

CASE REPORTS

Axillary and perianal leiomyosarcoma: report of two cases

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Abstract

Soft tissue leiomyosarcoma is a relatively rare malignant tumor. It may be difficult to be distinguished from gastrointestinal stromal tumors and Schwann cell neoplasms. To make a correct identification of soft tissue leiomyosarcoma, immunostaining with several smooth muscle differentiation markers (actin, calponin and desmin), and negative staining results with S100 (to rule out Schwann cell neoplasm), c-kit and CD34 (to rule out gastrointestinal stromal tumors) is needed. Prompt diagnosis and referral are desirable, since the size of the tumor at presentation is a continuous variable for the risk of local recurrence and metastatic disease. Chemosensitivity varies according to the tumor subtype, and the tumor grade, the patient's age, performance status, and the timing of metastatic disease further influence the likelihood of a response and survival. Chemotherapy is palliative for most patients with unresectable or metastatic disease. Ifosfamide and doxorubicin are routinely used in this setting; doxorubicin as a single agent is considered the drug of choice.

Keywords: soft tissue leiomyosarcoma, immunostaining, S100.

✉ Introduction

Leiomyosarcoma is an aggressive soft tissue sarcoma derived from smooth muscle cells typically of uterine, gastrointestinal or soft tissue origin. Sarcomas are malignant tumors arising from mesenchymal cell lines. They comprise a heterogeneous group of cancers, each with unique clinical, histological, and radiographic characteristics. Soft tissue sarcomas account for 0.7% of malignancies. Sarcomas are generally classified according to the normal cell line that they most closely resemble. Of all soft tissue sarcomas, approximately 5–10% are leiomyosarcomas [1]. Leiomyosarcoma of soft tissue is thought to arise from the smooth muscle cells lining small blood vessels. Leiomyosarcoma can also arise directly from the viscera, including the gastrointestinal tract and uterus. Leiomyosarcoma of soft tissue is discussed in this article, while the companion article addresses the uterine form of this disease. Gastrointestinal lesions are not included in this discussion. Primary leiomyosarcoma of bone is a distinct entity, which is quite rare. While histologically similar, soft tissue leiomyosarcoma has classically been subdivided into three groups for prognostic and treatment purposes: leiomyosarcoma of somatic soft tissue, cutaneous leiomyosarcoma and leiomyosarcoma of vascular origin [2]. A group of patients with leiomyosarcoma in the setting of immune dysfunction is also being discovered [3]. Leiomyosarcomas are

aggressive tumors that are often difficult to treat. The prognosis is poor, with survival rates among the lowest of all soft tissue sarcomas [4].

✉ Patients and Methods

We will describe two cases of patients with leiomyosarcoma of soft tissue with localization in right axilla and left ischio-rectal fossa.

The patient, C.V., 77-year-old man, OF 57213 from 03.11.2008, with a mass of the right axilla, functional impotence of the right upper limb, paresthesia of the right arm. From antecedents results that the patient was surgical treated for right axillary tumor in one year ago, the histological diagnosis was liposarcoma.

The physical examination showed the right axillary mass, measuring 8×12 cm, ovallary shape, unmoved consistency, irregular surface, mobilization on the deep plans, adherent on the superficial plans (Figure 1). The pulse was present of the right radial artery. The laboratory data on admission: Hb 12.3 g/dL, L 7800/mm³, glycemia 86 mg%, urea 42 mg%, Quick T. 100%, ASAT 15 iu, ALAT 18 iu, ECG normal, Rx chest: right pronounced broncho-vascular design hilio-basal.

On 04.11.2008, we perform the surgical treatment through axillary abord and we constate axillary-mass, round-ovallary shape, 10×8 cm adherent on the axillary fascia, but with mobility on the axillary vein and artery and on the brachial plexus.

Postoperative evolution was favorable. It was discharge in a good condition.

On light microscopy examination, the tumor mass was composed of spindle cell tumor composed of eosinophil mesenchymal cells forming fascicles intersecting at right angles with pushing margins. Tumor cells possessed hyperchromatic cigar-shape nuclei, prominent nucleoli and typical and atypical figures, epithelioid cells with round eosinophilic cytoplasm.

Immunohistochemical examinations cytokeratin (CKAE-1AE3), epithelial membrane antigen (EMA), S100-protein, CD117 ended with negative results. Tumor cells showed strong positivity for vimentin, desmin and smooth muscle actin (SMA) antisera. Ki-67 proliferation marker showed positivity in 30% of tumor cells.

The patient, R.M., 72-year-old female, admitted and operated in Surgical Clinic of Emergency County Hospital of Craiova for tumor of ischiorectal fossa. Postoperative evolution was favorable. The patient was discharge in a good condition after seven days. Immunohistochemical examinations showed: strong positivity for vimentin, desmin and smooth muscle α -actin (SMA) antisera. CD117-negative results in the tumor cells, CD34-negative results in the tumor, positive in vessels; p53-protein negative results in the tumor; S100-protein negative results; glial fibrillary acid protein (GFAP) slow focal positive results in the tumor; Ki-67 proliferation marker showed positivity in 10% of tumor cells.

The patient was treated with six cures of chemotherapy with methotrexate, antifolan, ifosfamide, cisplatin. Evolution was favorable so far six months ago when the patient remarked the reappearance of the tumor to ischiorectal fossa.

The patient was admitted in the Second Surgical Clinic of Emergency County Hospital of Craiova with tumor recidivated of left ischiorectal fossa. Physical examination showed recidivated tumor of left ischio-rectal fossa, measuring 3×4 cm, adherent of the superficial plans of anal canal (Figure 2). Rectal examination: anal canal and rectal ampulla normal aspect. Vaginal examination: vagina walls normal aspect.

The laboratory data: Hb 12.7 g/dL, L 8800/mm³, glycemia 96 mg/dL, urea 32 mg%, Quick T. 100%, ASAT 13 iu, ALAT 17 iu. ECG: sinus rhythm, QRS axe 60°, subdenivelated of ST segment in V1, V2, V5, V6. Rx chest: right pronounced broncho-vascular design hilio-basal.

Computerized tomography (CT): Liver with normal dimension and hemangioma in the VIIth segment, 20 mm in diameter. Pancreas, spleen, kidney, urinary bladder normal aspect. Normal aspect of ischio-rectal fossa and normal density of internal obturatorius muscle and levator ani muscle.

MRI pelvis: corpus uteri measuring 4.7/2.5 cm, with tumoral mass 5 mm in diameter, in the body zone of corpus uteri, fibromatous aspect. Ovary-shape tumor, measuring 20/13 mm, left perianal localization, hypo-signal on T1 – weighted images and greater signal intensity on T2 – weighted images, without pelvic adenopathy and without peritoneal fluid. Urinary bladder had a normal aspect (Figure 3).

On 15.01.2009, we performed the surgical treatment and we noticed a tumoral mass measuring 2.5/3 cm situated left side of anal canal, oval shape unmoved consistency, irregular surface. We removed this tumor upon healthy tissue. Postoperative evolution was favorable. It was discharged in a good condition.



Figure 1 – Right axillary mass, measuring 8×12 cm, ovalary-shape, unmoved consistency, irregular surface, mobilization on the deep plans, adherent on the superficial plans.



Figure 2 – Recidivated tumor of left ischio-rectal fossa, measuring 3×4 cm, adherent of the superficial plans of anal canal.

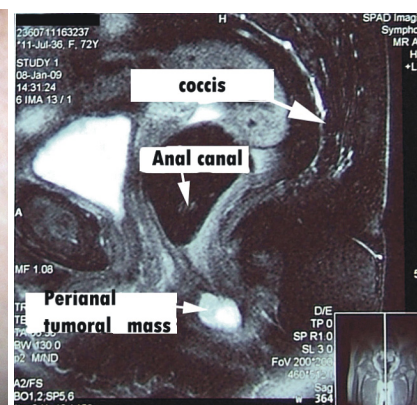


Figure 3 – Ovalary-shape tumor, measuring 20/13 mm, left perianal localization, hypo-signal on T1 – weighted images and greater signal intensity on T2 – weighted images.

Results

Primary cutaneous leiomyosarcoma are uncommon soft tissue tumors with more than 100 cases reported in literature. Leiomyosarcoma are divided into two subtypes depending on the location. The superficial dermal form of leiomyosarcoma is thought to arise from the arrector pili muscles whereas the deep subcutaneous

type is thought to arise from the smooth muscle of the vascular wall. Histologically, the tumor is composed of highly cellular fascicles of spindle-shaped cells. The fascicles are arranged in irregular interlacing bundles, often intersecting at right angles (Figure 4).

The cells have nuclei that are elongated and blunt-ended giving a “cigar” appearance. The degree of differentiation may vary within a single tumor. In some well-

differentiated areas, the cells resemble the typical smooth muscle cells of leiomyomas. Other areas may be poorly differentiated, with extensive cellular atypia and prominent nuclei and nucleoli. Mitotic figures are seen throughout the lesion. Criteria for malignancy remain controversial. Generally accepted, features of malignancy, include the presence of mitosis of the least one per 10-high-power fields, high cellularity, significant nuclear atypia and tumor giant cells (Figure 5).

Therefore, careful scrutinize of cytological details in multiple sections, clinicopathological correlation and immunohistochemistry are mandatory for definition

diagnosis. Unusual morphologic variants of cutaneous leiomyosarcoma have been described that can introduce difficulties for diagnosis including epithelioid, granular cell, desmoplastic, inflammatory and myxoid leiomyosarcoma. If the lesion is poorly differentiated, immunohistochemical studies can differentiate the muscular origin of the lesion. Classical immunophenotyping of leiomyosarcoma comprises positive vimentin, desmin and smooth muscle actin (SMA) staining. Our results confirm vimentin and SMA staining in both cases (Figures 6 and 7).

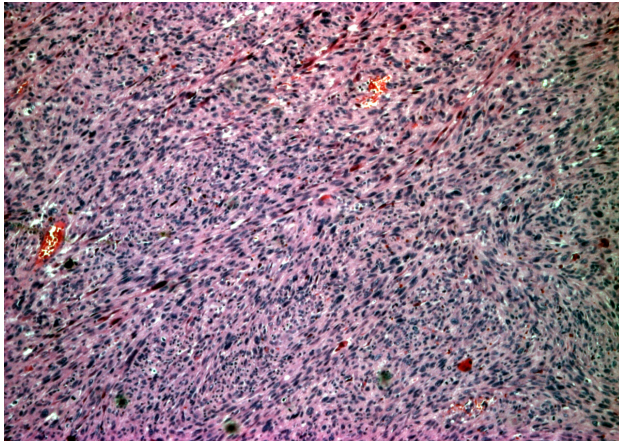


Figure 4 – The tumor is composed of highly cellular fascicles of spindle-shaped cells. The fascicles are arranged in irregular interlacing bundles, often intersecting at right angles (HE stain, ×100).

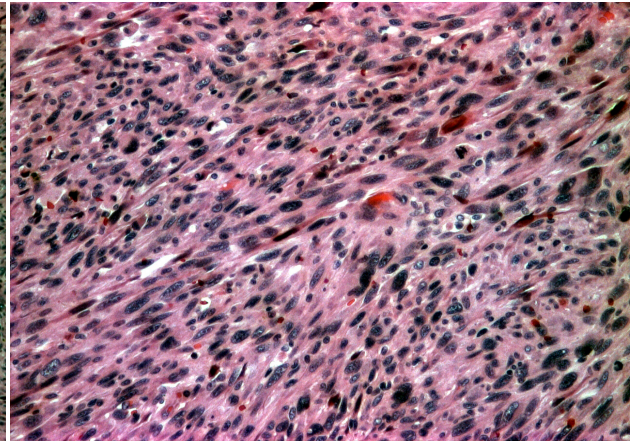


Figure 5 – Tumor cells possessed hyperchromatic cigar shaped nuclei, prominent nucleoli and numerous typical and atypical mitotic figures (HE stain, ×100).

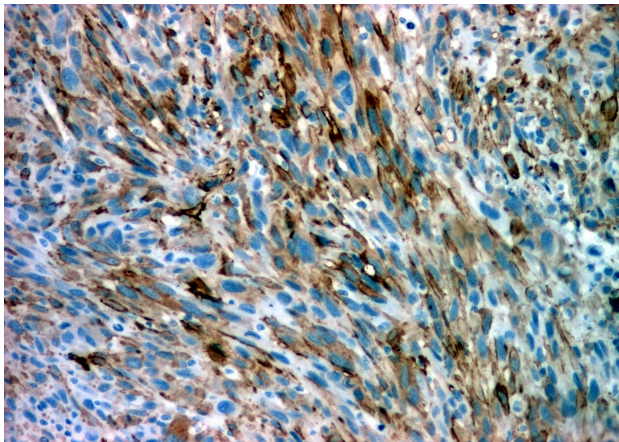


Figure 6 – Smooth muscle alpha actin, marker for differentiate smooth muscle, positive intracytoplasmic in tumoral cells. Tumor cells showed strong positivity for smooth muscle actin antiserum (×100).

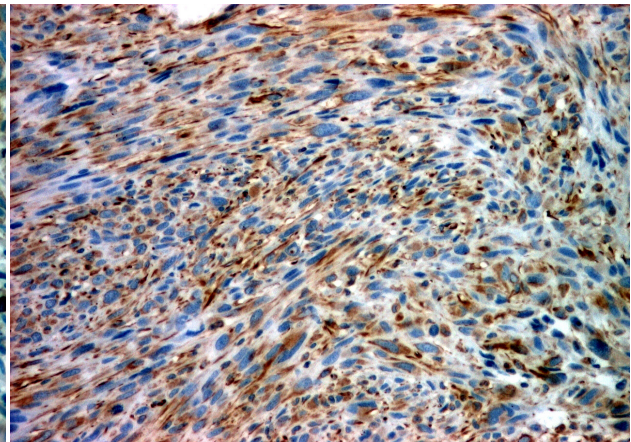


Figure 7 – Vimentin, mesenchymal marker, positive intracytoplasmic in tumoral cells, ×100.

SMA seems to be more sensitive than desmin for smooth muscle tumors, although the antibody is not always specific. Desmin staining is sensitive and specific for both normal and affected muscle tissue, but it does not differentiate between leiomyosarcoma and rhabdomyosarcoma. In our cases, both cases showed positive immunostaining with desmin. Some authors emphasize the polymorphism of the immunophenotype expression and the importance of using several antibodies. Pan-muscle actin HH35 is sometimes present focally. Like desmin, this marker is not specific because it can stain myofibroblasts and striated muscle.

Several benign or malignant tumor lesions are difficult to distinguish from leiomyosarcoma namely desmoplastic malignant melanoma (value of PS100 and HMB45 staining), spindle-cell angiosarcoma, spindle-cell synovial sarcoma, malignant striiform pleomorphic histiocytoma, schwannoma or plexiform neurofibroma and atypical fibroxanthoma.

Immunohistochemistry is a valuable diagnostic tool in these difficult cases. Electron microscopy can reveal intracytoplasmic myofilaments in cases, which are difficult to diagnose.

CD117 is a 145–160-kD cell membrane protein

encoded by the c-kit proto-oncogene (chromosome 4q11–12). The protein is a type III tyrosine kinase growth factor receptor for stem cell factor, also known as mast cell growth factor. CD117 is required for development and growth of a large number of cells expressing this protein. CD117 is expressed in mast cells, melanocytes and interstitial cells of Cajal.

S100 protein is a 21-kD highly acidic and water-soluble protein first isolated from brain but later shown to be produced by a wide variety of normal and neoplastic cells of mesodermal, neuroectodermal and epithelial origin. S100 protein may be found in the cell membranes, cytoplasm and nuclei. S100 protein is present in glial cells, Schwann cells and satellite cells (but not perineurial cells), melanocytes, myoepithelial cells, some glandular epithelia (breast, kidney), skeletal and heart muscle cells, fat cells, chondrocytes and follicular dendritic cells. In both cases, in our study S100 protein

was negative (is positive in liposarcoma) (Figure 8).

Leiomyosarcomas demonstrate a moderate degree of heterogeneity, not only at a conventional histological level but also in immunophenotypic terms. Classically, these tumors are potentially encountered in the soft tissues, as well as several viscera and selected bones. They are composed of interweaving fascicles of relatively uniform spindle cells, showing blunt-ended nuclei and fibrillar eosinophilic cytoplasm. However, myxoid, epithelioid and pleomorphic variants of leiomyosarcomas have been well documented, and these often represent challenging differential diagnosis problems. From an immunohistochemical perspective, the most frequent antigenic profile seen in smooth muscle sarcomas is that of positivity for vimentin, actin, desmin and collagen type IV or laminin with non-reactivity for keratin, EMA, S100 protein, myoglobin, HMB45, CD31, CD34 and CD57 (Figure 9).

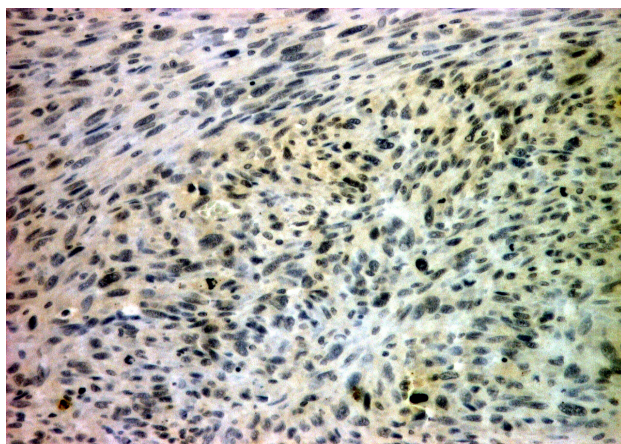


Figure 8 – S100-protein negative in tumoral cells (is positive in liposarcoma), $\times 100$.

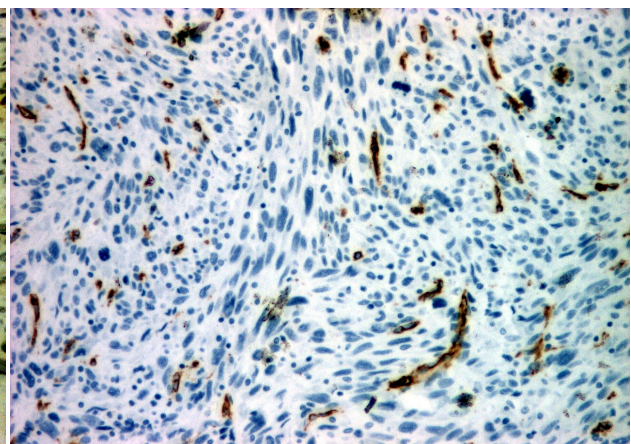


Figure 9 – CD31 endothelial marker showed intra-tumoral neovessels, $\times 100$.

However, leiomyosarcomas that arise in the uterine myometrium, urinary bladder, and pelvic soft tissues often express keratin in an “aberrant” fashion, as proven with immunoblotting studies done on fresh tumor tissue.

S100 protein may conversely be observed in superficial smooth muscles tumors – perhaps because of analogies with arrectores pilorum of the skin – and CD57 reactivity is apparent in roughly 50% of deep leiomyosarcomas with a “vascular” appearance. Miettinen (1988) has drawn attention to the fact that cytoplasmic staining for EMA is also evident in some smooth muscle tumors. However, this pattern is essentially meaningless, with only plasmalemmal labeling for EMA representing an epithelial lineage-specific profile of staining. Another phenotypic peculiarity of leiomyosarcomas is their tendency to express the Mic-2 protein, recognized by the monoclonal antibodies HBA71. Nevertheless, we have found it useful diagnostically in selected circumstances where aberrant keratin expression makes the interpretation of leiomyosarcomas somewhat tenuous, because sarcomas (which are routinely keratin-positive and may show “divergent” myogenic differentiation) have not been labeled for Mic-2.

A point of some importance is considering the immunophenotype of leiomyosarcomas is the coexpression of

“muscle-specific” (MSA) or “smooth muscle” actin (SMA) isoforms with desmin. A common practice in some centers is to rely exclusively on one of these markers to recognize all examples of leiomyoma and leiomyosarcoma. This is a flawed approach, in our opinion, because myogenic determinants are not necessarily synthesized by neoplastic smooth muscle cells in a syntonic fashion. In other words, SMA has now been reported in a considerable number of other lesions, including many with a myofibroblastic nature (Figure 10).

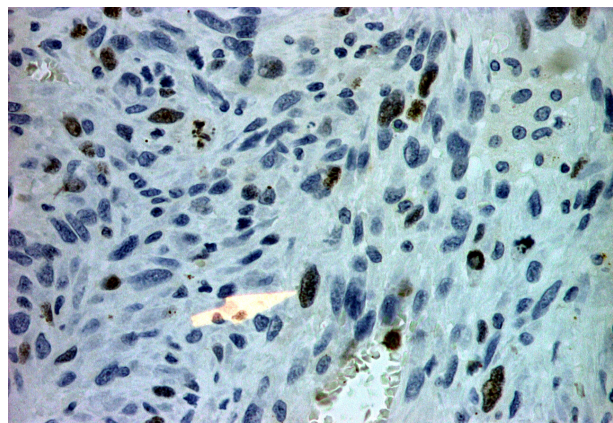


Figure 10 – Ki-67 proliferation marker showed positivity in 30% of the tumor cells, $\times 200$.

Discussion

There are no specific clinical features diagnostic of leiomyosarcoma of soft tissue that distinguish these tumors from other soft tissue sarcomas. Women are affected more than men (2:1), with the disease typically occurring in the 5th and 6th decades of life. This gender distribution may reflect the proliferation of smooth muscle that can occur in response to estrogen. The most common site of involvement of leiomyosarcoma is the retroperitoneum, accounting for approximately 50% of occurrences [5]. Leiomyosarcoma of somatic soft tissues, like other soft tissue sarcomas, often present as an enlarging, painless mass. Although these tumors are generally associated with small blood vessels, they usually do not present with signs or symptoms of vascular compression. However, when leiomyosarcoma arises from a major blood vessel, symptoms of vascular compromise or leg edema may be present, as well as neurological symptoms such as numbness from compression of an adjacent nerve. Soft tissue leiomyosarcoma typically affects adults, however it can present in childhood [3]. Most soft tissue sarcomas have no clearly defined etiology, although multiple associated or predisposing factors have been identified. Typically, once a lesion suspicious for a sarcoma has been discovered, diagnosis and staging studies are performed simultaneously. Initial imaging should include plain radiographs of the affected area, an MRI of the lesion, and a chest CT-scan. As Angiography may be a useful modality in cases involving a major blood vessel. CT scanning of the chest is useful to evaluate for the presence of metastatic disease in the lungs. The role of PET-scanning has not been studied in particular reference to leiomyosarcoma, but has been studied in other soft tissue sarcomas with early promising results. Biopsy is necessary to establish a specific diagnosis of leiomyosarcoma, and is often accomplished using a CT-guided core needle biopsy. This technique can be performed in most cases with less morbidity than an open incisional biopsy. Histologically, soft tissue leiomyosarcomas that arise in different anatomic locations are similar. However, based on the location of the tumor, prognosis and possible treatments differ. For this reason, leiomyosarcoma of soft tissues is divided into four groups: leiomyosarcoma of soft tissue retroperitoneal somatic soft tissue, leiomyosarcoma of cutaneous origin, leiomyosarcoma of vascular origin (large vessel), leiomyosarcoma in the immunocompromised host. Furthermore, there are sporadic case reports of primary leiomyosarcoma of bone, a clinically distinct entity.

Immunohistochemical analysis suggests that the cell line of origin of leiomyosarcoma is the smooth muscle cell. The most common site of leiomyosarcoma of soft tissue is the retroperitoneum, accounting for 50% of all cases [5]. Smooth muscle sarcomas arising from the abdominal viscera or uterus are considered to be distinct disease entities. Other sites of involvement include the deep soft tissues of the extremities and are referred to as leiomyosarcoma of somatic soft tissue [2]. Soft tissue leiomyosarcoma was at one time believed to arise from

leiomyomas, however, this is now thought to be an extremely rare occurrence. Most malignant leiomyosarcomas arise independently, and are not associated with benign tumors. Histological studies of somatic soft tissue leiomyosarcomas have shown that many, if not all, of these tumors arise directly from the smooth muscle cells lining small blood vessels. When the retroperitoneum is involved, presenting symptoms are usually vague abdominal discomfort, an abdominal mass and weight loss. Retroperitoneal leiomyosarcoma is an aggressive disease that is often not amenable to complete surgical resection. Leiomyosarcoma can arise within the dermis. When this occurs, it is referred to as cutaneous leiomyosarcoma. Unlike other forms of leiomyosarcoma, men are affected more than women at a ratio of 2:1 [6]. These lesions are typically small when first diagnosed (1–2 cm), and prognosis is generally good [7]. When leiomyosarcoma develops within the dermis itself, it is thought to be derived from the pillar arrecti [8]. Tumors that develop within subcutaneous tissue arise from small or microscopic vessels and should be considered leiomyosarcoma of somatic soft tissue. The behavior of these tumors is more consistent with that of deeper tumors than intradermal tumors. When the lesion is confined to the dermis, metastasis typically does not occur [6]. Deeper lesions can metastasize in up to 30–40% of cases, usually hematogenously to the lungs [7]. Treatment consists of wide resection, and is often curative when the lesion is initially confined to the dermis, regardless of histological grade.

The annual new cases in the U.S. are over 6000. The five-year survival rate after diagnosis is about 50%. What kind of biopsy is appropriate in the diagnostic process and treatment of a patient with a soft tissue mass? After taking medical history and performing physical examination, the tumor is first locally staged with MRI- or CT-scan before any biopsy [9]. Positron emission tomography might allow differentiation between a benign and malignant tumor [10]. The diagnostic accuracy of a CNB in referral centers is equivalent to incisional biopsies, although it may be difficult to differentiate a low-grade malignancy from a benign tumor mass [11]. The histological subtype and grade of the STS can be determined for the vast majority of core needle biopsies, and pathologists experienced in examining STS have a reproducible diagnostic accuracy approaching 95% to 99% when comparing core needle with incisional biopsy diagnostic approaches [11]. Incisional biopsy is the diagnostic procedure of choice if needle biopsy is not feasible; it provides sufficient tissues for histological diagnosis as well as other laboratory studies that may be occasionally useful, such as immunohistochemical or chromosomal analyses.

Sarcomas are still diagnosed after an unplanned excision, the so-called 'whoops approach'. The pathology report will describe an R1 (microscopically involved margin) or R2 (macroscopically involved margin) resection requiring further therapy. If further surgery may render a patient disease-free (R0 resection) or an R2 might become an R1 resection, re-resection is essential. If this aggressive surgical policy is applied, these patients are not apparently at risk for a worse

outcome as compared with patients primarily referred to a multidisciplinary sarcoma unit.

Combining functional imaging with anatomic detail may aid in the diagnostic effectiveness of both types of imaging techniques. For example, positron emission tomography (PET) scanning combined with MRI [12] can increase the utility of these techniques in certain specific situations. Magnetic resonance spectroscopy may be useful in some circumstances, such as assessing patient responses to neoadjuvant chemotherapy when resection has not yet been performed [13].

Soft tissue leiomyosarcoma was classified based on salient gene expression characteristics. Three types of leiomyosarcoma were proposed: (1) "simplification" of gene expression in leiomyosarcoma, characterized by dramatic down regulation of large number of genes; (2) "inflammation related" gene expression, characterized by the prominent presence of lymphocyte specific genes in the analysis; and (3) "neural" gene expression, characterized by neuronal gene expression. Cytologic analysis of fine-needle aspirates alone can be used to diagnose recurrent tumor [14] or nodal metastases. Regardless of how biopsy material is obtained, the specimen is best evaluated by a pathologist specializing in soft-tissue diseases.

Histological subtype should also be specified and may occasionally require immunohistochemical analysis, cytogenetics, or even electron microscopy. However, there is a high degree of discordance (2% to 40%) [15] even among expert sarcoma pathologists regarding STS histological subtyping and grade assignment, emphasizing the usefulness of histological peer (and even expert) review, as well as the importance of developing objective and standardized methods for sarcoma histopathological typing and grading.

Although the presence of regional lymph node involvement is considered stage IV disease, recent studies [16] suggest that nodal status may not confer as ominous a prognostic impact as distant metastatic disease. These contemporary analyses suggest that isolated lymph node metastases may more closely resemble an AJCC stage III rather than stage IV survival pattern. This possibility raises the question about appropriate management of lymphatic metastasis-prone STS histological subtypes, such as epithelioid sarcoma or synovial sarcoma, including the specific issue of whether such individuals should be offered sentinel node evaluation as part of their treatment program, perhaps under the aegis of a prospective clinical trial [17].

Local recurrent tumor, positive surgical margins, >50-year-old, >20 mitoses per high power field are adversely associated with survival.

Chemosensitivity varies according to the tumor subtype, and the likelihood of a response and survival is further influenced by the tumor grade, the patient's age, performance status, and the timing of metastatic disease [18]. Leiomyosarcoma, for example, responds variably to conventional chemotherapy, depending on the site and grade of the tumor. Uterine leiomyosarcoma is particularly aggressive, but it may respond to high-dose gemcitabine with docetaxel. Facial and scalp angio-

sarcoma may respond to paclitaxel [19], and taxanes may have broader utility against angiosarcomas at other sites. A pegylated liposomal formulation of doxorubicin (with reduced toxicity) [20] has also been reported to be active against angiosarcomas [21].

Chemotherapy is palliative for most patients with unresectable or metastatic disease. Ifosfamide and doxorubicin are routinely used in this setting; doxorubicin as a single agent is considered the drug of choice. Recent studies have reevaluated ifosfamide dosing, [22] high-dose ifosfamide with doxorubicin is commonly used for younger patients with aggressive tumors; response rates of approximately 50 to 60% have been reported. It remains unclear whether this approach improves survival, which is about 12 months in this situation [18].

Trabectedin (Yondelis, PharmaMar), a natural product from the marine tunicate *Ecteinascidia turbinata* that selectively inhibits DNA-transcription, [23] is a new agent that has shown some activity in advanced disease refractory to conventional cytotoxic drugs. It appears to induce a low rate of objective remission (4%) but a high rate of disease stabilization (a 24% rate of progression-free survival at six months), though it is moderately toxic [24].

✚ Conclusions

Surgery is the mainstay of treatment for soft-tissue sarcomas. Neoadjuvant or adjuvant radiation therapy is appropriate in some circumstances where local control is an issue. Radiotherapy is useful in selected cases. Chemotherapy is employed for the treatment of systemic disease. Conventional chemotherapy has little effect on the outcome of most tumors, but the availability of novel targeted agents may drastically improve the prognosis of some soft-tissue sarcomas, as has been demonstrated with imatinib in the case of gastrointestinal stromal tumors. Prompt diagnosis and referral are desirable, since the size of the tumor at presentation is a continuous variable for the risk of local recurrence and metastatic disease.

References

- [1] GUSTAFSON P, WILLÉN H, BALDETROP B, FERNÖ M, AKERMAN M, RYDHOLM A, *Soft tissue leiomyosarcoma. A population-based epidemiologic and prognostic study of 48 patients, including cellular DNA content*, Cancer, 1992, 70(1):114–119.
- [2] WEISS SW, GOLDBLUM JR, *Enzinger and Weiss's soft tissue tumors*, 4th edition, Mosby-Harcourt, Philadelphia, 2001, 37–51.
- [3] DE SAINT AUBAIN SOMERHAUSEN N, FLETCHER CD, *Leiomyosarcoma of soft tissue in children: clinicopathologic analysis of 20 cases*, Am J Surg Pathol, 1999, 23(7):755–763.
- [4] MANKIN HJ, CASAS-GANEM J, KIM JI, GEBHARDT MC, HORNICEK FJ, ZEEGEN EN, *Leiomyosarcoma of somatic soft tissues*, Clin Orthop Relat Res, 2004, 421:225–231.
- [5] GOLDEN T, STOUT AP, *Smooth muscle tumors of the gastrointestinal tract and retroperitoneal tissues*, Surg Gynecol Obstet, 1941, 73:784–810.
- [6] FIELDS JP, HELWIG EB, *Leiomyosarcoma of the skin and subcutaneous tissue*, Cancer, 1981, 47(1):156–169.
- [7] JENSEN ML, JENSEN OM, MICHALSKI W, NIELSEN OS, KELLER J, *Intradermal and subcutaneous leiomyosarcoma: a clinicopathological and immunohistochemical study of 41 cases*, J Cutan Pathol, 1996, 23(5):458–463.

- [8] HASIMOTO H, DAIMARU Y, TSUNEYOSHI M, ENJOJI M, *Leiomyosarcoma of the external soft tissues. A clinico-pathologic, immunohistochemical, and electron microscopic study*, Cancer, 1986, 57(10):2077–2088.
- [9] DEMAS BE, HEELAN RT, LANE J, MARCOVE R, HAJDU S, BRENNAN MF, *Soft-tissue sarcomas of the extremities: comparison of MR and CT in determining the extent of disease*, AJR Am J Roentgenol, 1988, 150(3):615–620.
- [10] BAR-SHALOM R, YEFREMOV N, GURALNIK L, GAITINI D, FRENKEL A, KUTEN A, ALTMAN H, KEIDAR Z, ISRAEL O, *Clinical performance of PET/CT in evaluation of cancer: additional value for diagnostic imaging and patient management*, J Nucl Med, 2003, 44(8):1200–1209.
- [11] HOEBER I, SPILLANE AJ, FISHER C, THOMAS JM, *Accuracy of biopsy techniques for limb and limb girdle soft tissue tumors*, Ann Surg Oncol, 2001, 8(1):80–87.
- [12] SOMER EJ, MARSDEN PK, BENATAR NA, GOODEY J, O'DOHERTY MJ, SMITH MA, *PET-MR image fusion in soft tissue sarcoma: accuracy, reliability and practicality of interactive point-based and automated mutual information techniques*, Eur J Nucl Med Mol Imaging, 2003, 30(1):54–62.
- [13] VAIDYA SJ, PAYNE GS, LEACH MO, PINKERTON CR, *Potential role of magnetic resonance spectroscopy in assessment of tumour response in childhood cancer*, Eur J Cancer, 2003, 39(6):728–735.
- [14] TROVIK CS, BAUER HC, BROSIÖ O, SKOOG L, SÖDERLUND V, *Fine needle aspiration (FNA) cytology in the diagnosis of recurrent soft tissue sarcoma*, Cytopathology, 1998, 9(5):320–328.
- [15] COINDRE JM, TERRIER P, BUI NB, BONICHON F, COLLIN F, LE DOUSSAL V, MANDARD AM, VILAIN MO, JACQUEMIER J, DUPLAY H, SASTRE X, BARLIER C, HENRY-AMAR M, MACÉ-LESECH J, CONTESSO G., *Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group*, J Clin Oncol, 1996, 14(3):869–877.
- [16] BEHRANWALA KA, A'HERN R, OMAR AM, THOMAS JM, *Prognosis of lymph node metastasis in soft tissue sarcoma*, Ann Surg Oncol, 2004, 11(7):714–719.
- [17] BLAZER DG III, SABEL MS, SONDAK VK, *Is there a role for sentinel lymph node biopsy in the management of sarcoma?*, Surg Oncol, 2003, 12(3):201–206.
- [18] VAN GLABBEKE M, VAN OOSTEROM AT, OOSTERHUIS JW, MOURIDSEN H, CROWTHER D, SOMERS R, VERWEIJ J, SANTORO A, BUESA J, TURSZ T, *Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens – a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study*, J Clin Oncol, 1999, 17(1):150–157.
- [19] FATA R, O'REILLY E, ILSON D, PFISTER D, LEFFEL D, KELSEN DP, SCHWARTZ GK, CASPER ES, *Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face*, Cancer, 1999, 86(10):2034–2037.
- [20] JUDSON I, RADFORD JA, HARRIS M, BLAY JY, VAN HOESSEL Q, LE CESNE A, VAN OOSTEROM AT, CLEMONS MJ, KAMBY C, HERMANS C, WHITTAKER J, DONATO DI PAOLA E, VERWEIJ J, NIELSEN S, *Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group*, Eur J Cancer, 2001, 37(7):870–877.
- [21] EILING S, LISCHNER S, BUSCH JO, ROTHaupt D, CHRISTOPHERS E, HAUSCHILD A, *Complete remission of a radio-resistant cutaneous angiosarcoma of the scalp by systemic treatment with liposomal doxorubicin*, Br J Dermatol, 2002, 147(1):150–153.
- [22] VAN OOSTEROM AT, MOURIDSEN HT, NIELSEN OS, DOMBERNOWSKY P, KRZEMIENIECKI K, JUDSON I, SVANCAROVA L, SPOONER D, HERMANS C, VAN GLABBEKE M, VERWEIJ J; EORTC SOFT TISSUE AND BONE SARCOMA GROUP, *Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients*, Eur J Cancer, 2002, 38(18):2397–2406.
- [23] D'INCALCI M, JIMENO J, *Preclinical and clinical results with the natural marine product ET-743*, Expert Opin Investig Drugs, 2003, 12(11):1843–1853.
- [24] YOVINE A, RIOFRIO M, BLAY JY, BRAIN E, ALEXANDRE J, KAHATT C, TAAMMA A, JIMENO J, MARTIN C, SALHI Y, CVITKOVIC E, MISSET JL, *Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients*, J Clin Oncol, 2004, 22(5):890–899.

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