Primary Peritoneal Angiosarcoma: A Case Report

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Abstract. Peritoneal angiosarcoma is an extremely rare sarcoma (0.01287% incidence per 100,000) with an aggressive clinical course and a poor prognosis. We herein report a case of a young man with diagnosis of angiosarcoma whose tumor adhering to the inferior wall of his bladder and omentum was initially thought to be rhabdomyosarcoma. His disease state progressively worsened, despite initiation of different types of chemotherapies. Blood was tested for cytokine and soluble receptor levels. Unexpectedly and never previously reported, very high levels of interleukin-6 (IL-6), osteopontin, and prolactin were found. Surprisingly, angiogenic cytokines levels were low. The patient died 5 months after initial presentation. In the present report, we discuss the difficulties in diagnosing this rare sarcoma and possible therapeutic targets, including the IL-6 pathway that may provide more effective ways in controlling this cancer in its metastatic stage.

In the analysis of the Surveillance, Epidemiology and End Results (SEER) program, in the period from 1978-2001, angiosarcoma was reported in 4.1% of 26,758 cases of soft tissue sarcoma (1). Our analysis of SEER data in the period from 1973-2010 returned 45 cases of peritoneal angiosarcoma with an incidence per year and 100,000 population to be 0.0001287. There was no difference in trend in incidence between years and the 5-year survival rate was 20.8% (95% confidence interval: 7.9%-37.9%) for all stages.

Angiosarcoma is an aggressive, rapidly proliferating and quickly metastasizing malignant neoplasm, derived from endothelial cells and forming irregular blood-filled spaces. Due to lack of symptoms at the early stage it is often diagnosed when it is already spread widely, and even then it is frequently misdiagnosed as rhabdomyosarcoma. There is no effective therapy for angiosarcoma and this disease has a poor and, ultimately, fatal prognosis. Herein, we report a case in which the diagnosis was made only after substantial disease progression and we discuss possible therapeutic targets that could help with selection of more appropriate systemic treatment that may prolong survival of those patients.

Case Report

A 22-year old man, originally from Uruguay, without significant previous medical history, presented complaining of acute left inguinal pain associated with dysuria. As part of his initial evaluation, he was seen by a surgeon who ruled-out presence of hernia and ordered an abdominal ultrasound that reported a mass compressing the bladder (Figure 1A). The patient was admitted to the hospital for further evaluation and empirical antibiotic treatment for a possible abscess was started. There was no fever or leukocytosis. Follow-up abdominal tomography did not show a change in shape or size of the mass and therefore the decision was made to perform an exploratory laparotomy five weeks after initial presentation. The operative description reported a vascularised tumor that adhered to the inferior wall of the bladder and omentum.

Abbreviations: AUC: Area under the curve; CDX2: Caudal-related homeobox transcription factor 2; CEA: carcinoembryonic antigen; FGF: fibroblast growth factor; G-CSF: granulocyte colony-stimulating factor; gp100: HMB-45 antigen; HGF: hepatocyte growth factor; IL-6: interleukin-6; MRI: magnetic resonance imaging; PDGF: platelet-derived growth factor; PECAM-1: platelet endothelial cell adhesion molecule-1; S100: S100 calcium binding protein; SCF: stem cell factor; SEER: Surveillance, Epidemiology and End Results; sEGFR: soluble epidermal growth factor receptor; sHER-2-neu: serum human epidermal growth factor receptor 2; sIL-6R alfa: soluble interleukin-6 receptor alpha subunit; sTie-2: soluble Tie2; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; VEGFA: vascular endothelial growth factor A; WHO: World Health Organization.

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The initial pathological evaluation revealed mesenchymal malignant neoplasia suggestive of rhabdomyosarcoma. Immunohistochemistry was positive for cytokeratin, vimentin, S100 calcium binding protein (S100) and calretinin, and negative for CD34, smooth muscle actin (specific anti-actin, gamma 2 Antibody (HHF35)), desmin, cytokeratin CK7, CK20, CK 5-6, carcinoembryonic antigen (CEA) and Caudal-related homeobox transcription factor 2 (CDX2). Immunohistochemistry results suggested a tumor of non-epithelial origin, but an undifferentiated carcinoma could not be ruled out.

The oncology service was consulted and further evaluation was initiated. On the 11th week, after initial presentation, the patient developed right-side hemiparesis with aphasia that self-resolved within 50 min. A magnetic resonance imaging (MRI) of the head revealed a left cortical and subcortical subacute frontoparietal infarct. Subsequently, the patient developed ascites, weakness and anorexia. Thirteen weeks after initial presentation, a positron emission tomography (PET) showed highly-metabolically active processes in the right-side abdomen, pelvis and rectus abdominal muscle compatible with metastasis (Figure 1B). Consequently the patient developed shortness of breath, while abdominal ultrasound revealed worsening ascites. Paracentesis was then performed with removal of 3 litres of bloody peritoneal fluid with resulting temporary improvement in shortness of breath.

On week 15 after initial presentation, chemotherapy with carboplatin area under the curve (AUC)=2 intravenously weekly and docetaxel 40 mg/m² intravenously weekly for 4 weeks was started. With no visible impact on amount of ascites with carboplatin and docetaxel chemotherapy on week 16, an anti-angiogenic and anti-metalloproteinase treatment was attempted with daily oral administration of cyclophosphamide 50 mg, doxycycline 100 mg and spironolactone 200 mg. A partial decrease of the amount of ascites was observed. Soon after, chemotherapy with cisplatin was given through an intraperitoneal catheter.

The pathological tissue was sent for a second opinion. On routine sections, the tumor showed typical features of a high-grade malignancy with marked nuclear atypia and numerous mitotic figures. As malignant mesothelioma was clinically a diagnostic consideration and areas of the tumor consisted of loosely cohesive epithelioid cells, immunohistochemical stains for cytokeratin (CK) 5/6, calretinin and WT-1 were performed and the tumor was found to be negative for CK 5/6 and also for nuclear staining of WT-1 and calretinin. Other areas of the tumor displayed variably anastomosing vascular channels lined by atypical cells that merged into networks of epithelioid cells (Figure 2). Scattered cells displayed intra-cytoplasmic lumens. The tumor was strongly positive for CD31 (Figure 3), and variably positive for CD34 and Factor VIII supporting the diagnosis of a vascular tumor. Kaposiform hemangioendothelioma was considered because of the young age of the patient and the abdominal location, but the tumor did not consist of characteristic spindle cell fascicles, numerous capillaries and slit-like luminal spaces. A diagnosis of angiosarcoma was made on the basis of morphological and immunohistochemical features of the tumor.

In order to better understand the pathobiology of peritoneal angiosarcoma and identify potential therapeutic targets we performed analyses of cytokines present in blood. The following soluble biomarkers in plasma were quantified...
by the Bio-Plex Pro Human Cancer Biomarker Panel 1, 16-plex (Bio-Rad, Hercules, California, USA); soluble epidermal growth factor receptor (sEGFR), fibroblast growth factor (FGF-basic), follistatin, granulocyte colony-stimulating factor (G-CSF), hepatocyte growth factor (HGF), serum human epidermal growth factor receptor-2/neu (sHER2/neu), soluble interleukin-6 receptor alpha subunit (sIL-6Rα), leptin, osteopontin, platelet-derived growth factor-AB/BB (PDGF-AB/BB), platelet endothelial cell adhesion molecule-1 (PECAM-1), prolactin, stem cell factor (SCF), soluble Tie2 (sTIE-2) and soluble vascular endothelial growth factor receptor-1 and receptor-2 (sVEGFR-1 and sVEGFR-2). Assays were performed according to the manufacturer’s protocol. Bio-Plex Manager software was used for data acquisition and obtaining concentration values from standard curves. VEGF was measured with Human VEGFA ELISA kit (Thermo Scientific, Hanover Park, Illinois, USA) per instructions. Concentration of human VEGF was calculated from standard curve by Excel. Each measurement was taken in triplicate. Data were shown by average of estimated concentration and standard deviation.

Results of the assays are shown in Figure 4. Very high levels of IL-6, osteopontin and prolactin were found. In addition, high levels of HGF and sTie-2 receptor were also found in plasma, with surprisingly low levels of VEGFA and PDGF.

Although the VEGF pathway in our cytokine analyses was not activated, based on a recent report in the literature of up-regulated hypoxia-inducible factor pathway and increased level of VEGF (2), treatment with a VEGF inhibitor was suggested. Pazopanib (VEGF inhibitor) 400 mg (per os) daily was started with the goal of achieving an 800 mg (per os) daily dose. Unfortunately, the patient’s hemodynamic condition quickly worsened, requiring daily transfusions of blood, plasma and albumin transfusions. Due to intractable vomiting the patient was unable to continue intake of oral pazopanib and died a few days later, five months after initial presentation.

Discussion

Sarcomas, which account for approximately 1% of all adult malignancies and 12% of pediatric cancers, are a varied and rare group of malignant tumors that can originate from any of the mesodermal tissues (3-5). It is a group of malignancies with different genetic alterations, clinical behaviors and a broad histopathological spectrum. More than 50 histological types of soft tissue sarcomas have been identified by the World Health Organization (WHO) classification. The WHO classifies most soft tissue sarcomas according to the presumptive tissue of origin (e.g., liposarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma and angiosarcoma) (6).

Angiosarcomas are a wide range of malignant endothelial vascular neoplasms that can arise from vascular elements of a variety of sites. They can be linked to various predisposing factors and risk factors such as genetic predisposition (e.g., Li Fraumeni syndrome, neurofibromatosis type 1), exposure to chemicals (vinyl chloride and thorium dioxide), chronic inflammation and lymphedema. In our patient, we could not identify any risk factors. The incidence of angiosarcoma is approximately 0.01 per 100,000 cases, usually in older adults but it can develop at any age. This malignancy is usually multi-centric and tends to recur locally, spread widely and have a high rate of lymph
node and systemic metastases. Angiosarcomas are often misdiagnosed and the rate of tumor-related death is high with a 5-year survival rate of only 20% (7, 8).

Peritoneal angiosarcomas are rare tumors of the peritoneum which may be histologically difficult to differentiate from other malignancies, such as mesotheliomas and they usually behave aggressively, resulting in 100% mortality. It may arise at the site of previous radiation treatment to the serous membranes. Clinical presentation varies, depending on the location of the malignancy (4).

Angiosarcoma may be confused with other vascular tumors (e.g., epithelioid and spindle cell hemangioendotheliomas, histiod hemangioma and malignant endovascular papillary angioendothelioma). It is easily confused with carcinoma, with epithelioid forms of sarcoma, with malignant melanoma or mesothelioma. In their cytoplasm, tumor cells contain intermediate filaments (vimentin, occasional tonofilaments and keratin) and pinocytotic vesicles. The rounded epithelioid-shaped cells may exhibit a rhabdoid morphology. Indeed in our case, the first histopathological diagnosis was rhabdomiosarcoma and the immunohistochemistry study could not rule-out other types of undifferentiated carcinoma. In immuno-

hitochemistry, anti-CD31 antibodies are one of the most specific endothelial cell markers since CD31 (platelet-endothelial cell adhesion molecule) is a highly sensitive, specific antigen for endothelial differentiation (Figure 3). In addition, factor VIII is also a related antigen which identifies tumors of endothelial origin. Mutations in the vascular endothelial growth factor receptor-2 (VEGFR2, also called Flk1/KDR) are seen in a subset of these patients. The majority of lesions express vimentin and also CD34 antigen, BNH9 (an endothelial marker), and cytokeratins (seen in 74%, 72% and 35% of cases, respectively). Some of the tumors have actin expression and a prominent pericytic component. Because gp100 (HMB-45 antigen), a melanocytic marker, was not expressed, this helped to rule-out melanoma.

Malignant ascites is the most frequent manifestation of malignant peritoneal angiosarcomas (our patient presented with hemorrhagic ascites). The mechanism proposed includes obstruction of the sub-diaphragmatic lymphatics and non-obstructive factors such as up-regulation of immunomodulators (interleukin-2 (IL-2), tumor necrosis factor (TNF) and interferon-α (IFN-α), as well as VEGF). Contrary to previous suppositions, in our patient, levels of

Figure 4. Mean (+SD) cytokine and soluble receptor levels from plasma, expressed in pg/ml.
pro-angiogenic factors were either at the level of detection or of normal physiologic values (VEGFA, HGF, FGF, PDGF-AB). Unexpectedly and never previously reported, very high levels of IL-6, osteopontin, and prolactin were found. IL-6 is commonly elevated in lymphedema (9) and cancer (10). In a context of sarcoma, IL-6 production was reported in one report where viral IL-6 was reported to induce production of vascular growth factor in Kaposi’s sarcoma (11). Our report is the first to demonstrate high levels of IL-6 in angiosarcoma. Osteopontin impacts on increased cancer cell proliferation, metastatic potential, drug resistance and stem-like behaviour (12). In the case described here, levels of osteopontin were thousands of times higher than normal. Prolactin is implicated in breast cancer tumorigenesis (13). In our case, elevated levels of IL-6, prolactin and osteopontin were consistent with very aggressive behavior of angiosarcoma. Targeting the IL-6 pathway with novel therapeutics in development may provide more effective ways of controlling this cancer in its metastatic stage.

The primary treatment of angiosarcoma is radical surgery with complete resection and adjuvant radiotherapy for the local disease. This is not always possible taking into account the site of origin and tumor extension. The recommended chemotherapy for metastatic angiosarcoma includes anthracyclines, taxanes and ifosfamide. In addition low-dose liposomal doxorubicin or doxorubicin, alone or in combination, have shown positive results (14). Novel strategies to treat angiosarcoma including inhibition of the tyrosine kinase activity of VEGFRs, which can also decrease the permeability of vessels and the formation of malignant ascites, can be explored; however, our case suggests an absence of high angiogenic stimulation that has been previously hypothesized (15, 16). Our observation needs to be replicated in order to further define the role of VEGF in angiosarcoma.

The rarity of peritoneal angiosarcoma makes it difficult to obtain insight into the pathobiology of this tumor. Therefore, every case in which angiosarcoma is eventually diagnosed should be thoroughly analyzed with the potential aim of identifying signs, symptoms and biomarkers that differentiate this cancer from other closely-related cancers. Our unique case provides information about the potential role of IL-6, osteopontin and prolactin in the pathogenesis of peritoneal angiosarcoma.

Consent

Written informed consent was obtained from the patient and his family for publication of this Case Report and accompanying images. A copy of the written informed consent is available for review by the Editor-in-Chief of this journal.

Conflicts of Interest

The Authors declare they have no competing interests.

Authors’ Contributions

All Authors read and approved the final manuscript. JL reviewed literature, collected the data and wrote the paper. MA treated the patient, collected the data and wrote the paper. EW performed pathological analyses on the diagnostic tissue. SG performed analyses of the SEER database on incidence and mortality of peritoneal angiosarcoma. AZD treated the patient (provided advice), reviewed the literature and wrote the paper.

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