Primary splenic angiosarcoma: case report and literature review

Angiossarcoma primário de baço: relato de caso e revisão da literatura

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Abstract

This paper describes a case of an aggressive primary splenic angiosarcoma in a 29-year-old man and makes a review of its clinical findings, pathologic reports, treatment and prognosis. Angiosarcomas comprise less than 1% of soft tissue sarcomas, and only a small percentage of these tumors arise in the spleen. These tumors usually represent a diagnostic challenge for the pathologist in view of its variegated histology, and the development of new immunohistochemical markers for vascular tumors like CD31 (platelet-endothelial cell adhesion molecule) helps to rule out other diagnoses. There is no standard chemotherapy treatment for angiosarcomas, and the prognosis of splenic angiosarcoma is particularly poor.

Key words: angiosarcoma; splenic neoplasms; chemotherapy; pathology; immunohistochemistry

Resumo

É relatado um caso de angiossarcoma primário de baço em um homem de 29 anos, fazendo-se a revisão dos achados clínicos, diagnóstico anatomopatológico, tratamento e prognóstico. Angiossarcomas correspondem a menos de 1% dos sarcomas de tecidos moles, e somente uma pequena fração surge no baço. Esses tumores frequentemente apresentam-se como um desafio diagnóstico para o patologista, tendo em vista as variações na histologia, e o desenvolvimento de novos marcadores em painéis de imuno-histoquímica, como o CD31, ajudam a descartar outros diagnósticos. Devido à raridade desse tumor não existe um consenso em relação ao tratamento quimioterápico e, via de regra, o prognóstico é ruim.

Palavras-chave: angiossarcoma; tumores esplênicos; quimioterapia; patologia; imunohistoquímica
Introduction
This paper describes a case of a primary splenic angiosarcoma, probably the first related in our country. It is important to have this case documented, as this is a very rare tumor, of difficult diagnosis, and there is no standard methods of treatment.

Splenic malignant vascular tumors are extremely rare. Angiosarcomas comprise less than 1% of soft tissue sarcomas, and only 4% of these tumors arise in the spleen\(^{1,2}\). In our review, only 78 cases have been reported\(^{3-11}\). Langhans, in 1879, was the first author to describe this unusual tumor\(^{12}\), which usually represents a diagnostic challenge for the pathologist in view of its variegated histology.

The age range of patients with splenic angiosarcoma was 19 to 84 years with a peak in the 5th decade of life. The distribution by sex tends to be equal (25 men and 22 women)\(^{3-7,10,11}\). The most common clinical signs and symptoms are splenomegaly, 92%; abdominal pain mostly in the upper left quadrant, 83%; weight loss, 40%; spontaneous splenic rupture with hemoperitoneum, 30%\(^{2,10}\); fever, 10%; and fatigue, 5\%\(^{10}\). Among reported cases, 12.5% underwent exploratory laparotomy without diagnostic suspicion\(^{7}\).

Laboratory results indicated cytopenia of some type in 91% of cases, specially anemia in 70%\(^{3,7}\), and coagulation tests were abnormal: 8%, with 5% of disseminated intravascular coagulation\(^{3}\). In our review, metastases occurred preferentially to the liver\(^{15}\), bone or bone marrow\(^{48}\), lymph nodes\(^{3}\), central nervous system\(^{2}\), myocardium\(^{1}\), kidney\(^{11}\), pancreas\(^{11}\), and thyroid\(^{11}\). The median time for diagnosis of metastases was 8 months\(^{3-7,10}\).

Case report
In January/95, a 29-year-old white male was admitted to The Hospital de Clínicas de Porto Alegre Emergency Room with fever (38.5°C), nausea, and vomiting. This was the third episode in a period of three months, and it was associated with transient anorexia and mild weight loss (3 kg). Past history disclosed intermittent diffuse abdominal pain, without any irradiation, first noticed in September/94. The patient’s physical examination revealed pale and moist skin, tachicardia, hypotension, and elicited acute pain in the upper left abdominal quadrant with signs of peritoneal irritation. Initial laboratory results showed mild anemia (Ht 35%, Hb 10.1 g/dl), leukocytosis (22,600 cells/µl with 22% of bands), normal renal, hepatic, and coagulation tests, and amylase 21IU/L.

The patient underwent an exploratory laparotomy that disclosed moderate hematic ascites, an enlarged homogeneous liver, enlarged celiac lymph nodes, and an enlarged ruptured spleen, with petreous consistency and capsular adherences. Splenectomy with hepatic and lymph node biopsies were performed. The immediate postoperative period was uneventful, and the patient was discharged, asymptomatic, a week later.

Pathologic test results reported an undifferentiated malignant neoplasm with extensive necrosis, resembling an angiosarcoma or malignant histiocytosis (Figures 1 and 2). Reactional liver and lymphoid hyperplasia were also detected. The immuno peroxidase staining performed in our Pathology Unit and in the Mayo Clinic Pathology Unit was negative for LCA (leukocyte common antigen),NSE (neuron-specific enolase), cytokeratins, S-100 protein, vimentin, desmin, CD30; positive for anti-Factor VIII and strongly positive for CD31 (Figure 3). These findings allowed a diagnosis of an anaplastic angiosarcoma (grade IV) to be established.

After discharge, the patient remained asymptomatic until February/95, when he started with lombosacral pain associated with abdominal pain. The physical examination, plain X-ray films, abdominal ultrasound, and laboratory results were all normal. In 3/3/95 he was admitted with fever (38.5-39°C), nausea and vomiting. The physical examination disclosed only diffuse abdominal and lombosacral pain. An abdominal ultrasound showed at least three enlarged celiac trunk lymph nodes and hepatomegaly. Bone scan was compatible with possible metastatic involvement of lumbar vertebrae, right parietal bone, and the 8th costovertebral angle. Laboratory results reported anemia...
(Ht 34%, Hb 9.6g/dl), a constant leukocytosis (20,000-30,000 cells/μl with shift to the left), negative serial blood, urine and catheter cultures, a normal serum proteinogram, lactate dehydrogenase (LDH) of 2,000IU/L and alkaline phosphatase of 829IU/L. The bone marrow biopsy and smear showed a diffuse infiltration by anaplastic malignant cells.

Chemotherapy was started, with the use of doxorubicin 25mg/m² IV bolus D1-3 plus ifosfamide 1.5/m² IV in 1 hour D1-3 in 3/10/95. Two days after the beginning of chemotherapy, the patient developed tumoral lysis syndrome (hiperkalemia 7.7 mEq/L, calcium 6.5 mg/dl and uric acid 13.0 mg/dl) and a severe coagulation disorder with hematuria, diffuse petechiae, rapid fall in red cell (Hb 9.8 to 4.5g/dl) and platelets counts (110,000 to 10,000/μl). A rapid progression to respiratory insufficiency was seen, with hypoxemia (PO₂ 53%) and pulmonary infiltrates on chest X-ray compatible with adult respiratory distress syndrome or parenchymal hemorrhage. The patient was transferred to the intensive care unit, but despite the treatment, progressed to refractory cardiac arrest in 3/12/95.

**Discussion**

Angiosarcomas are malignant tumors that show some morphological and functional properties shared with normal endothelium. They may behave as very differentiated neoplasms, resembling benign hemangiomas, or as aggressive undifferentiated and anaplastic tumors, and it is very difficult to differentiate angiosarcomas from carcinomas and melanomas.

Angiosarcomas are one of the most rare soft tissue neoplasms. Although they may develop at any site, they tend to develop in superficial soft tissue and skin. The clinical aspect and behavior have a direct relation with the primary site.

In a specific setting of undifferentiated tumors, final diagnosis may be established by determining the immunohistochemical profile. Antibodies to the factor VIII-related antigen, the most extensively used marker for the endothelium, are not too reliable, as only 25% of angiosarcomas present enough protein to allow for immunohistochemical
confirmation. The hematopoietic stem cell antigen - CD34 - is present in most angiosarcomas\(^{16}\), but it is also present in other soft tissue tumors, including epithelioid sarcoma. Until now the CD34 (platelet-endothelium adhesion molecule) has been the most reliable marker of endothelial cell line\(^{16}\).

Splenic angiosarcoma is the most common non-lymphoid malignant neoplasm of the spleen\(^{14,17}\), and is extremely rare and aggressive\(^{3,18}\). The spleen is most frequently replaced by a diffuse mass of tumor nodules, with prominent hemorrhage and necrosis. Histologically, one can see an intricately vascular channel coated by atypical endothelial cells, sheets of fusiform cells, and solid areas\(^{1,17,18}\). They are distinguished from other vascular tumor findings of cytological atypia, abundant mitosis and the presence of solid areas. The differential diagnosis from other non-vascular sarcomas and metastatic neoplasms, in cases in which the vascular pattern is not so clear-cut, may be done using the immunohistochemical techniques described elsewhere\(^{1,16}\).

Because of the rarity of this tumor, there is no standard regimen of treatment\(^{5}\). The use of chemotherapy is under investigation for angiosarcomas of any site, and several studies with animal models are ongoing. The combination of vincristin, doxorubicin, and cyclophosphamide (VAC) in fifteen dogs with hemangiosarcoma resulted in a median survival for all dogs of 172 days (mean survival = 316 days), with acceptable toxicity (neutropenia 11/15, severe enteritis 4/15, cardio-toxicity 3/15, and sepsis 2/15)\(^{22}\). Sixteen dogs with a histologic diagnosis of hemangiosarcoma were treated with surgery and combined doxorubicin/cyclophosphamide\(^{23}\). The results showed a trend for improved survival in dogs with localized disease (Stage I) receiving combined therapy. The median survival was 250 days, with a mean of 403 days. Survival for dogs with stage I, II and III disease was also improved with combined therapy. The overall median survival was 202 (mean: 285 days). Toxi-cities included mild to moderate neutro-penia and lethargy, anorexia, vomiting, diarrhea, and fever\(^{9-15,19}\). Chemotherapy with doxorubicin and cyclophosphamide seems to improve survival with acceptable morbidity in canine patients with early stages of the disease.

A 45-year-old Japanese woman, who received combined chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone after undergoing splenectomy, showed a partial response. The authors highlight that effective chemotherapy for angiosarcomas are yet to be developed\(^{8}\). Cunningham\(^{24}\) described a case of primary ovarian angiosarcoma in which a short remission was achieved with intensive chemotherapy with ifosfamide and doxorubicin. A case report of an 82-year-old female with a lower extremity angiosarcoma was described by Feurstein et al.\(^{25}\). The patient was successfully treated by retro-grade intravenous perfusion with vinblastin and vincristin with subsequent resection of tumor. Silverman\(^{26}\) described a case of a patient with metastatic angio-sarcoma of the breast who achieved a long-term clinical and pathological remission after treatment with methotrexate. The 30-year course of her disease is the longest reported survival with documented metastatic angiosarcoma. The UCLA Medical Center treated twenty-eight patients with angiosarcoma of the head and neck (9 with multifocal disease) between 1955 and 1990. Follow-up ranged from 3 to 159 months, with a median of 32 months. The overall prognosis was poor, with a 5-year disease-free survival of 26% (7/27 patients). Distant metastases has developed in nine patients at last follow-up. Eight percent (1/12 patients) remained disease free vs. 67% (4/6 patients) who received postoperative radiation therapy only, without chemotherapy. Only one (14%) of seven patients treated with radiation therapy was rendered disease-free. It was noted that angiosarcoma usually presents as a poorly differentiated neoplasm and it is frequently associated with multifocal disease, that there is propensity for both local recurrence and distant metastases, and it is suggested that combined therapy offers the best chance for long-term control in patients with angiosarcoma of the head and neck\(^{27}\). Angiosarcomas arising on the head and neck of elderly (malignant hemangioendothelioma) have extremely poor prognosis, and a Japanese author - Masuzawa\(^{28}\) - proposed chemotherapy (CYVADIC; cyclophosphamide, vincristine, doxorubicin, and dacarbazine) and the use of intrarterial infusion of doxorubicin and 5-fluorouracil as a combination therapy, but toxicity was high.
and, unfortunately, there was no evidence that this chemotherapeutic trial improved the prognosis.

The use of recombinant interferon alpha-2a in an heterogeneous group of five pediatric patients with progressive, invasive angiomatous diseases, including pulmonary hemangiomatosis, angiosarcoma, or massive hemangioma with associated consumptive coagulopathy was tested. Four patients had partial response, and the patient with angiosarcoma had a decrease in size and number of tumor nodules. Responses occurred during periods of 2 to 20 months of treatment. Each of the four surviving patients had improved linear growth and weight gain during interferon treatment(29).

The use of radiotherapy may help in the treatment of an enlarged painful spleen or bone metastases.

The prognosis of splenic angiosarcoma is very poor. In the review of Falk(3), the follow-up of 38 patients disclosed that 30 (79%) died in a median time of six months after diagnosis. Eight patients survived at least 12 months. Only two of the initial 38 patients were believed to be alive without disease, an indication of a very aggressive neoplasm.

References


