Oncol 2010;3(1):93-97.
29. Hart LL, Weinberg JB. Metastatic hemangiopericytoma with prolonged survival. Cancer 1987;60(4):916-20.