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CASE REPORT

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Leiomyomatosis with vascular invasion. A unified pathogenesis regarding leiomyoma with vascular microinvasion, benign metastasizing leiomyoma and intravenous leiomyomatosis

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Abstract Three uterine leiomyomas with vascular invasion (LWVI), two of which were associated with pulmonary leiomyomatous nodules, and a case of intravenous leiomyomatosis (IVL) invading the vena cava and extending to the right atrium, are described. Despite their histological benignity, these lesions have a strong tendency to metastasize and are closely related to the so-called benign metastasizing leiomyoma (BML). From a clinical point of view, the pulmonary nodules of LWVI are stable or slowly-growing. The IVL was a "worm-like" tumour that presented as a cardiac mass. On the basis of their histological and immunohistological features, a unified histogenetic view of LWVI, IVL and BML of the uterus is proposed. LWVI and BML may be the same pathological entity and microscopic vascular invasion may represent the metastatic mechanism of BML. Alternatively, LWVI may be the initial stage of IVL. In rare instances, IVL may be associated with distant parenchymal (pulmonary) metastases. LWVI seems to be the precursor of both BML and IVL.

Key words Leiomyomatosis · Leiomyoma with vascular invasion · Metastasizing leiomyoma · Intravenous leiomyomatosis · Uterus

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Introduction

Leiomyomatosis is defined as a neoplastic nodular and/or diffuse proliferation of histologically benign smooth muscle cells, occurring most frequently in women between the ages of 40 and 60 years. Most of the tumours arise in the uterus, the large veins (inferior vena cava and pelvic veins) and the lungs.

Intravenous leiomyomatosis (IVL) is a rare subgroup of this entity [8, 9, 21]. Despite its cytohistological benignity, it represents the most biologically aggressive counterpart of leiomyomatosis, because of the vascular invasion, and the metastatic potentiality. The vascular invasion may occur as the result of either microscopic permeation of small vessels or massive growth within large veins [3, 4, 5, 8, 9, 16, 18, 19, 20, 21, 23, 25]. Examples of uterine metastasizing leiomyoma and intravenous leiomyomatosis were first described by Steiner [24] and Marshall and Morris [17].

This study will focus on the morphological and immunohistological features of these tumours, particularly the relationship between "bulky type" intravenous leiomyomatosis, growing extensively within large veins, leiomyoma with vascular invasion (LWVI), that penetrates the leiomyomatous microvasculature, and so-called "benign metastasizing leiomyoma (BML) of the uterus".

Three cases of uterine leiomyomas with micro-macroscopic vascular invasion, two of which were associated with pulmonary localization of leiomyomatosis, and one case of intravenous leiomyomatosis originating from the uterine veins and extending to the right atrium, through the vena cava, are described. The first diagnosis of each case was made in four different laboratories of Anatomic Pathology: Padua (Italy), Minneapolis (USA), Catania (Italy), and Aviano (Italy). Case 1 has been previously reported separately by two of us [5].

Case reports

Table 1 summarizes the main clinical and pathological findings, and follow-up data of the four patients.

Case 1

The patient was admitted for a work-up of small non-calcified multiple pulmonary nodules (Fig. 1). Seven years prior to admission, she had undergone a hysterectomy for uterine leiomyoma. A wedge resection of the pulmonary middle lobe was performed. The pulmonary lesions grossly appeared as small (1 cm diameter max.) rounded, firm, whitish-grey nodules, with a fasciculated cut-surface.

Histologically, the lesions appear to be well-circumscribed but not encapsulated (Fig. 2). They consist of interlacing fascicles of spindle-shaped smooth muscle cells with eosinophilic and fibrillary cytoplasm and elongated nuclei with finely dispersed chromatin. No nuclear atypia or mitoses are evident. The nodules are lined by a monostratified cuboidal epithelium, which in some places extends into cleft-like spaces or forms gland-like structures. In some of them, macrophages with intensely PAS-positive, diastase-resistant, granular cytoplasm are observed (Fig. 3). Small, disseminated nodules of leiomuscular tissue, similar to those described above, are evident in the surrounding lung parenchyma. Immunohistochemically [6], the tumour cells are positive for alpha-actin and desmin. Cytoplasmic positive staining for cytokeratins PKK1, CAM 5.2, AE1, AE3, is evident in the epithelial cells that line the nodules and their pseudoglandular spaces. Macrophages are labelled by Mac 3.87 and KP1.

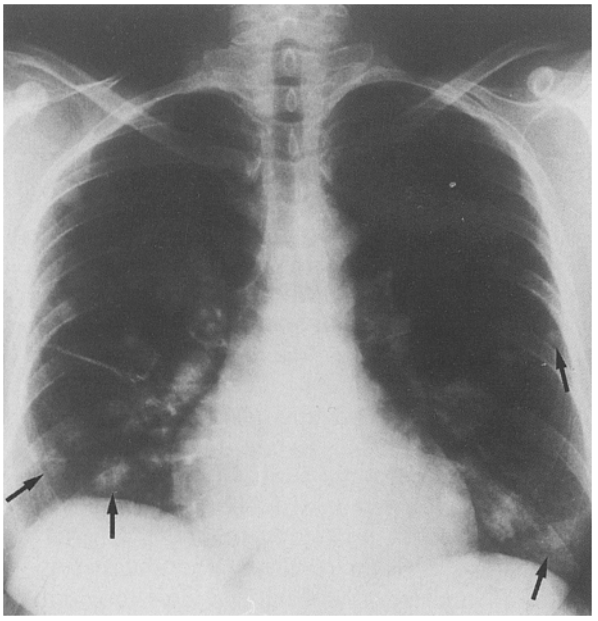

Fig. 1 Case 1. Small non-calcified bilateral multiple pulmonary nodules (*arrows*)

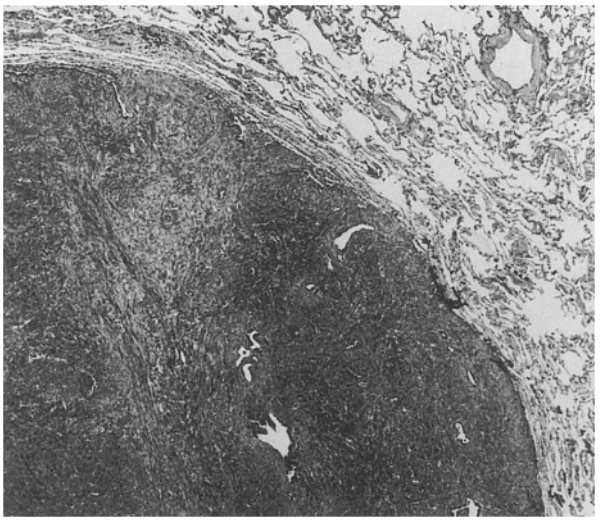

Fig. 2 Case 1. Well-circumscribed non-encapsulated pulmonary nodule with pseudoglandular spaces. ×25

Table 1 Clinico-pathological findings and follow-up data of the patients (*A&W*, alive and well)

Case	Age/sex	Clinical findings	Pathological findings	Follow-up
1 From Padua, Italy	46/F	Hysterectomy for uterine mass (1981); asymptomatic multiple pulmonary nodules (1987) symptomatic pelvic mass (1990)	Uterine leiomyoma with vascular invasion; pulmonary leiom yomatosis with gland-like spaces; pelvic leiomyoma	A&W after 3 years from removal of pelvic mass with persistent asymptomatic pulmonary nodules (CT-scan)
2 From Minneapolis Usa	69/F	Hysterectomy for uterine mass (1969); asymptomatic multiple pulmonary nodules (1969) slowly-growing since 1987; resection of the middle lobe of right lung (1989)	Uterine intravenous leiomyomatosis; pulmonary leiomyomatosis with gland-like spaces	A&W at the last examination (1992) with slight enlargement of pulmonary nodules (x-ray)
3 From Catania Italy	56/F	Palpitation dyspnoea; intracardiac mass extending to the right pelvic veins through the inferior vena cava (1989); uterine enlargement; wedge resection of tumour; hysterectomy was refused (1989)	Intravenous leiomyomatosis of the uterus extending to the right atrium	A&W after 4 years from surgery
4 From CRO Aviano Italy	42/F	Pelvic pain; menorrhagia; middle sided pelvic mass originating from the uterus (1991); multiple myomectomy (1991)	Uterine leiomyoma with vascular invasion	A&W after 3 years from surgery

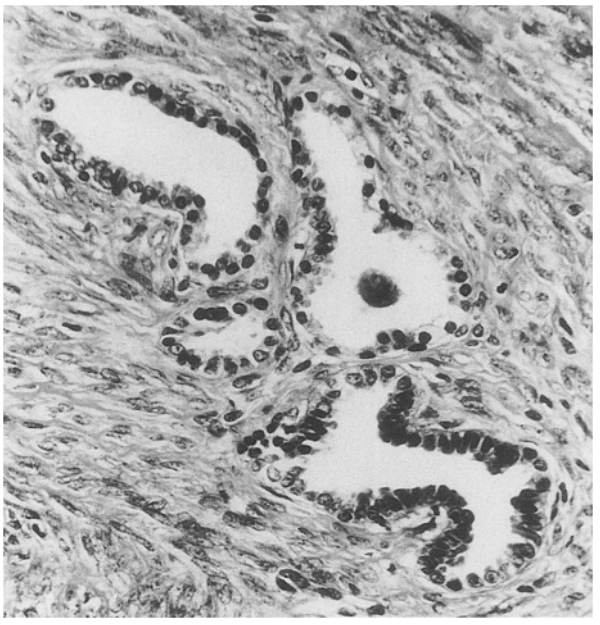

Fig. 3 Case 1. Pseudoglandular spaces lined by cuboidal epithelium with macrophages in their lumens. (PAS) ×240

The pelvic mass, which was extensively sampled, was immunoreactive with anti-desmin and anti-actin antibodies. The histopathological diagnosis of leiomyoma was confirmed.

In order to define better the pathological condition, histological slides of the uterine leiomyoma were reviewed, and the previously ignored angioinvasive features were detected. The tumour was made up of multiple nodules in the thickness of the myometrium and showed neither cytologic atypia nor mitotic activity. Six slides with tumour tissue were available for review.

Case 2

The surgical specimen of hysterectomy removed in 1969 showed multiple subserosal and intramural nodules with a fasciculated cut-surface, measuring up to 8 cm in diameter. In addition, the broad ligament was bilaterally thickened and distorted by nodular masses which appeared to be located in the uterine veins, lying free in the lumen or adherent to the intima.

Histologically both the intramural uterine neoplasms and the intravascular tumour are composed of benign smooth muscle with prominent vascularity, oedema and areas of hyaline degeneration. No mitoses are evident.

The specimens obtained from the pulmonary lobectomy in 1989, contained two firm, white, whorled oval nodules well-demarcated from the surrounding lung tissue measuring 1.8×1.5 cm in diameter. No haemorrhage or necrosis were noted.

Histologically the nodules are composed of bundles of spindle-shaped cells with fibrillary cytoplasm, without cytological atypia and virtually no mitotic activity. Gland-like spaces lined by bronchial epithelium are entrapped within this muscular tissue. Masson's trichrome stain confirmed the fibroleiomuscular nature of the lesion.

By immunohistochemistry the spindle-shaped cells show cytoplasmic positivity for desmin and alpha smooth muscle actin. Pseudoglandular spaces are positive for cytokeratins.

Case 3

The resected cardiac tumour mass, occupying the right atrium and extending to the right pelvic veins through the inferior vena cava, was a firm, white, worm-like mass, measuring 25 cm in length

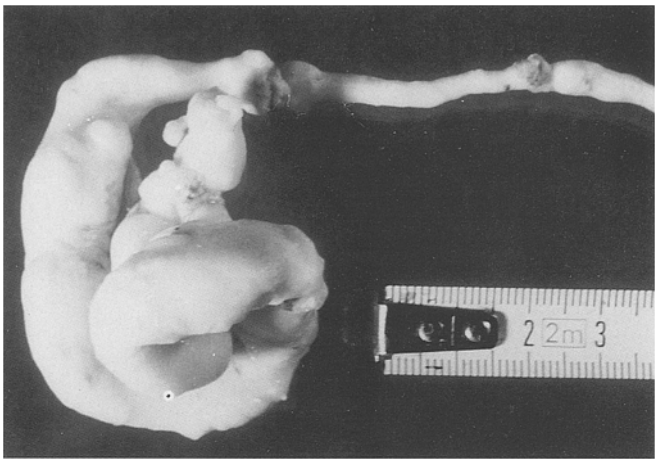

Fig. 4 Case 3. Intravenous leiomyomatosis. Intracaval worm-like, white mass, measuring 25 cm in length

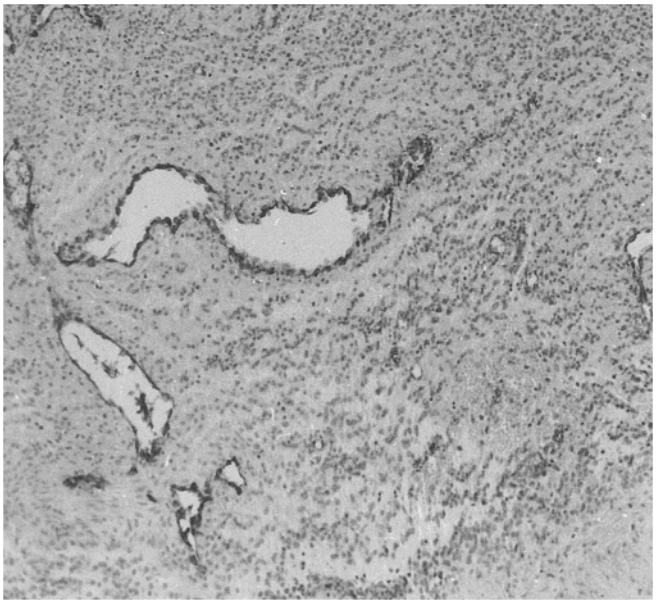

Fig. 5 Case 3. Intravenous leiomyomatosis. Endothelial lining of the blood vessels expressed Factor VIII-related antigen (avidin-biotin peroxidase complex stain). ×60

(Fig. 4). Histological examination shows that it is mainly composed of muscular blood vessels of various sizes and spindle-shaped or polygonal cells which are sometimes immersed in a myxoid and hyalinized matrix. The cytoplasm is eosinophilic and fibrillary. There is extensive fibrosis and calcification within the tumour, but neither necrosis nor pleomorphic mitotically-active tumour cells are seen.

Immunohistochemically, the endothelial lining of the blood vessels reveals the Factor VIII related antigen (Fig. 5). Most tumour cells are positive for desmin and smooth muscle specific actin, while weak expression of vimentin is restricted to about 40% of the cells.

Case 4

The surgical specimens from multiple myomectomy consisted of three firm nodules with a max. diameter of 1, 1.5 and 7 cm. On section, they were whitish with a fasciculated cut-surface.

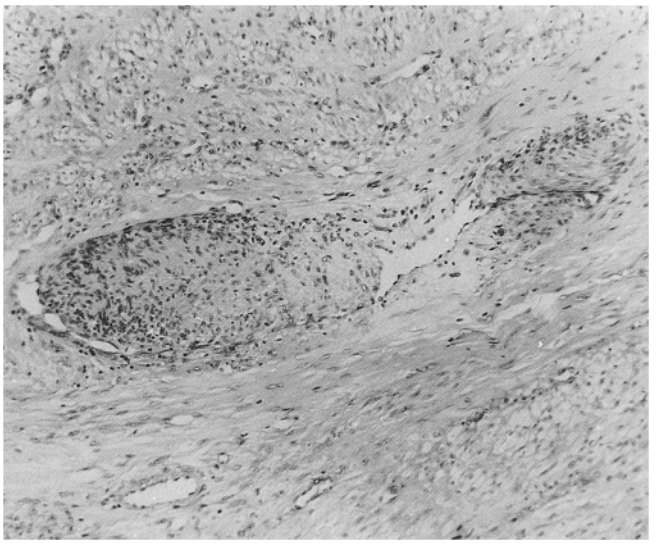

Fig. 6 Case 4. Uterine leiomyoma. Microscopic intravascular pattern of growth. ×100

Histologically, the nodules are composed of bundles of spindle-shaped cells, devoid of cytologic malignancy, that frequently show a microscopic intravascular pattern of growth (Fig. 6). Immunohistochemical studies, using the antibodies against Factor VIII-related antigen desmin and smooth muscle actin (HHF 35), confirm the presence of endothelium-covered proliferations of smooth muscle within the lumens of the vessels.

Discussion

It has been shown that histologically benign typical leiomyomas may invade blood vessels. Their mitotic index is low and there are no quantitative differences between conventional leiomyoma and those with vascular invasion in S-phase fraction of the cells [10]. The angioinvasive tumours have been defined as either intravenous leiomyomatosis or leiomyomas with vascular invasion. The former refers to a cord-like type of growth inside the lumens of large veins, and the latter to microscopic vascular invasion [8]. Histological variants of IVL, similar to those of conventional leiomyoma, have been described [4, 8, 9]. An angiomatoid pattern [16, 19], resulting from the presence of thick-walled blood vessels within the leiomyomatous proliferation may also occur, as in our case 3.

A unified histogenetic view regarding IVL and LWVI has been proposed [11]: IVL would be the macroscopic counterpart of LWVI, the latter being the initial stage of the pathological condition. This unified histogenetic view is in keeping with the notion that the tumour originates in either the musculature of the veins – uterine or extrauterine – or the uterine leiomyomas [18]. Another entity, named benign metastasizing leiomyoma [1, 24], shows some clinico-pathological similarities to IVL and LWVI. The conflicting terminology, namely "benign" and "metastasizing", reflects its benign histological appearance in contrast to the presence of metastases from the primary site, which is generally the uterus, to other organs such as lung, lymph nodes, bone, skeletal muscle, subcutaneous tissue, retroperitoneal space [1, 2, 4, 22].

Although some authors deny any relationship between BML, LWVI, and IVL [16], the metastatic potential of BML must involve vessels as a route for diffusion of the muscle cells, implying invasion of the blood vessels by the tumour [9, 18]: our cases 1 and 2 support this opinion. We suggest that there are no differences between LWVI and BML [18], and that cases of BML without histological evidence of vascular invasion may be due to insufficient sampling of the primary tumour [20].

Furthermore our case 2 is an interesting example of IVL metastasizing to the lungs. Other investigators [8, 23] have also described similar cases indicating a close relationship between LWVI and IVL. This observation refutes the assumption that IVL is able to grow only within large veins, lacking metastatic potential.

IVL and LWVI may thus be the same pathological entity with different clinical features. In IVL, intravenous growth predominates, and may extend along the vena cava to the right atrium. Metastases beyond the primary location of the tumour are the main feature of LWVI-BML.

The diagnosis of pulmonary localization of leiomyomatous tissue in the female sex raises the question of the existence of primary forms of pulmonary leiomyomatosis. The cases of Kaplan and colleagues [14] and the description of another case involving a 9-year-old female child [13] are in keeping with this possibility.

However, some authors [12, 26] considering pulmonary leiomyomas as a secondary lesion, stress the very frequent association of pulmonary and uterine leiomyomas and some also propose various pathogenic explanations, including the view that multiple localizations may derive from a multifocal origin [7]. However, multifocal origin, which may explain some cases involving multiple synchronous tumours without lung involvement (leiomyomatosis peritonealis disseminata) is debatable for most of the cases in which there are only uterine and pulmonary lesions. In such cases a close relationship between a primary uterine and a secondary pulmonary localization is more plausible.

This study indicates that vascular invasion in leiomyomas of the uterus may occur both microscopically and macroscopically, but that these invasions seem to be only different aspects of the same pathological condition. No clinico-pathological differences emerge between vascular invasion inside or outside the leiomyomas, as demonstrated in our cases 1 and 2. Furthermore our case 1 is an example of tumour that was presumably incompletely excised at the time of hysterectomy. This would explain the persistent or recurrent pelvic tumour which was found 10 years after hysterectomy.

Long-term follow-up of patients with intravascular leiomyomatosis is recommended [15].

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