Vascular smooth muscle tumors: Review of the literature

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Abstract Vascular smooth muscle tumors are very rare. They can be benign or malign. Intravascular leiomyomatosis is a benign neoplasm that extends through the veins and carries significant morbidity. Angioleiomyoma is a benign neoplasm of the extremities that carries minimal morbidity. Vascular leiomyosarcomas are malign neoplasms derived from vascular smooth cells. They are usually localized to the inferior vena cava, but can also arise from the pulmonary arteries or veins or other peripheral vessels. This study reviews literature for epidemiology, clinical presentation, diagnosis and management of patients with vascular smooth muscle tumors.

Introduction

Vascular smooth muscle tumors are very rare and include a variety of neoplastic lesions characterized histologically by their similarity to adult smooth muscle tissue. They can be benign or malignant, with an incidence of 300 benign tumors and 1 malignant tumor per 100,000 soft tissue tumors. Intravenous leiomyomatosis (IVL) is a benign smooth muscle neoplasm that extends non-invasively, through the venous system, increasing however the risk of morbidity and mortality. Angioleiomyoma is a benign tumor arising from the vascular smooth muscle and it occurs in the extremities and the head. It is also known as angio-myoma, vascular leiomyoma, or dermal angioma. Vascular leiomyosarcomas (LMS) are unusual malign tumors that attack arteries less often than veins. Lesions of the inferior vena cava represent the largest subgroup of these neoplasms. Other primary sites are involved far less frequently. Pulmonary vein LMS are extremely uncommon and are outnumbered in the literature by those of the pulmonary artery. This study reviews literature for epidemiology, clinical presentation, diagnosis and management of patients with IVL, angioleiomyoma, and vascular LMS.

Intravenous leiomyomatosis

Etiology

IVL is a rare smooth muscle cell tumor that grows within the venous channels without invading them. About 200 cases have been reported in the literature so far. It was first
described by Durl and Horman in 1907. The exact etiology of this neoplasm is not entirely known. Two contrasting theories have been presented, both of which have supporting evidence. The first one suggests that the neoplasm arises from estrogen-induced smooth muscle cell proliferation in the venous wall of the uterine veins, while the second one suggests that the neoplasm arises from uterine leiomyomas that invade the venous system. The extension of the tumor is mostly through the uterine veins and can progress along the veins into the inferior vena cava. Further extension into the right-sided cardiac chambers will lead to intracardiac leiomyomatosis. More than 100 cases of intracardiac leiomyomatosis have been reported in the English literature until now (Table 1).

Epidemiology
Leiomyoma shows a predilection for pre-menopausal women. Half of the patients have had prior pregnancies. Since 1900, only 73 cases of cardiac leiomyomatosis have been reported and 60% of the reports were within the last 15 years. However, it is believed that diagnosis is still significantly underestimated because it is easily missed particularly at early stages when the tumor’s extension remains inside the small vessels of myometrium and cannot be detected with facility. The median age of diagnosed cases is 47 years.

Clinical presentation
Clinical onset of these tumors usually reflects the extension of the lesions. The majority of the patients present with numerous non-specific symptoms that include vaginal bleeding, pelvic pain, dyspnea, syncope, and congestive heart failure. Other symptoms include fatigue, abdominal pain, ascites, peripheral edema, and deep vein thrombosis. Predominant cardiac symptoms have been reported in 10% of the patients, and in 50% of them uterine enlargement is observed. However, the patients may be completely asymptomatic, and correct diagnosis relies on a higher index of suspicion.

IVL should be suspected when extraterine tumor is observed in the form of wormlike or nodular plugs within pelvic veins during operation or unexpectedly after microscopic examination of a hysterectomy specimen.

Imaging
Echocardiography
In patients with intracardiac leiomyomatosis, transthoracic echocardiography can show the presence of a free-flowing echogenic intracardiac mass, in the right cavities or in the pulmonary arteries. Tricuspid regurgitation can also be shown. Transesophageal echocardiography usually reveals an elongated, mobile, serpent-like polypoid mass proceeding from the inferior vena cava into the right atrium and ventricle, passing through the tricuspid valve.

Computed tomography and magnetic resonance
Magnetic Resonance and 16-, 32-, 64- and 128-slide multidetector computed tomographic angiography are the most sensitive methods to reveal IVL even in early stages without intracardial leiomyomatosis. Heterogeneous uterine mass that can be seen unilaterally or bilaterally into the iliac veins and in the inferior vena cava is the most common finding. Masses in the subhepatic region extending down to...
the pelvis, tumor masses within the ovarian veins or the renal veins have also been reported.\(^3\)

**Macroscopical, immunological, and histological findings**

Excised tumors are often rubbery with a tan to whitish appearance.\(^7\) The largest lesion ever reported was 35 cm in length.\(^7\) IVL are often free-floating and elongated. Grossly, the lesion is characterized by coiled masses within the myometrium and serpentinous extensions into the uterine veins.\(^1,2\)

In immunological studies the tumor cells are diffusely and strongly positive on smooth muscle markers, including desmin and smooth muscle actin,\(^3\) confirming their smooth muscle nature. They show bizarre nuclear morphology with hyperchromatic multilobulated nuclei. The mitotic activity is low, with mitotic index of less than 1 per 50 high-power fields. The cells range from highly cellular spindle cell masses to cellular ones marked by fibrosis, hydropic change, and perivascular hyalinization.\(^1,2\) Tumors positive for CD34 are often non-thrombogenic due to the presence of an endothelial surface layer.\(^1,7\)

Several reports included immunohistochemically positive reactions of the intravascular parts of the tumor\(^9\) with antibodies against estrogen and progesterone receptors, and it was suggested that a high concentration of serum estradiol and a high level of tissue estrogen receptor are related to the IVL and potentially influence the growth of the smooth muscle cells.\(^9,10\) The latter theory could be potentially confirmed because the highest incidence rate of recurrence is found in patients with normal ovarian activity. It was also suggested that occasionally hormonal therapy should be considered in cases of unresectable residual tumors.\(^9\) The detection of cytoplasmic estradiol and progesterone receptors in both the intravascular tumor and leiomyosarcoma would allow consideration of the use of an antiestrogen such as Tamoxifen to control the progress of the disease, although there is not any report of efficacy in the literature.\(^9\)

**Treatment**

Surgical resection is the treatment of choice.\(^1,2,7,10\) Attempts must be made to remove the entire neoplasm, which usually involves hysterectomy.\(^1\) Incomplete excision can result in recurrence of the neoplasm. Recurrence rate of 30% from 7 months to 17 years follow-up has been reported.\(^2,7\) In a study by Butany et al.\(^1\) there was a 12.5% of recurrence after complete excision in 8.6 months' follow-up. When treating IVL, even if risk of pulmonary embolism is low, a temporary inferior vena cava filter can prevent from potential embolism during surgical maneuvers. When both abdominal and thoracic approach is needed, a two-stage operation can be considered. The slow growth of the tumor allows a safe interval between two major surgical procedures. The advantages of two-stage strategy are the shorter operative times, despite the risks of a second general anesthesia, and the less risk of bleeding, as systemic heparinization mandatory for one-stage cardiopulmonary bypass, is actually avoided. In the thoracic approach the tumor should be resected below the level of the renal veins to facilitate easier vascular control in the second-stage laparotomy.\(^3\) because higher vascular control requires mobilization of the liver via a right thoracoabdominal incision, with its associated morbidities. In addition, clamping of the cava above the hepatic vein congruence will significantly reduce the preload, necessitating an axillofemoral venous bypass.\(^3\)

It has been suggested that recurrence may show the same pattern even after hysterectomy and bilateral adnexectomy. This shows that the tumor growth is independent of the presence of the uterus and although histologically benign, might be considered clinically malignant.\(^10\) When recurrence is seen, reintervention is actually universally recommended to achieve long-term disease-free survival.\(^10\)

**Angioleiomyoma**

**Etiology/epidemiology**

Minor trauma, venous stasis and hormonal changes, especially estrogenic, have been proposed as etiological features. The presence of chronic inflammatory infiltrates in some lesions supports the venous stasis theory.\(^4\) Another theory suggests that the lesions could be hamartomatous as has been demonstrated by the presence of mature fat cells.\(^4\)

They account for 5% of all benign neoplasms of soft tissues and their prevalence in eastern South Africa is 10 times that of the Caucasian population living in temperate climates.\(^4\)

**Histology**

In 1973 Morimoto\(^11\) studied 241 cases of angioleiomyoma and classified them into three histological types:

1. Solid: The most common type which has closely packed smooth muscle and many small, split-like vascular channels. This type of tumors is three times more common in females than in males.
2. Venous: Thick, easily identifiable muscular walls distinguish this type. These tumors occur more commonly in males.
3. Cavernous: The vascular channels are dilated with less smooth muscles. This is the most uncommon type. These tumors occur 4 times more common in males than in females.

Morimoto\(^11\) also grouped these tumors into two groups: the larger group of extremity tumors, where they are mainly of the solid type, often painful, and the smaller group of head tumors, where they are usually of the venous type and painless.

**Clinical presentation**

The typical finding is a solitary, small, slow-growing, firm, mobile, subcutaneous nodule. Most of them are less than 2 cm in size.\(^4\) Pain is the most striking clinical feature of angioleiomyoma. It is often paroxysmal and is provoked by exposure to cold and wind.\(^4\)
Imaging

On ultrasound, it shows well-defined margins and a homogeneous structure, suggesting benign nature. Color-duplex shows high resistance in intratumor arteries, suggesting the presence of muscular arteries. Magnetic resonance shows the tumors hypertensive and isointense to skeletal muscle. For an extremity mass with mixed areas of hypo and isointensity to skeletal muscle of T2-weighted images and hypointense rim, a diagnosis of muscular leiomyoma should be considered.  

Treatment

Simple excision for biopsy is often curative. Recurrences have occasionally been reported.  

Leiomyosarcoma

Etiology/epidemiology

Unlike IVL, LMS are malignant neoplasms derived from vascular smooth muscle. They represent about 5–7% of all soft tissue sarcomas. They most often affect the gastrointestinal system and the uterus, less frequently the respiratory apparatus, and rarely the limbs. The adult population is most susceptible, particularly the women. A theory for the explanation of female predominance is that growth and proliferation of the smooth muscle is likely to be influenced by pregnancy and estrogenic stimulation. LMS can be distinguished as intraperitoneal and retroperitoneal, cutaneous, and other systemic arteries. Review of the published literature identified 19 reported cases of peripheral (non pulmonary/non aortic) arteries LMS. Arterial LMS are equally distributed between pulmonary artery (the most frequent localization, approximately 50% of the cases) and other systemic arteries. Review of the published literature identified 19 reported cases of peripheral (non pulmonary/non aortic) arteries LMS. They refer to 9 women and 10 men. These 19 patients ranged from 33 to 79 years old with an average age of 58.6 years. Since the initial report by Perl in 1871, there have been 218 cases of LMS of the inferior vena cava reported, and over the last 18 years 70.4% of reported LMS occurred in the inferior vena cava. The male to female ratio is 3:7 with a mean age of 56.9 ± 7.9 years. LMS have been reported to arise in the pulmonary arteries and veins with a ratio of 20:1. Pulmonary vessel LMS has a male to female ratio of 1:2. Four cases of LMS of the portal and large mesenteric veins have been reported in the literature until now.

Clinical presentation

Abdominal pain is the most common symptom for neoplasms occurring in any region of the body and is referred from 45.7% of the patients. Deep vein thrombosis or venous distension are observed in 12% and 20% of the patients respectively. Inferior limb edema is also a common symptom. When the localization is a pulmonary vessel, symptoms like palpitation, dizziness, syncopal attacks, dyspnea and eventual right-heart failure can be present. In peripheral artery localization the main symptoms are pain and vascular insufficiency. However, in approximately one third of the patients the diagnosis is incidental as the patients are asymptomatic. Therefore, the diagnosis is often delayed, despite the tumor’s large size, and it remains asymptomatic for a long time.

Diagnosis

Common laboratory tests reveal albuminuria when the hepatic or renal veins are involved. Polycythemia and microangiopathic anemia can also be observed. Gastrointestinal and intravenous contrast studies demonstrate an extrinsic mass effect when the localization is the inferior vena cava. In ultrasonography of the abdomen the tumor appears as a mass with homogeneous or heterogeneous sound patterns. Doppler ultrasound gives information about patency of the portal or systemic venous system.

Computed tomography and magnetic resonance

Computed tomography and magnetic resonance are the most sensitive examinations and confirm the presence of the tumor, its pattern or growth, relationship to the surrounding structures, and the presence of caval obstruction. On computed tomography the tumor appears as low density, solid, or heterogeneous mass compressing or silhouetting, involving or arising from the inferior vena cava. Magnetic resonance gives similar information but the sagittal section is more informative as to the extent of the tumor and tumor thrombus.

Angiography

On angiography, LMS exhibit variable degrees of vasculability. Hypervascular tumors derive their blood supply from the hepatic artery or its branches, adrenal, lumbar, gastric, pancreatoduodenal, or gastroduodenal artery. Other findings can be distortion, stretching, or compression to adjacent structures. Angiography cannot differentiate caval LMS from retroperitoneal LMS. In arterial localization of LMS, the arteriogram may confuse it with pseudoaneurysms.

Histology

LMS of the inferior vena cava exhibits a typical pattern of interlacing sweeping bundles of spindle-shaped cells with elongated, blunt-ended nuclei with a tendency to palisade. Mitotic figures can vary within the same tumor. Mononuclear giant cells can be present at a variable degree, and areas of necrosis are commonly seen. Masson’s trichrome and Van Gieson’s stain indicate the presence of collagen tissue. Immunohistochemical and ultrastructural studies reflect features found in soft tissue sarcoma of other sites. The tumor cells display desmin, vimentin, and smooth cell actin, but not S-100 protein. A high desmin immunoreactivity rate exceeding that seen in other soft tissue LMS is also noted. Myofibrils, intracytoplasmic vesicles, and occasional tight junctions between tumor cells are described.
Biological behavior

LMS of the inferior vena cava are considered to be slowly growing tumors. In a review of 89 resected and 43 non-resected LMS of the inferior vena cava,41 three cases of rather rapid growth rate were identified.62,64,68 In these cases the tumor was not present on previous laparotomy performed 6–24 months for unrelated disorders. The tumor metastasize late in the course of the disease and spreads mainly systemically and most commonly to the lungs and the liver, but no organ is exempt. Lymph node metastasis occurs less frequently.41

Management

Surgical

Complete surgical resection is the mainstay of treatment for vascular LMS.69 Whenever possible, surgical resection should be used to completely remove the primary tumor intact and en bloc with any directly involved adjacent structures that can be sacrificed. Ideally, a margin of uninvolved normal tissue would be resected with the tumor, given the high incidence of local recurrence when lesser resections are performed.36 The necessary disruption of the vascular system will usually require vascular reconstruction after resection. The location of the primary tumor and its extent will dictate the type and complexity of the reconstruction required to reestablish arterial flow or caval flow. Tumor thrombectomy alone, even if not curative, can prevent death from liver failure and right heart outflow tract obstruction in some cases.41

Radiation

Adjuvant radiation therapy, either pre- or postoperatively, decreases the rates of local recurrence of LMS.36 Some authors69,70 suggested that high-dose-rate intraoperative radiation improves local control; however, the utility of radiation therapy in this setting should be ultimately be determined by prospective randomized trials.

Chemotherapy

Effective systemic chemotherapy for the treatment of LMS of soft tissues is at least controversial.36 Toxicity is significant, and systemic chemotherapy would only be considered for large high-grade tumors, recurrent tumors, and metastatic disease. Appropriate follow-up for these tumors should monitor for focal recurrence (with CT or MRI every 3–4 months36) and for pulmonary metastasis (with CT of chest every 4–6 months36) during the first 5 years postoperatively.

Prognosis

Prognosis following complete resection varies according to the histologic features of the primary tumor. In a review of inferior vena cava LMS,41 in Grade I (with minimal, few, or less than five mitotic figures per high-power field), survival with no evidence of disease for 3 months to 13 years was noticed in 64.3% of the patients. In grade II (moderately differentiated tumor), survival with no evidence of the disease for 9 months to some years was observed in 60% of the patients, and local recurrence developed 20%. In grade III (poorly differentiated tumor, with frequent or more than 10 mitotic figures per high-power field), survival with no evidence of the disease for 2–15 months was seen in 57% of the patients, whereas systemic spread occurred within 3 months to 2 years in 43%. However, other authors62 did not find a correlation between mitotic activity and clinical outcome.

Conclusions

Vascular smooth muscle neoplasms that extend through blood vessels are extremely rare, difficult to be diagnosed early, and complex to treat.

IVL is a benign smooth muscle cell tumor that grows within the veins. It is a complex disease that carries significant morbidity, and multidisciplinary surgical approach is the key for an accurate tumor excision.

Angioleiomyoma is a benign tumor which commonly presents between the third and fifth decade of life. It is painful in over half of the cases. It should be considered in the differential diagnosis of painful nodular lesions of the extremity. It causes minimal morbidity and excision is usually curative.

Vascular LMS are potentially aggressive neoplasms. The management of these tumors is today oriented toward preoperative staging and complete surgical resection with vascular reconstruction. However, prognosis depends also on the size and the grade of the tumor. The only therapeutic modality associated with prolonged survival is complete surgical resection with clean margins, followed by adjuvant radiation therapy.

References


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