Treatment of intimal sarcoma of peripheral veins

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ABSTRACT

INTRODUCTION: Intimal sarcoma is an extremely rare group of undifferentiated pleomorphic sarcoma arising from the intimal layer of vessels accounting for only 1% of all sarcomas, intimal sarcoma of large veins are even less common.

CASES PRESENTATION: We present two cases of intima sarcoma, one originated form the basilar vein and the other from the cephalic vein, the first one was treated with surgery and postoperative chemotherapy followed by Radiotherapy (RT), the second case was treated with isolated limb perfusion followed by marginal resection and RT. Both patients progressed to the lungs in a short time, the first case was treated with metastasectomy of the lung and is without evidence of disease 7 months after surgery; the second case treated with isolated limb perfusion has stable disease.

DISCUSSION: Intimal sarcoma are very aggressive tumors, with a high metastatic potential, the two patients progressed to lung in a short time (2 months) after local treatment. Both cases exhibit good response to chemotherapy and metastasectomy with a disease – free period of 7 months.

CONCLUSION: We propose that given the aggressive behavior of these tumors, they should be treated with chemoradiotherapy postoperative, either by systemic chemotherapy or isolated limb perfusion for the limb sparing surgery in this histology.

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1. Introduction

This work has been reported in line with the SCARE criteria [30]. Intimal sarcoma (IS) is defined as a malignant tumor arising in the tunica intima of large blood vessels. In the systemic circulation, most of IS derived from the aorta artery, accounting for only 1% of all sarcomas [1]. The primary neoplasm of the major blood vessels is divided into three categories based on their site of origin: a) From large veins (extremely rare group) b) Pulmonary artery and c) Aorta and its branches.

Large vessel intimal sarcomas tend to occur in the elderly with a history of peripheral vascular disease, and usually present with advanced disease with an aggressive course. The differential diagnosis of Intimal sarcomas should include benign lesions as well other soft tissue sarcoma (STS), diagnostic approach should have a high degree of suspicious, clinical manifestations are unpecific. Imaging should include an adequate high-quality studies such as a Magnetic resonance imaging (MRI) preoperative to determine resectability as well as a CT scan of the chest, abdomen and pelvis to exclude metastatic disease [2–8].

Vascular neoplasms are classified as intimal sarcomas, angiosarcomas and leiomyiosarcomas; this last one represent most of the peripheral arterial tumors; To differentiate intimal sarcomas from the other two, histology and immunohistochemistry is needed. 26% of intimal sarcomas are well differentiated.

The cornerstone of treatment is extrapolated of STS, surgery with margins greater than 1 cm, limb-sparing surgery with RT are the standard of treatment [11,12]. For Stage II and III STS, preoperative chemoradiation, chemotherapy alone or with hyperthermia, postoperative chemotherapy are options but not the standard of treatment (as the literature shows not benefit). Preoperative RT increase wound complications and postoperative RT improves local control but not overall survival [16–23]. For unresectable disease the options of treatment include RT alone, chemoradiation or chemotherapy alone with the same considerations; tumors that become resectable can be treated with surgery follow by RT with or without chemotherapy [24]. Regional limb therapy has been evaluated with good results to preserve the limb, tumor necrosis factor – alpha and melphalan appear to have the best results [25–29].

There is very limited data available in the literature on surveillance strategies for STS, physical examination is the most important factor. No data exists in the follow up either with MRI, CT scans or

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Ultrasound. The median survival time is only a few months; aggressive tumors that can metastasize, the life expectancy is usually about 12–18 months [9].

2. Clinical case 1

A 61-year-old man presented with progressive increase in left forearm, physical examination reveals a multilobular, heterogenous mass of 5 × 6 cm, in the middle third, without impaired mobility, no distal neurovascular compromise, corresponding with the cephalic vein in the forearm.

The CT scan showed only the presence of a small rounded hypodense mass located in diaphragmatic dome, hepatic segment VIII measuring 12 mm compatible with simple cyst.

An incisional biopsy of the forearm was obtained and reported as pleomorphic and spindle cell sarcoma, intermediate grade at least. The tumor cells stained strongly positive for vimentin, which is found in both benign and malignant mesenchymal tumors, but were negative for other immunohistochemical stains such as Desmin (smooth muscle origin), cytokeratin and S100 protein (to ruled out metastatic carcinoma and melanoma respectively). The absence of CD34 staining argued against sarcoma origin of endothelial cells such angiosarcoma and malignant endothelioma.

In a multidisciplinary session, it was decided to take the patient to isolated limb perfusion with melphalan, in order to reduce its size followed by limb sparing surgery. The surgery was performed without any complications and type II Wieberdink toxicity was recorded. The after-treatment response was evaluated three months later as stable disease per RECIST 1.1 criteria (Figs. 1 and 2). Surgical procedure was done with a tumor marginal resection. The specimen consisted as an irregular vein, with overall dimensions of 20.1 × 5.9 × 4.2 cm. The final diagnosis was a high degree pleomorphic spindle cell sarcoma with cartographic necrosis that affects the whole course of the vessels compatible with intimal sarcoma. The immunohistochemistry was positive for vimentin and negative for S-100, CD56, MDM2 and CD34 (Figs. 3 and 4).

It was decided to continue with adjuvant radiotherapy completing a dose of 66 Gy in 33 fractions. 2 months after the end of adjuvant radiotherapy, the presence of multiple bilateral pulmonary nodules was documented, the largest with a diameter of 31 mm in the right parahiliar side. He received 6 cycles of doxorubicin as palliative chemotherapy. Currently the patient is without local recurrence, with stable lung metastatic disease and a 100% Karnofsky score, ECOG 0 and the limb with full functionality.

3. Clinical case 2

A 29 years old male diagnosed with Hodgkin lymphoma in 2004 treated with first- and second-line chemotherapy regimens, who achieved a complete response with no evidence of disease. In 2014 he was diagnosed with deep vein thrombosis secondary to a tumor in the left arm, Imaging studies reported a tumor in the medial compartment and middle third of the left arm apparently originated from the basilica vein, about 5 × 3 cm in its greater axes (Fig. 5). Core Needle biopsy reported a high-grade sarcoma with pleomorphic areas and production of osteoid material compatible with an intimal sarcoma.

Surgery was the first line of treatment, the findings were a left arm tumor, in the proximal third, 5 × 4 cm, subfascial, infiltrating the biceps muscle medially, with abundant newly formed vessels,
obliterating the basilica vein, displacing the neurovascular structures.

The pathology findings were a tumor of 7 × 6 × 4.5 cm, poorly defined, with firm and cystic areas and necrotic internal bleeding. Immunohistochemistry was positive for vimentin and negative for CD 34 (Fig. 6).

Adjuvant treatment consisted of chemotherapy (gemcitabine 6 cycles) plus radiotherapy (60 Gy standard fractions). Lung progression was documented 2 months later and was treated with pulmonary metastasectomy. The patient is currently being followed with no evidence of recurrence seven months later.

4. Discussion

Intimal sarcoma is an extremely rare group of undifferentiated pleomorphic sarcoma arising from the tunica intima or associated with a great vessel; IS represent only 1% of all sarcomas [1]. The defining features of these tumors are intraluminal growth with obstruction of the lumen and seeding of emboli. The incidence of pulmonary intimal sarcoma is almost twice of aortic origin. The mean age at diagnosis is 48 years old for patients with pulmonary intimal sarcoma and 62 years old for those with aortic intimal or peripheral large veins [4]. The primary neoplasm of the major blood vessels is divided into three categories based on their site of origin: a) From large veins, b) Pulmonary artery and c) Aorta and its branches.

Over 60% of reported sarcomas of the aorta and its branches are intimal sarcomas, arising from the tunica intima, rather than from endothelial, medial or adventitial cells [2]. In adults, the most common subtypes are undifferentiated pleomorphic sarcomas including the historically defined malignant fibrous histiocytoma. The latter are predominantly located in the left atrium. Regarding sarcomas arising in large vessels, the sites most frequently involved are the pulmonary arteries and the aorta, followed by venous sarcomas, especially of the inferior vena cava [3].

Large vessel intimal sarcomas tend to occur in the elderly with a history of peripheral vascular disease, and usually present with advanced disease with an aggressive course. Many are centrally located, and can present as an asymptomatic thoracic aneurysm, or with dyspnea, sudden death, or distal embolization. Aortic intimal sarcomas have also been reported at the site of prior vascular anastomoses [2]. The differential diagnosis of Intimal sarcomas should include benign lesions as well other soft tissue sarcoma (STS). History and physical examination are an essential element of the workup, contrary to other STS, this type of tumor must never be biopsied. Diagnostic approach should have a high degree of suspicion, the clinical manifestations are unspecific, symptomatic thoracic aneurysm, dyspnea, distal embolization or sudden death for tumors at the aorta, this mistaken diagnosis can lead to inapropriate therapy, such as anticoagulation or thrombolysis [2–4] or local pain, claudication, motor or sensory loss, or as a mass in peripheral localization [5,8]. Imaging should include an adequate and high-quality imaging studies, an MRI preoperative of the extremity in compromise to determine resectability as well an IV contrast CT scan of the chest, abdomen and pelvis to exclude secondary tumors or metastatic disease. There is no data regarding the use of PET scans in this type of tumors.

The most common histologic subtype in the vessels is leiomyosarcoma, which tends to grow to a large size without metastasizing. The prognosis is dismal, because many patients present with locally advanced or metastatic disease at the time of initial diagnosis [8]. Burke and Virmani classified luminal sarcomas as poorly differentiated (intimal), angiosarcoma, and leiomyosarcoma [11]. To differentiate intimal sarcomas from these other two, histology and immunohistochemistry patterns are used. Angiosarcomas show endothelial cells on microscopy and stain positively for vimentin factor VIII and CD34. Leiomyosarcomas, on the other hand, have characteristic spindle – shaped cells and stain positively for desmin and actin. Intimal sarcomas, which have an unknown cell of origin, usually show undifferentiated cells with variable immunophenotyping [2].

In a review of 180 primary sarcomas of large arteries, 109 (61%) were classified as intimal sarcomas, and of these, 28 (26%) were well differentiated. Differentiated intimal sarcomas show a spectrum of histopathological morphologies with variable immunophenotyping. Commonly reported types include angiosarcoma, leiomyosarcoma, myxofibrosarcoma, epithelioid hemangioendothelioma, myxoid chondrosarcoma, and undifferentiated pleomorphic sarcoma (or malignant fibrous histiocytoma). Rarer differentiations such as osteosarcoma and rhabdomyosarcoma have been reported in pulmonary artery and aortic origin intimal sarcoma [2].

Understanding the pathogenesis of graft-associated sarcomas involves understanding not only the tumor as a sarcoma but also its precursor lesions. Wright described atypia in proliferative endothelial cells around grafts in guinea pig models.
Intermediate variants between atypical proliferative endothelium and frank carcinoma have also been described and have been named intravascular papillary endothelial hyperplasia (also known as Masson’s pseudoangiosarcoma) and low-grade, epithelioid-sarcoma-like hemangioendothelioma. Whether these can progress to angiosarcoma is unknown. Thalheimer et al. postulated that the MDM-2/p53 pathway is instrumental in the pathogenesis of intimal sarcoma. In his studies, 20% of tumor cells were positive for p53, implicating this pathway [10].

One reason why the pathogenesis and precursor lesions are not well described is because they usually do not present until late in the process during surgery or at autopsy. These tumors usually have symptoms that mimic atherosclerosis or thromboembolic disease and are treated as such without undergoing the proper screening modalities for diagnosis. For the reported cases, the time lag from graft placement until presentation with malignancy ranged from 4 months to 17 years. The specific time at which early changes begin on the pathway to malignancy in the endothelium is unknown [10].

The treatment of the soft-tissue sarcoma of the extremity on early stages (tumors with a size of <5 cm superficial or <5 cm deep, without regional or distance disease, low or intermediate histologic grade) is surgery with margins greater than 1 cm or by removal of the intact fascial plane [11]. Limb-sparing surgery with RT is the standard of treatment with a recurrence rate of 15% and no statistical difference in overall survival (83% Vs 88% at five years) and disease-free survival (71% Vs 78% at five years) as compared to amputation [12]. Positive margins after resection increased the recurrence rate from 12% to 38% at 6 years compared to negative margins [13]. Re-resection may be necessary if the surgical margins are 1 cm or less and without an intact fascial plane. However, if it is not possible to obtain clear margins after re-resection, RT should be offered. [14]. Postoperative RT in early stage is not always needed with adequate margins [15].

For stage II – III (tumors with intermediate and high histologic grade 2 or 3) the treatment options should be decided by a multidisciplinary team. Preoperative chemoradiation (Adriamycin, ifosfamide and dacarbazine 3 cycles interdigitated with 44 Gy of RT) has been shown to improve overall survival (79% Vs 45%) and disease-free survival (81% Vs 50%) with a significant toxicity but is not a standard treatment [16]. Chemotherapy alone is not associated with benefit in high-grade tumors; [17] the addition of hyperthermia improves local control but the technique is not highly reproducible [18]. The anthracycline – based preoperative chemotherapy (doxorubicin, ifosfamide or epirubicin and ifosamide) 6 cycles improve disease-free survival in patients with good performance and high risk of recurrence (69% Vs 44% only with surgery or surgery plus RT), but is not a standard treatment because others study’s show not benefit [20,21]. Preoperative RT increase wound complications (35% Vs 17% in postoperative RT group) but is an option in limb-sparing surgery with a similar control of post-

Fig. 6. a) Pathological complete piece, b) y c) axial H & E staining 400X, d) immunohistochemistry positive for vimentin and e) CD 34 negative.
operative RT [19]. Postoperative RT improves local control in high grade lesions like intimal sarcoma tumors but not in overall survival (74% Vs 56%) [22,23].

Unresectable disease can be treated primarily with RT (70–80 Gy) with local control of 70% in lesions 5 cm or less, 40% lesion 5–10 cm and 25% for more than 10 cm [24]. Other treatment options are chemoradiation or chemotherapy followed by wide margin resection if the initial lesion become resectable. Isolated limb perfusion has been evaluated with good results in unresectable disease in an attempt reduce general toxicity; tumor necrosis factor – alpha and melphalan appear to have greater activity and less toxicity than doxorubicin, with overall response rate of 75%, with a limb salvage form 81–87% of the perfused limbs, with a complete response of 22%, local recurrence rate of 27–30% (highest for multifocal tumors and after previous radiotherapy) a distant failure of 40% with a mean disease specific survival of 54% at 10 years [25–28]. The resection after isolated limb perfusion should be a marginal resection, because the recurrence rate do not differ from wide resections [29].

There is very limited data available in the literature on surveillance strategies for STS. The physical examination is of most important value. No data exists in the follow up either with MRI, CT scans or Ultrasound. In STS, the ultrasound was slightly better than MRI at detecting local recurrences with better sensitivity and specificity at a lower cost [6]. However, both of our patients had distant recurrence to the lungs and not in the primary site. Routine use of chest radiographs or CT should be considered, preferably CT scan within the 4–6 month after surgery, if negative we recommend chest radiograph every 4 months the first year followed up by a chest CT scan every 6–12 months.

There is no data regarding prognosis in this type of tumors. It is determined by stage at diagnosis, including resectability, degree of metastasis and tumor margin free. In STS, the most important prognostic factors include histological grade, tumor size and location. Intimal sarcoma of the aorta is usually diagnosed postoperatively or at autopsy; the median survival time is only a few months, these are aggressive tumors that can metastasize to bones and visceral organs, including the liver, kidneys, adrenal glands, and lungs. Pulmonary artery intimal sarcoma, most commonly diagnosed at surgery or autopsy can metastasize to the brain, pancreas, adrenal glands, and lungs. The prognosis after the onset of symptoms is unfavorable; life expectancy is usually 12–18 months [9].

5. Conclusions

Intimal sarcomas are an extremely rare group of undifferentiated pleomorphic sarcomas. We propose that given the aggressive behavior of these tumors, they should be handled with chemoradiotherapy postoperative, however, isolated limb perfusion is a viable option for the limb sparing surgery in this histology.

Conflict of interest statement

None of the authors have conflict of interest.

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Ethical approval

Approval has been given.

Consent

This work has been reported in line with the SCARE criteria. [30] Written informed consent was obtained from the patient for publication of this case report and case series and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Dr. Javier López-Gómez – Design, data collection, data analysis, writing the paper.

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Dra. Ma. Alejandra Salazar-Alvarez – Data collection and writing the paper.

Dr. Rodrigo Y. Adame – Data collection and writing the paper.

Dr. Dorian Y. García-Ortega – Data analysis, data interpretación and writing the paper.

Dr. Mario Cuellar-Hübbe – Data analysis, data interpretación and writing the paper.

Guarantor

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